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❖ Bridged Heterocycles

Nitrogen-Bridged, Natural Product-Like Octahydrobenzofurans and Octahydroindoles: Scope and Mechanism of Bridge-Forming Reductive Amination via Caged Heteroadamantanes

Steven. M. Wales,^[a] Holly V. Adcock,^[b] William Lewis,^[a] Daniel Hamza,^[b] and Christopher J. Moody*^[a]

Abstract: The biological significance of sp³-rich synthetic scaffolds with natural product-like features yet distinct global frameworks is being increasingly recognised in medicinal chemistry and biochemistry. Taking inspiration from the vast array of bioactive, bridged alkaloids, we report the synthesis of unique, densely functionalised tricyclic scaffolds based on nitrogen-bridged, octahydrobenzofurans and octahydroindoles. These heterocycle-rich frameworks were assembled by a one-pot, two-step bridge-forming reductive amination process, which was shown to proceed via caged, heteroadamantane intermediates that thermodynamically drive an *exo-endo* epimerisation, enabling intramolecular aza-Michael addition over the concave face of the fused bicyclic precursors. In addition to evaluating the scope of this aza bridge-forming reaction, further stereochemical complexity was introduced by subsequent diastereoselective ketone reductions and other manipulations. Finally, strategic diversity points (amino, carboxy) were decorated with common medicinal chemistry fragments, providing a set of exemplar derivatives with Lipinski compliant physicochemical properties.

Introduction

Humanity has a constant need for the development of new small molecule therapeutics that provide improved target selectivity, overcome developing resistance and/or act on new biological targets. In the modern era, the increasing complexity of emerging drug targets (e.g., protein-protein interactions^[1]) underscores the need for high quality, lead compounds in the drug development process. In the crucial lead optimisation stages and beyond, molecules with increased stereochemical complexity, saturation, functionality and rigidity have a distinct advantage,^[2] such that there is greater potential for highly specific target binding with minimal entropic penalty and for improving potency and selectivity through exploration of discrete vectors around a three-dimensional-like surface.^[3–5] These desirable structural features are often manifested in polycyclic natural products and their derivatives, which have not only found application as

pharmaceutical drugs^[6] but have also informed the design of synthetically tractable, non-natural biological tools and medicines with diverse biological activities.^[7–9]

Polycyclic alkaloids in which nitrogen is incorporated into a bridged ring system represent a vast and important subset of biologically active natural products,^[10,11] many of which are included on the World Health Organisation's Model List of Essential Medicines.^[12] Prominent examples include the central nervous system drugs morphine (**1**, Figure 1) and atropine (**2**) and the antimalarial agent quinine (**3**).^[13a] Non-natural, nitrogen polyheterocycles such as the antiemetic granisetron (**4**) and the benzomorphan analgesic pentazocine (**5**) are also among FDA-approved medications based on aza-bridged frameworks.^[13]

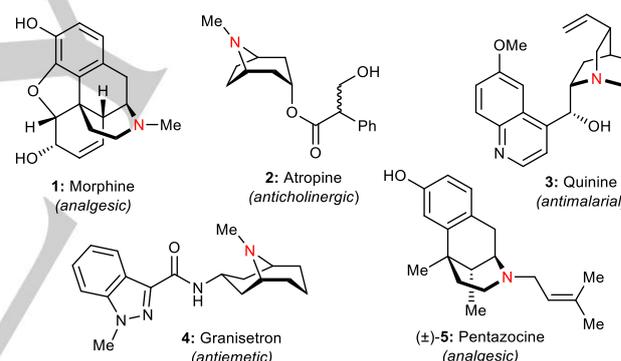


Figure 1. Natural and synthetic nitrogen-bridged, polycyclic drugs.

In our ongoing efforts^[14] to develop innovative scaffolds for the European Lead Factory (ELF) drug discovery initiative,^[15] we became interested in work by Johnson^[16] and separately, Coeffard and Greck,^[17] describing enantio- and diastereoselective organocatalysed annulations of quinols and quinamines (**6**) with α,β -unsaturated aldehydes (Scheme 1). In a compelling application of the bicyclic products **7**, Johnson reported one example of a reductive amination to give **8a**, in which the existing rings were bridged via an aza-Michael addition, enabled by an uncommon *exo-endo* epimerisation at C-3 proven by deuterium incorporation.^[16,18] While a small number of bridged alkaloids or derivatives incorporating the analogous carbocyclic skeleton of **8** (where X = CH₂ or [CH₂]₂) as a substructure have been described,^[19] the polyheterocyclic framework of **8** (where X = O, NR) comprising both fused and bridged saturated heterocycles has otherwise not been reported. Thus, intrigued by the unique, densely decorated skeleton of **8** as a starting point for drug discovery, we present here our preliminary investigations into the synthesis of analogues of **8** (**8b–i**) and further derivatives (**16a–z**), including an evaluation of the scope and limitations of the

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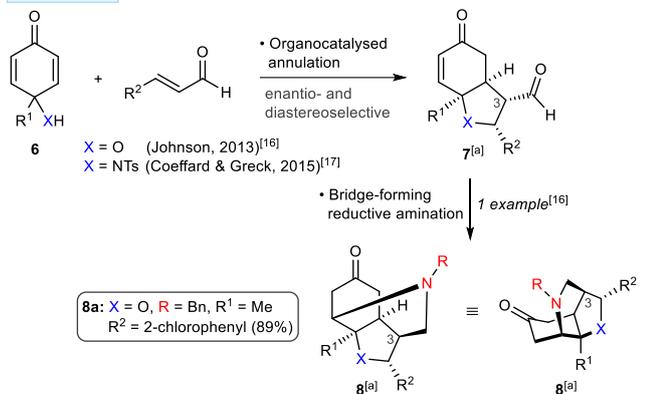
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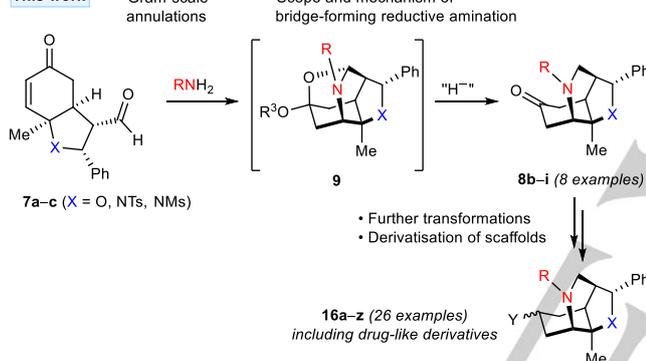
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bridge-forming reductive amination with respect to the amine (RNH₂). In addition, we have identified a driving force for the *exo-endo* epimerisation of the formyl-bearing stereocentre (C-3) that occurs during the reductive amination, through the isolation and characterisation of stable, (pre-reduction) caged intermediates (**9**).

Previous work (Johnson/Coeffard & Greck)



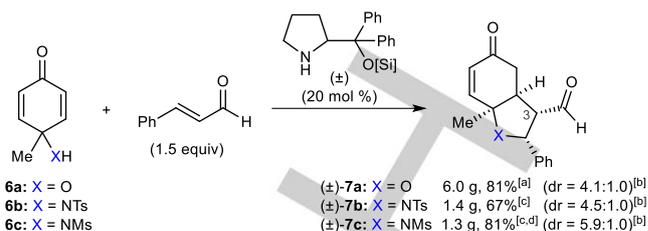
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Scheme 1. Previous and current work. a) Depicted as the opposite enantiomer to reported.

Results and Discussion

Given the main objectives of this study were to explore derivatives of **8** with variations in R and Y (structure **16**, Scheme 1) and to uncover the mechanism of the bridge-forming reductive amination, the substituents at R¹ and R² (structures **7** and **8**, Scheme 1) were fixed throughout as methyl and phenyl, respectively. Thus, the required bicyclic adducts **7a-c** were prepared from cinnamaldehyde and the corresponding quinol or *N*-sulfonylquinamine using the respective organocatalysis conditions described previously (Scheme 2).^[16,17] We demonstrated successful scale-up (up to 6.0 g obtained) with comparable yields and diastereoselectivities to previously reported. In all cases, however, the products were prepared as racemates as preferred for first generation screening collections via the ELF's Joint European Compound Library (JECL).^[20]



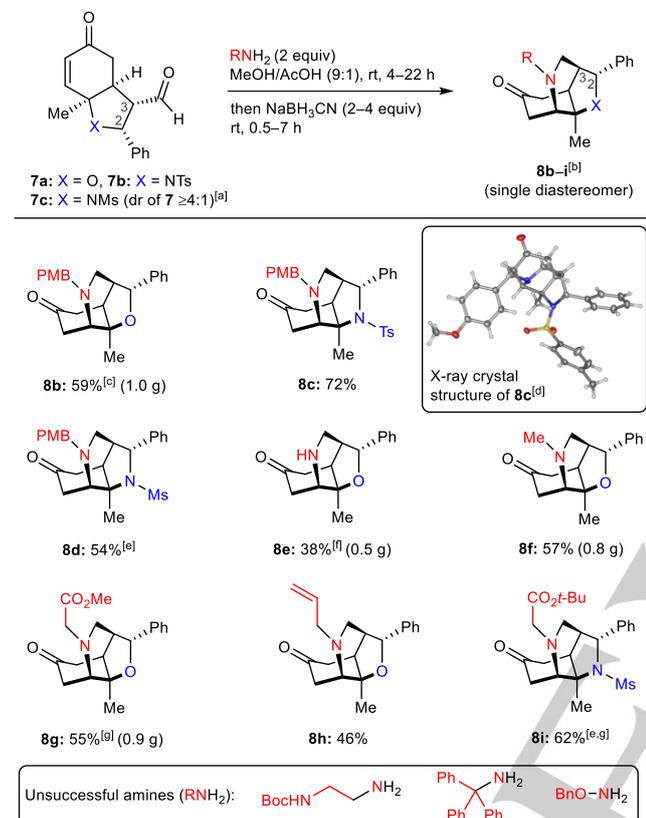
Scheme 2. Annulation reactions. a) Conditions: [Si] = TMS, 4-nitrobenzoic acid (20 mol %), toluene, rt, 40 h. b) Diastereomeric ratio determined by ¹H NMR and refers to the ratio of the major diastereomer (depicted) relative to the sum of others combined. c) Conditions: [Si] = TBS, NaOAc (1 equiv), CHCl₃, 55 °C, 96 h (+ 10 mol % catalyst after 65 h). d) Isolated with an unidentified side product (purity = 81 mol %).

Although up to two other diastereomers accompanied the formation of **7a-c** in each case (Scheme 2), we strategically did not attempt their separation from the major isomers and the relative configurations of these minor components were not determined. Instead, using the diastereomeric mixture of **7** directly in the next step (Scheme 3) was expected to prove more practical and avoid potential losses to the overall yield of **8**, given the diastereoconvergent nature of the subsequent bridge formation with respect to **7** and its C-3 epimer.^[21] Accordingly, the bridge-forming reductive amination was investigated using the diastereoenriched bicyclic adducts **7a-c** (Scheme 3). Reaction conditions for the one-pot process were directly adapted from Johnson's seminal example,^[16] although reaction times for the initial condensation and subsequent reduction varied depending on the substrate (**7a-c**) and amine (RNH₂) used (see the Supporting Information). Products (**8**) epimeric at C-2 were not observed in the crude reaction mixtures, indicating that any minor diastereomers in precursor **7** epimeric at C-2 reacted via other pathways. In fact, the desired tricyclic **8** was generally the sole product observed after work-up by NMR spectroscopic analysis, which suggested oligomerisation as a competing pathway to account for the overall mass balance.^[22] This facilitated the straightforward isolation of all bridged products (**8**) as single diastereomers following flash chromatography.

Our opening experiment to assess the reaction scope was carried out with benzofuran **7a** and 4-methoxybenzylamine to give **8b** in 59% yield (Scheme 3).^[23] Next, reactions with 4-methoxybenzylamine were successfully extended to sulfonamides **7b** and **7c** to give octahydroindole-containing tricycles **8c** and **8d** in 72% and 54% yields, respectively. The structure of **8c** was confirmed by X-ray crystallography. Amines of biological relevance and/or downstream synthetic utility were then evaluated and were found to be well tolerated including methylamine, glycine esters and allylamine to give **8f-i** in moderate yields (46–62%). The *N*-unsubstituted cyclic amine **8e** was also directly accessible from **7a** and ammonium acetate using this methodology, however a decrease in yield was observed (38%).^[24] A notable feature of this method is its practical simplicity: all reactions were performed under air at room temperature with standard grade solvents and reagents. This aided the straightforward preparation of selected polycycles **8b** and **8e-g** on synthetically useful scales (5 mmol) which were isolated in 0.5–1.0 g quantities (percentage yields shown in

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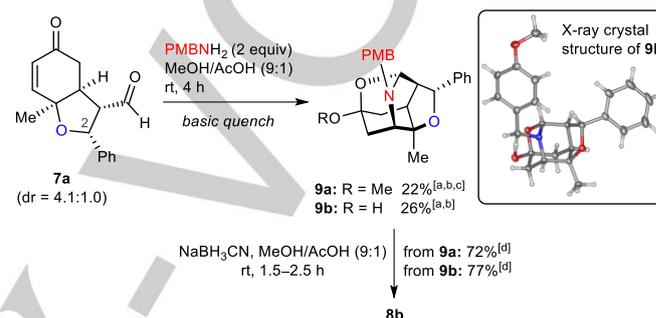
Scheme 3). Amines that did not form the desired product **8** when combined with **7a** under the standard conditions included *N*-Boc-ethylenediamine, triphenylmethylamine and *O*-benzylhydroxylamine. In these cases, the reactions proceeded with complete consumption of **7a**, but gave intractable mixtures containing, at most, traces of the desired products as ascertained by ¹H NMR spectroscopic analysis.



Scheme 3. Scope of the bridge-forming reductive amination. a) Reactions performed on 1.0–5.0 mmol scale. See Scheme 2 for precise dr of reactants **7a–c**. b) Yields are isolated yields as single diastereomers and are uncorrected for any diastereomers in **7a–c** epimeric at C-2. c) Diastereomeric ratio of precursor **7a** = 2.1:1.0. d) The X-ray crystal structure of **8c** is depicted as the opposite enantiomer to drawn. e) Yield uncorrected for impurity (19 mol %) in precursor **7c**. f) Reaction performed with NH₄OAc (3 equiv) as the ammonia source. g) Reaction performed with the corresponding amine hydrochloride salt (2 equiv) with NEt₃ (2 equiv) as an additive.

With a collection of tricyclic scaffolds **8b–i** prepared, we proceeded to investigate the mechanism of the reductive amination process. To gain further insight into the C-3 *exo–endo* epimerisation, we attempted to isolate the reaction intermediates from amine condensation by omitting the subsequent reduction step. Accordingly, **7a** was treated with 4-methoxybenzylamine under the acidic conditions and the reaction was quenched after complete consumption of **7a** (Scheme 4). Interestingly, analysis of the organic extract by NMR spectroscopy revealed complete disappearance of both the aldehyde and enone (alkene) functional groups of **7a**, indicating that an aza-Michael addition had likely taken place in the absence of the reducing agent. Although several unidentified products were formed, the major

product **9** was isolated by flash chromatography in the form of separable acetal **9a** and hemiacetal **9b** (48% combined yield). It should be noted that the isolated ratio of **9a/9b** (0.8:1.0) was significantly decreased from that originally observed in the crude mixture (≥5:1), indicating that partial acetal–hemiacetal exchange occurred during silica gel chromatography.^[25] Otherwise, both forms of **9** were stable and could be fully characterised and stored without any special precautions. This enabled confirmation of the caged structure of **9b** by X-ray crystallography, which is reminiscent of natural products such as fusidilactone C,^[26] tetrodotoxin,^[27] daphnezimine A^[28] and caloundrin B^[29] that contain heteroadamantane cores with O–C–O or O–C–N linkages.

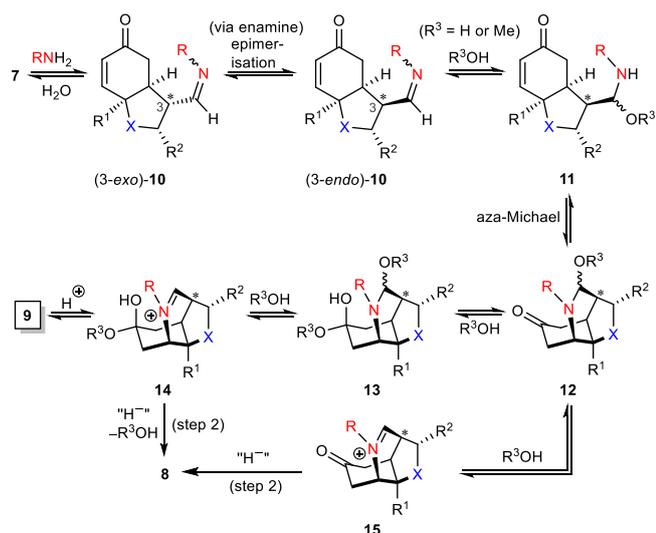


Scheme 4. Isolation of key intermediate **9** in the bridge-forming reductive amination. a) Isolated yield after silica gel chromatography as a single diastereomer, uncorrected for any diastereomers in **7a** epimeric at C-2. b) Ratio **9a/9b** before silica gel chromatography ≥5:1. c) Isolated with 12 mol % of a minor product, tentatively assigned as the corresponding caged aminal (see the Supporting Information). d) Yield determined by ¹H NMR with mesitylene as internal standard.

When the isolated samples of **9a** and **9b** were separately subjected to the standard reduction conditions with NaBH₃CN (Scheme 4), clean formation of tricyclic product **8b** was observed in both cases (72% and 77% NMR yields, respectively).

Based on the above findings (Scheme 4), a dynamic mechanism is proposed for the bridge-forming process, whereby aza-Michael addition occurs prior to reduction (Scheme 5).^[30,31] Initial condensation of aldehyde **7** and the amine (RNH₂) would give imine (3-*exo*)-**10**, which could undergo reversible epimerisation to diastereomer (3-*endo*)-**10** under the acidic conditions. Addition of water or methanol to (3-*endo*)-**10** would provide hemiaminal (ether) **11**, which places the nitrogen in the required orientation to undergo an intramolecular aza-Michael addition to the concave face of the enone.^[32] Subsequent hemiacetal formation at the ketone of tricycle **12** (via **13**) would enable intramolecular trapping of the derived iminium ion **14** to produce the observed, stable intermediate **9**, which presumably drives the overall equilibrium and the initial epimerisation of **10**. Upon addition of the hydride source (step 2), the irreversible reduction of iminium ions **14** or **15** perturbs the equilibrium and promotes cleavage of the heteroadamantane core of **9** by sequential hemiaminal ether fragmentation and acetal collapse, ultimately giving the half-caged product **8**.

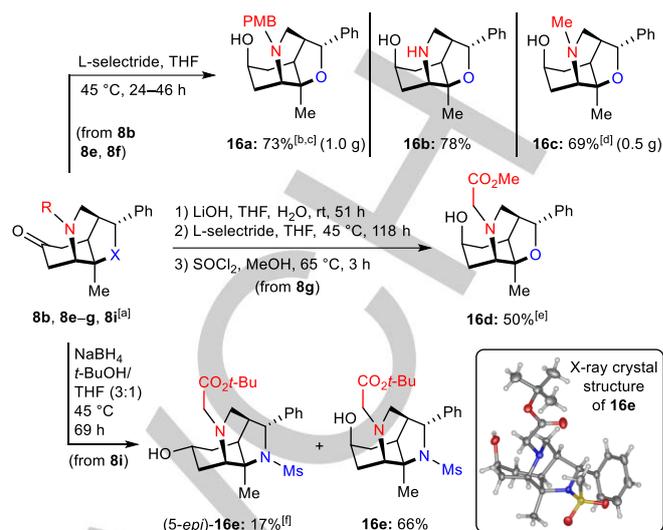
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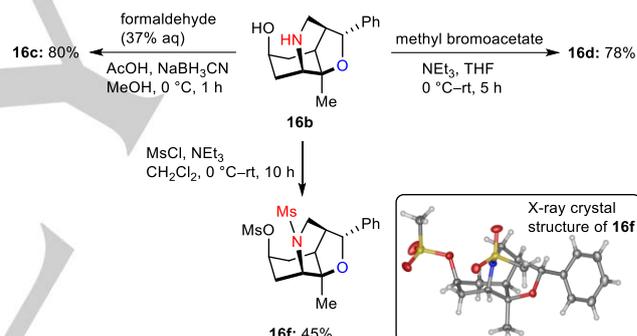
Scheme 5. Proposed mechanism of the bridge-forming reductive amination.

To gain access to fully-saturated core derivatives, the prochiral ketone of selected polycycles **8b**, **8e–g** and **8i** was subjected to diastereoselective reduction under substrate dependent conditions (Scheme 6). Treatment of **8b**, **8e** and **8f** with L-selectride resulted in exclusive equatorial hydride delivery to give axial alcohols **16a–c** in 69–78% yields. Again, this transformation was demonstrated on preparative scales, with up to 1.0 g of material isolated (for **16a**). The relative stereochemistry of **16b** was determined by X-ray crystallographic analysis of the dimethylsulfate derivative **16f** (Scheme 7), while **16c** was independently prepared from **16b** by reductive N-methylation thus confirming the analogous stereochemistry (Scheme 7). The structure of **16a** was assigned by analogy.

In general, the sterically encumbered ketone of scaffold **8** proved relatively slow to reduce, which introduced some chemoselectivity issues in the presence of the ester functionalities of **8g** and **8i**. For example, reduction of the methyl ester group in **8g** occurred at a competitive rate to ketone reduction using both L-selectride and NaBH₄ (in THF or *i*-PrOH). This necessitated ‘protection’ of the methyl ester as the lithium carboxylate salt prior to ketone reduction with L-selectride, allowing isolation of alcohol **16d** (50%) over a three-step process (Scheme 6). An alternative synthesis of **16d** via N-alkylation of **16b** with methyl bromoacetate (78%) was also carried out to confirm the expected relative stereochemistry (Scheme 7). The *tert*-butyl ester of **8i** was also incompatible with L-selectride but proved inert to NaBH₄, allowing selective ketone reduction to give a mixture of diastereomers **16e** (66%) and (5-*epi*)-**16e** (17%) which were separated by column chromatography (Scheme 6). Similar to the previous reductions with L-selectride, the major diastereomer **16e** had the axial configuration at the hydroxy group as confirmed by X-ray crystallography.

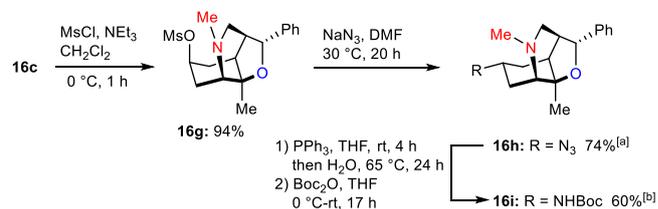


Scheme 6. Synthesis of alcohols **16a–e** by diastereoselective ketone reduction. Structures of starting materials **8b**, **8e–g** and **8i** are shown in Scheme 3. a) Yields are isolated yields as single diastereomers. b) Reaction performed at –40 °C–rt. c) 13% of **8b** was recovered. d) 26% of **8f** was recovered. e) 14% starting material was recovered in the form of a methyl enol ether (see the Supporting Information). f) Isolated dr = 14:1.



Scheme 7. Divergent synthesis of **16c**, **16d** and **16f** from amine **16b**.

To introduce other useful functionality, representative alcohol **16c** was converted into mesylate derivative **16g** in high yield (94%, Scheme 8), which was subjected to nucleophilic S_N2 displacement with sodium azide to give **16h** (74%). Subsequent Staudinger reduction and treatment with Boc₂O gave the protected primary amine **16i** in 60% yield over the two steps.

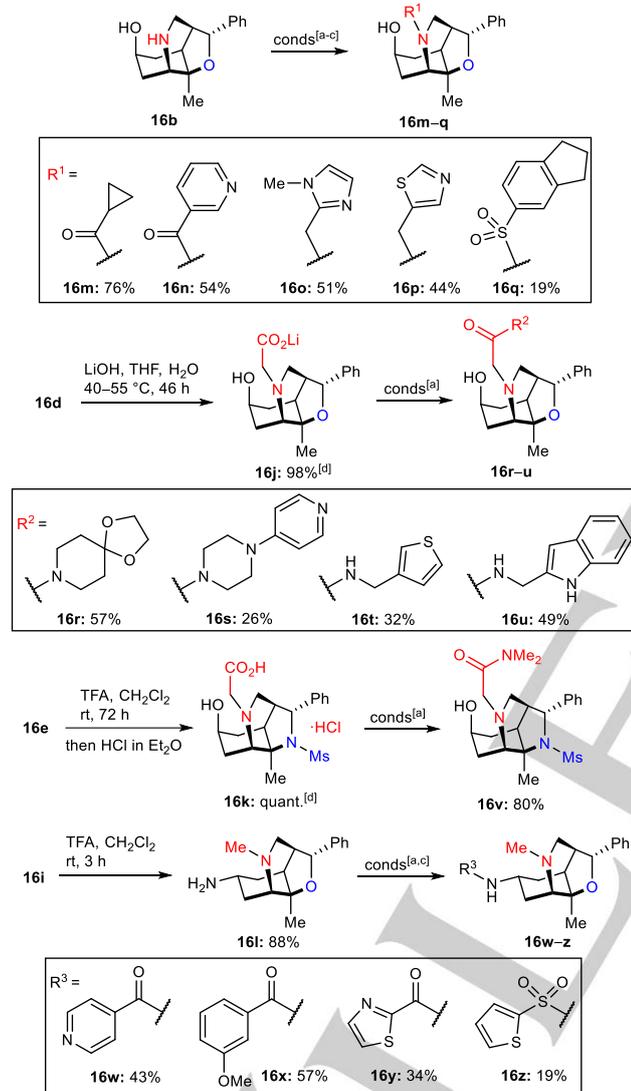


Scheme 8. Synthesis of Boc-protected amine **16i**. a) Isolated with a minor alkene impurity (7% w/w) arising from elimination of MsOH. b) Yield uncorrected for alkene impurity (7% w/w) in azide **16h**.

By design, several of the reduced scaffolds (**16**) were decorated with modifiable (protected) amino or carboxy groups,

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thus presenting opportunities to create larger compound libraries by further derivatisation. To demonstrate this capability, esters **16d** and **16e** and *N*-Boc-amine **16i** were deprotected to give intermediates **16j–l**, which, along with amine **16b**, were elaborated in divergent fashion to an exemplar set of 14 final compounds **16m–z** using standard transformations (Scheme 9). Except for **16v**, these derivatives (**16m–z**) were prepared using high-throughput techniques (plate format/preparative HPLC purification) and the yields are unoptimised.



Scheme 9. Synthesis of derivatives **16j–z**. a) Amidation conditions: amine/carboxylic acid, HATU, NEt(*i*-Pr)₂, DMF, rt, 16 h. b) Reductive alkylation conditions: aldehyde, (NMe₄)BH(OAc)₃, AcOH, DMF, rt, 16 h. c) Sulfonation conditions: sulfonyl chloride, pyridine, DMF, rt, 16 h. d) Yield of crude product after work-up, judged to be of ≥ 90 mol % purity by NMR spectroscopic analysis. Used in the next step without further purification.

Analysis of the 14 exemplar compounds **16m–z** using the computational model LLAMA^[33] predicts favourable pharmacokinetic properties^[34] within Lipinski space:^[35] specifically: an average molecular weight of 401, AlogP of 2.3, topological polar surface area of 61.1 Å² and low rotatable bond

count of 3.4 (Table S1). The average “fraction sp³” of the molecules (**16m–z**), many of which have been decorated with (hetero)aromatic groups, is 0.55 (Table S1), which is above the average “fraction sp³” (0.47) of marketed drugs from 1980–2009.^[2a] Further, the overall three-dimensional nature of the tricyclic scaffolds is supported by an average plane-of-best-fit (PBF)^[36] deviation of 1.1 Å (Table S1), which compares favourably with that of the ChEMBL database^[37] of published bioactive compounds (average PBF for ChEMBL compounds = 0.6 Å).^[3] Taken collectively, these data reveal an encouraging physicochemical profile that would appear to make these scaffolds promising candidates for biological screening.

Conclusion

A total of thirty four derivatives (**8b–i** and **16a–z**) of densely functionalised tricyclic scaffolds based on aminomethyl-bridged, octahydrobenzofurans and indoles have been prepared. Construction of the key aza-containing bridge was achieved by a one-pot, two-step reductive amination process, in which a formyl group on the convex face of the bicyclic precursor was linked to the concave face of a distal enone via a stereodynamic amino-condensation process, driven by the formation of stable heteroadamantane intermediates. This (reductive) bridge-forming reaction was amenable to a variety of amines with associated biological relevance and/or downstream synthetic utility and has provided preparative access to (octahydro)benzofuran and *N*-sulfonylindole-based tricycles, which were further elaborated by diastereoselective reduction and other standard transformations, including to 14 drug-like examples (**16m–z**).

These synthetically tractable scaffolds (**16**) contain many attractive features for biological applications including a high heterocycle and sp³-content and provide numerous points of potential diversity to be explored in further synthetic and biological studies (i.e., X, Y, R, R¹, R² of structures **8** and **16** in Scheme 1). Furthermore, the elucidation of the bridge-forming reductive amination pathway opens up intriguing opportunities to create even greater structural and stereochemical complexity by the diastereoselective addition of carbon nucleophiles to the half-caged iminium ions (**14** or **15**) in the second step of the bridge-forming process.

Experimental Section

General Methods: All reactions were carried out in standard laboratory glassware with magnetic stirring. Thin layer chromatography (TLC) was performed on aluminium-backed Silica Gel 60 plates with fluorescent indicator F254. Visualisation was accomplished with UV light, a ninhydrin staining solution and/or a phosphomolybdic acid staining solution. Flash chromatography was performed under positive air pressure using Silica Gel 60 of 230–400 mesh (40–63 μm). Melting points were determined using a Gallenkamp (Griffin) Melting Point Apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Bruker ALPHA FTIR Spectrometer with neat samples. Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded on Bruker 300 MHz, 400 MHz or 500 MHz

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spectrometers as specified. Spectra acquired in CDCl_3 are reported relative to tetramethylsilane (^1H : $\delta = 0.00$ ppm) and solvent resonance (^{13}C : $\delta = 77.0$ ppm). Spectra acquired in CD_3OD are reported relative to solvent resonance (^1H : $\delta = 3.31$ ppm; ^{13}C : $\delta = 49.0$ ppm). High resolution mass spectrometry (HRMS) was performed on a Bruker MicrOTOF II mass spectrometer with electrospray ionisation. Cambridge Crystallographic Data Centre (CCDC) deposition numbers are as follows: compound **8c**: 1812879, compound **9b**: 1812878, compound **16e**: 1812881, compound **16f**: 1812880.

Synthesis of **7a–c** via Organocatalysed Annulation

(±)-(2*R*,3*S*,3*aS*,7*aS*)/(2*S*,3*R*,3*aR*,7*aR*)-7*a*-Methyl-5-oxo-2-phenyl-2,3,3*a*,4,5,7*a*-hexahydrobenzofuran-3-carbaldehyde (**7a**):

Based on a literature procedure,^[16] to a mixture of quinol **6a** (3.564 g, 28.71 mmol), 4-nitrobenzoic acid (959.6 mg, 5.74 mmol) and the racemic organocatalyst (±)- α,α -diphenylprolinol trimethylsilyl ether (1.869 g, 5.74 mmol) in reagent grade toluene (114.8 mL) was added neat *trans*-cinnamaldehyde (5.42 mL, 43.06 mmol) and the mixture was stirred at rt under an air atmosphere for 40 h. The solvent was removed under reduced pressure and EtOAc (120 mL) was added. The solution was washed with saturated NaHCO_3 (2 × 50 mL) to remove the benzoic acid, dried (Na_2SO_4) and concentrated. Flash chromatography (126 g silica, 22% to 28% EtOAc/light petroleum) gave **7a** (5.971 g, 81%, dr major/[others combined] = 4.1:1.0) as a yellow gum. The major diastereomer was assigned as the all-exo isomer (shown above) based on agreement with literature data.^[16] TLC (40% EtOAc/light petroleum): R_f 's = 0.53 [minor diastereomer], 0.43 [major diastereomer], 0.33 [minor diastereomer] (UV or phosphomolybdic acid stain). IR: $\nu = 2974, 2737, 1716, 1675, 1120, 1044, 700$ cm^{-1} . ^1H NMR (300 MHz, CDCl_3 , major diastereomer only): $\delta = 9.00$ (d, $J = 2.1$ Hz, 1H), 7.39–7.25 (m, 5H), 6.72 (dd, $J = 10.3, 1.9$ Hz, 1H), 6.09 (dd, $J = 10.3, 1.1$ Hz, 1H), 5.23 (d, $J = 9.4$ Hz, 1H), 3.14 (dd, $J = 9.3, 2.0$ Hz, 1H), 3.09–3.05 (m, 1H), 2.72 (dd, $J = 17.4, 5.3$ Hz, 1H), 2.56 (ddd, $J = 17.4, 2.2, 1.1$ Hz, 1H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3 , major diastereomer only): $\delta = 198.9, 196.4, 152.0, 136.9, 129.9, 128.9, 128.5, 126.4, 79.6, 79.2, 60.5, 43.1, 37.3, 23.3$. HRMS (ES^+): calcd. for $\text{C}_{17}\text{H}_{20}\text{NaO}_4$ [$\text{M}+\text{MeOH}+\text{Na}$] $^+$ 311.1254, found 311.1249. The obtained mixture of diastereomers was used in the next step without any complications.

(±)-(2*R*,3*S*,3*aS*,7*aS*)/(2*S*,3*R*,3*aR*,7*aR*)-7*a*-Methyl-5-oxo-2-phenyl-1-(4-toluenesulfonyl)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indole-3-carbaldehyde (**7b**):

Based on a literature procedure,^[17] to a mixture of quinamine **6b** (1.387 g, 5.00 mmol), sodium acetate (410.2 mg, 5.00 mmol) and the racemic organocatalyst (±)- α,α -diphenylprolinol *tert*-butyldimethylsilyl ether (367.6 mg, 1.00 mmol) in reagent grade chloroform (50 mL) was added neat *trans*-cinnamaldehyde (0.94 mL, 7.50 mmol) and the mixture was stirred at 55 °C under an initial air atmosphere for 65 h (sealed flask with argon balloon equaliser). A second portion of the solid TBS organocatalyst (183.8 mg, 0.50 mmol) was added and stirring continued at 55 °C for a further 31 h (total reaction time = 96 h). The solvent was removed under reduced pressure and the residue subjected to flash chromatography (36 g silica, 30%

EtOAc/light petroleum) giving **7b** (1.369 g, 67%, dr major/[others combined] = 4.5:1.0) as a light orange solid. The major diastereomer was assigned as the all-exo isomer (shown above) based on agreement with literature data.^[17] TLC (40% EtOAc/light petroleum): R_f 's = 0.52 [major diastereomer], 0.38 [minor diastereomer], 0.32 [minor diastereomer] (UV). IR: $\nu = 1676, 1331, 1148, 1053, 676, 585, 544$ cm^{-1} . ^1H NMR (300 MHz, CDCl_3 , major diastereomer only): $\delta = 9.00$ (d, $J = 1.3$ Hz, 1H), 7.61 (dd, $J = 10.5, 2.2$ Hz, 1H), 7.22–7.03 (m, 5H), 6.95–6.87 (m, 4H), 5.98 (dd, $J = 10.5, 1.1$ Hz, 1H), 5.48 (d, $J = 9.7$ Hz, 1H), 3.33 (ddd, $J = 12.4, 9.9, 1.3$ Hz, 1H), 3.11 (ddt, $J = 12.4, 4.8, 2.2$ Hz, 1H), 2.73 (dd, $J = 17.8, 5.3$ Hz, 1H), 2.57 (ddd, $J = 17.8, 2.3, 1.2$ Hz, 1H), 2.27 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3 , major diastereomer only): $\delta = 197.5, 195.1, 151.6, 143.0, 138.1, 136.2, 128.8, 128.6, 128.2, 127.6, 127.1, 127.0, 66.4, 63.3, 55.1, 44.0, 36.1, 24.1, 21.3$. HRMS (ES^+): calcd. for $\text{C}_{24}\text{H}_{27}\text{NNaO}_5\text{S}$ [$\text{M}+\text{MeOH}+\text{Na}$] $^+$ 464.1503, found 464.1510. The obtained mixture of diastereomers was used in the next step without any complications.

(±)-(2*R*,3*S*,3*aS*,7*aS*)/(2*S*,3*R*,3*aR*,7*aR*)-7*a*-Methyl-5-oxo-2-phenyl-1-methanesulfonyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indole-3-carbaldehyde (**7c**):

Based on a literature procedure for the tosyl analogue,^[17] to a mixture of quinamine **6c** (1.006 g, 5.00 mmol), sodium acetate (410.2 mg, 5.00 mmol) and the racemic organocatalyst (±)- α,α -diphenylprolinol *tert*-butyldimethylsilyl ether (367.6 mg, 1.00 mmol) in reagent grade chloroform (50 mL) was added neat *trans*-cinnamaldehyde (0.94 mL, 7.50 mmol) and the mixture was stirred at 55 °C under an initial air atmosphere for 65 h (sealed flask with argon balloon equaliser). A second portion of the solid TBS organocatalyst (183.8 mg, 0.50 mmol) was added and stirring continued at 55 °C for a further 31 h (total reaction time = 96 h). The solvent was removed under reduced pressure and the residue subjected to flash chromatography (20 g silica, 33% to 40% EtOAc/light petroleum) giving a pale orange solid (1.346 g) which consisted of **7c** with a minor diastereomer (dr major/minor = 5.9:1.0) and an unidentified side product (ratio of combined diastereomers/side product = 4.3:1.0). The mass of the mixed sample obtained (1.346 g) was equivalent to 81% yield of **7c** with 81 mol % purity (yield and purity for combined diastereomers). The major diastereomer was assigned as the all-exo isomer (shown above) by analogy with the known *N*-tosyl analogue.^[17] TLC (40% EtOAc/light petroleum): R_f 's = 0.39 [unknown side product], 0.32 [major diastereomer], 0.22 [minor diastereomer] (UV or weak with phosphomolybdic acid stain). IR: $\nu = 1679, 1326, 1145, 962, 758, 702, 520$ cm^{-1} . ^1H NMR (300 MHz, CDCl_3 , major diastereomer only): $\delta = 9.09$ (d, $J = 0.9$ Hz, 1H), 7.52–7.19 (m, 6H), 5.96 (dd, $J = 10.5, 1.1$ Hz, 1H), 5.47 (d, $J = 9.6$ Hz, 1H), 3.39 (ddd, $J = 12.4, 9.6, 1.0$ Hz, 1H), 3.28 (ddt, $J = 12.4, 4.7, 2.2$ Hz, 1H), 2.83–2.74 (m, 1H), 2.70–2.61 (m, 1H), 2.49 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3 , major diastereomer only): $\delta = 197.2, 195.0, 151.6, 137.0, 129.4, 129.2, 127.8, 127.1, 65.6, 63.1, 55.0, 44.8, 44.6, 36.2, 23.6$. HRMS (ES^+): calcd. for $\text{C}_{18}\text{H}_{23}\text{NNaO}_5\text{S}$ [$\text{M}+\text{MeOH}+\text{Na}$] $^+$ 388.1190, found 388.1186. The obtained mixture was used in the next step without any complications.

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Synthesis of 8b–i via Bridge-Forming Reductive Amination**(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-8-(4-Methoxybenzyl)-7a-methyl-2-phenylhexahydro-7,3-(epiminomethano)benzofuran-5(4H)-one (8b):**

To a mixture of annulation product **7a** (1.185 g, 4.62 mmol, dr major/[others combined] = 2.1:1.0) and 4-methoxybenzylamine (1.21 mL, 9.25 mmol) in reagent grade MeOH (41.6 mL) was added AcOH (4.6 mL) and the solution was stirred at rt under an air atmosphere for 4 h. Solid NaBH₃CN (581.1 mg, 9.25 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 30 min at rt under air. A second portion of NaBH₃CN (209.5 mg, 4.62 mmol) was added and stirring continued for a further 2 h. The mixture was poured into NaOH (2 M in water, 65 mL) and most of the MeOH was then removed under reduced pressure. Brine (20 mL) and water (10 mL) were added and the product was extracted with EtOAc (130 mL + 30 mL). The combined extracts were dried (Na₂SO₄) and concentrated. ¹H NMR spectroscopic analysis of the residue showed the desired product and caged acetal **9a** (from incomplete reduction) in an approximate 11:1 molar ratio, respectively. Flash chromatography (54 g silica, 18% to 25% EtOAc/light petroleum) gave **8b** (1.035 g, 59% [uncorrected for diastereomeric impurities in starting material], single diastereomer) as a colourless foam. TLC (40% EtOAc/light petroleum): *R*_F = 0.44 (UV or phosphomolybdic acid stain). IR: ν = 2899, 2799, 1707, 1510, 1241, 1001, 727, 700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.36–7.29 (m, 6H), 7.27–7.19 (m, 1H), 6.89–6.83 (m, 2H), 5.22 (s, 1H), 3.79 (s, 3H), 3.69 (ABq, $\Delta\delta_{AB}$ = 0.10, *J* = 13.3 Hz, 2H), 3.21–3.15 (m, 1H), 2.87 (dd, *J* = 17.4, 2.8 Hz, 1H), 2.76 (dd, *J* = 12.6, 3.3 Hz, 1H), 2.59–2.49 (m, 3H), 2.36–2.26 (m, 3H), 1.68 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 209.6, 158.7, 144.0, 130.5, 129.6, 128.0, 126.7, 125.0, 113.7, 82.7, 79.3, 63.0, 56.7, 55.2, 48.7, 47.9, 40.2, 39.0, 38.6, 22.1. HRMS (ES⁺): calcd. for C₂₄H₂₈NO₃ [M+H]⁺ 378.2064, found 378.2065.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-8-(4-Methoxybenzyl)-7a-methyl-2-phenyl-1-(4-toluenesulfonyl)octahydro-5H-7,3-(epiminomethano)indol-5-one (8c):

To a mixture of annulation product **7b** (409.5 mg, 1.00 mmol, dr major/[others combined] = 4.5:1.0) and 4-methoxybenzylamine (0.26 mL, 2.00 mmol) in reagent grade MeOH (9.0 mL) was added AcOH (1.0 mL) and the suspension was stirred at rt under an air atmosphere for 6 h (after 5.5 h the mixture became fully homogenous). Solid NaBH₃CN (125.7 mg, 2.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 30 min at rt under air. A second portion of NaBH₃CN (62.8 mg, 1.00 mmol) was added and stirring continued for a further 20 min. The mixture was poured into NaOH (2 M in water, 15 mL) and most of the MeOH was then removed under reduced pressure. Brine (20 mL) was added and the product was extracted with EtOAc (50 mL + 25 mL). The combined extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (11.7 g silica, 30% EtOAc/light petroleum) gave **8c** (383.6 mg, 72% [uncorrected for diastereomeric impurities in starting material], single diastereomer) as a pale yellow solid; m.p. 98–100 °C. TLC (40% EtOAc/light petroleum): *R*_F = 0.51 (UV). IR: ν = 2937, 1710, 1511, 1243, 1152, 1088, 672, 542 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.51 (d, *J* = 8.1 Hz, 2H), 7.37–7.33 (m,

2H), 7.17–6.98 (m, 5H), 6.96–6.87 (m, 4H), 5.20 (s, 1H), 3.98–3.90 (m, 1H), 3.81 (s, 3H), 3.77 (d, *J* = 12.8 Hz, 1H), 3.61 (d, *J* = 12.8 Hz, 1H), 2.86 (dt, *J* = 17.8, 2.5 Hz, 1H), 2.78 (dd, *J* = 12.9, 3.4 Hz, 1H), 2.65–2.52 (m, 2H), 2.47–2.33 (m, 3H), 2.33 (s, 3H), 1.97–1.91 (m, 1H), 1.89 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, one ArC signal 'missing' due to overlap): δ = 208.9, 158.7, 142.2, 141.1, 140.3, 130.2, 128.7, 127.8, 126.93, 126.91, 126.6, 113.6, 68.5, 66.7, 62.2, 57.5, 55.1, 47.6, 46.8, 41.9, 39.1, 37.9, 21.3, 21.2. HRMS (ES⁺): calcd. for C₃₁H₃₅N₂O₄S [M+H]⁺ 531.2312, found 531.2321.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-1-Methanesulfonyl-8-(4-Methoxybenzyl)-7a-methyl-2-phenyloctahydro-5H-7,3-(epiminomethano)indol-5-one (8d):

To a mixture of annulation product **7c** (333.4 mg, 1.00 mmol, dr major/minor = 5.9:1.0, 81 mol % purity) and 4-methoxybenzylamine (274.4 mg, 2.00 mmol) in reagent grade MeOH (9.0 mL) was added AcOH (1.0 mL) and the solution was stirred at rt under an air atmosphere for 4 h. Solid NaBH₃CN (125.7 mg, 2.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 30 min at rt under air. NaOH (2 M in water, 12 mL) was added and most of the MeOH was then removed under reduced pressure. Water (20 mL) was added and the product was extracted with EtOAc (30 mL + 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (14.8 g silica, 30% EtOAc/light petroleum) gave **8d** (244.9 mg, 54% [uncorrected for impurities in starting material], single diastereomer) as a colourless solid; m.p. 183–186 °C. TLC (50% EtOAc/light petroleum): *R*_F = 0.39 (UV or phosphomolybdic acid stain). IR: ν = 2909, 2798, 1698, 1511, 1323, 1247, 1144, 1019, 766, 705, 520 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.43 (d, *J* = 8.6 Hz, 2H), 7.38–7.25 (m, 5H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.07 (s, 1H), 3.82–3.76 (m, 4H), 3.71 (d, *J* = 12.8 Hz, 1H), 3.57 (d, *J* = 12.8 Hz, 1H), 2.90–2.80 (m, 4H), 2.75 (dd, *J* = 12.9, 3.5 Hz, 1H), 2.72–2.59 (m, 2H), 2.46 (dd, *J* = 16.8, 2.4 Hz, 1H), 2.42–2.33 (m, 2H), 2.00–1.95 (m, 1H), 1.92 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 208.8, 158.8, 141.9, 130.2, 130.0, 128.5, 127.5, 126.2, 113.6, 68.2, 66.2, 62.0, 57.5, 55.1, 47.6, 46.6, 45.1, 42.1, 39.1, 37.8, 21.0. HRMS (ES⁺): calcd. for C₂₅H₃₁N₂O₄S [M+H]⁺ 455.1999, found 455.2006.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-7a-Methyl-2-phenylhexahydro-7,3-(epiminomethano)benzofuran-5(4H)-one (8e):

To a mixture of annulation product **7a** (1.282 g, 5.00 mmol, dr major/[others combined] = 4.1:1.0) and ammonium acetate (1.156 g, 15.00 mmol) in reagent grade MeOH (45.0 mL) was added AcOH (5.0 mL) and the solution was stirred at rt under an air atmosphere for 18.5 h. Solid NaBH₃CN (628.4 mg, 10.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 30 min at rt under air. A second portion of NaBH₃CN (314.2 mg, 5.00 mmol) was added and stirring continued for a further 3.5 h. After cooling in an ice bath, NaOH (2 M in water, 68 mL) was added. Most of the MeOH was then removed under reduced pressure. Brine (40 mL) was added and the product was extracted with EtOAc (100 mL + 50 mL). The combined extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (54 g silica, MeOH/[35% aqueous NH₃]/EtOAc = 4:1:95) gave **8e** (486.7 mg, 38% [uncorrected for diastereomeric impurities in

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starting material], single diastereomer) as an off-white solid; m.p. 46–48 °C. TLC (MeOH/[35% aqueous NH₃]/EtOAc = 5:1:94): R_F = 0.13 (UV or ninhydrin stain). IR: ν = 2930, 1704, 1083, 1022, 969, 732, 700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.39–7.31 (m, 4H), 7.29–7.23 (m, 1H), 5.17 (s, 1H), 3.06 (dt, J = 5.5, 2.7 Hz, 1H), 2.98 (dd, J = 14.8, 1.6 Hz, 1H), 2.88 (ddd, J = 14.7, 3.0, 1.3 Hz, 1H), 2.65–2.55 (m, 4H), 2.43–2.36 (m, 1H), 2.36–2.22 (m, 2H), 1.64 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 208.9, 143.4, 128.2, 127.0, 124.9, 83.0, 79.7, 59.2, 49.8, 45.4, 42.9, 40.2, 38.5, 21.9. HRMS (ES⁺): calcd. for C₁₆H₂₀NO₂ [M+H]⁺ 258.1489, found 258.1488.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-7a-Methyl-8-Methyl-2-phenylhexahydro-7,3-

(epiminomethano)benzofuran-5(4H)-one (8f): To a solution of annulation product **7a** (1.282 g, 5.00 mmol, dr major/[others combined] = 4.1:1.0) in reagent grade MeOH (40.0 mL) was added a commercial solution of MeNH₂ (2.0 M in MeOH, 5.00 mL, 10.00 mmol), followed by AcOH (5.0 mL) and the mixture was stirred at rt under an air atmosphere for 17 h. Solid NaBH₃CN (628.4 mg, 10.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 1 h at rt under air. A second portion of NaBH₃CN (628.4 mg, 10.00 mmol) was added and stirring continued for a further 3 h. After cooling in an ice bath, NaOH (2 M in water, 70 mL) was added. Most of the MeOH was then removed under reduced pressure. Brine (40 mL) was added and the product was extracted with EtOAc (100 mL + 50 mL). The combined extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (41 g silica, EtOAc/NEt₃/light petroleum = 65:1:34) gave **8f** (776.6 mg, 57% [uncorrected for diastereomeric impurities in starting material], single diastereomer) as a pale yellow foam. TLC (EtOAc/NEt₃/light petroleum = 80:1:19): R_F = 0.38 (UV or weak with phosphomolybdic acid stain). IR: ν = 2888, 2795, 1703, 1120, 1053, 1002, 725, 700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.37–7.30 (m, 4H), 7.27–7.20 (m, 1H), 5.18 (s, 1H), 3.12–3.06 (m, 1H), 2.93–2.78 (m, 2H), 2.61–2.52 (m, 3H), 2.47 (s, 3H), 2.37–2.25 (m, 3H), 1.70 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 209.4, 143.9, 128.1, 126.8, 125.0, 82.8, 79.3, 64.6, 50.8, 48.5, 41.1, 39.6, 38.6, 38.1, 22.1. HRMS (ES⁺): calcd. for C₁₇H₂₂NO₂ [M+H]⁺ 272.1645, found 272.1644.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-8-Carbomethoxymethyl-7a-methyl-2-phenylhexahydro-7,3-

(epiminomethano)benzofuran-5(4H)-one (8g): To a mixture of annulation product **7a** (1.282 g, 5.00 mmol, dr major/[others combined] = 4.1:1.0), glycine methyl ester hydrochloride (1.256 g, 10.00 mmol) and NEt₃ (1.012 g, 10.00 mmol) in reagent grade MeOH (45.0 mL) was added AcOH (5.0 mL) and the solution was stirred at rt under an air atmosphere for 21.5 h. Solid NaBH₃CN (628.4 mg, 10.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 30 min at rt under air. A second portion of NaBH₃CN (314.2 mg, 5.00 mmol) was added and stirring continued for a further 2.5 h. After cooling in an ice bath, NaOH (2 M in water, 35 mL) was added to raise the pH to 9 (*care must be taken for this substrate to prevent saponification of the ester by ensuring the pH does not rise above 9*), followed by brine (80 mL) and the product was extracted with EtOAc (150 mL + 100 mL). The combined extracts were dried (Na₂SO₄) and

concentrated, then placed under high vacuum for 1 h to remove residual water carried through into the organic extracts due to the presence of MeOH. Flash chromatography (40.3 g silica, 35% to 38% EtOAc/light petroleum) gave **8g** (909.2 mg, 55% [uncorrected for diastereomeric impurities in starting material], single diastereomer) as a pale yellow foam. TLC (60% EtOAc/light petroleum): R_F = 0.45 (UV or phosphomolybdic acid stain). IR: ν = 2902, 1705, 1195, 1140, 1000, 736, 700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.39–7.30 (m, 4H), 7.28–7.20 (m, 1H), 5.34 (s, 1H), 3.73 (s, 3H), 3.43 (s, 2H), 3.20–3.16 (m, 1H), 3.10–3.02 (m, 1H), 2.75–2.66 (m, 2H), 2.60–2.54 (m, 2H), 2.40 (dd, J = 17.2, 3.7 Hz, 1H), 2.36–2.31 (m, 2H), 1.69 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 208.9, 171.1, 143.8, 128.0, 126.8, 125.0, 82.6, 79.1, 64.4, 55.2, 51.7, 48.4, 48.3, 40.1, 39.7, 38.5, 22.0. HRMS (ES⁺): calcd. for C₁₉H₂₄NO₄ [M+H]⁺ 330.1700, found 330.1700.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-8-Allyl-7a-methyl-2-phenylhexahydro-7,3-

(epiminomethano)benzofuran-5(4H)-one (8h): To a mixture of annulation product **7a** (512.6 mg, 2.00 mmol, dr major/[others combined] = 4.1:1.0) and allylamine (0.30 mL, 4.00 mmol) in reagent grade MeOH (18.0 mL) was added AcOH (2.0 mL) and the solution was stirred at rt under an air atmosphere for 22 h. Solid NaBH₃CN (251.4 mg, 4.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 1 h at rt under air. A second portion of NaBH₃CN (251.4 mg, 4.00 mmol) was added and stirring continued for a further 6.5 h. After cooling in an ice bath, NaOH (2 M in water, 32 mL) was added. Most of the MeOH was then removed under reduced pressure. Brine (20 mL) was added and the product was extracted with EtOAc (50 mL + 25 mL). The combined extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (23.2 g silica, 20% EtOAc/light petroleum) gave **8h** (276.2 mg, 46% [uncorrected for diastereomeric impurities in starting material], single diastereomer) as a pale yellow gum. TLC (50% EtOAc/light petroleum): R_F = 0.63 (UV or phosphomolybdic acid stain). IR: ν = 2902, 2800, 1706, 1121, 1000, 915, 729, 700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.37–7.29 (m, 4H), 7.27–7.19 (m, 1H), 5.97–5.82 (m, 1H), 5.31–5.11 (m, 3H), 3.32–3.13 (m, 3H), 2.90 (dd, J = 12.6, 3.5 Hz, 1H), 2.80 (dd, J = 17.3, 2.7 Hz, 1H), 2.55 (d, J = 3.8 Hz, 2H), 2.46 (d, J = 12.6 Hz, 1H), 2.37–2.25 (m, 3H), 1.69 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 209.5, 143.9, 135.8, 128.0, 126.7, 125.0, 117.4, 82.7, 79.3, 63.2, 56.5, 48.5, 48.2, 40.1, 38.7, 38.6, 22.1. HRMS (ES⁺): calcd. for C₁₉H₂₄NO₂ [M+H]⁺ 298.1802, found 298.1805.

(±)-(2R,3S,3aS,7S,7aR)/(2S,3R,3aR,7R,7aS)-8-Carbotert-butoxymethyl-1-methanesulfonyl-7a-methyl-2-phenyloctahydro-5H-7,3-(epiminomethano)indol-5-one (8i):

To a mixture of annulation product **7c** (333.4 mg, 1.00 mmol, dr major/minor = 5.9:1.0, 81 mol % purity), glycine *tert*-butyl ester hydrochloride (335.3 mg, 2.00 mmol) and NEt₃ (202.4 mg, 2.00 mmol) in reagent grade MeOH (9.0 mL) was added AcOH (1.0 mL) and the mixture was stirred at rt under an air atmosphere for 21 h. Solid NaBH₃CN (125.7 mg, 2.00 mmol) was added at once (*caution: gas evolution*) and stirring was continued for 30 min at rt under air. A second portion of NaBH₃CN (62.8 mg, 1.00 mmol) was added and stirring continued for a further 3.5 h. After cooling

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in an ice bath, NaOH (2 M in water, 10 mL) was added. Most of the MeOH was then removed under reduced pressure. Brine (20 mL) was added and the product was extracted with EtOAc (50 mL + 25 mL). The combined extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (13.2 g silica, 27% to 30% EtOAc/light petroleum) gave **8i** (279.3 mg, 62% [uncorrected for impurities in starting material], single diastereomer) as a colourless solid; m.p. 177–180 °C. TLC (50% EtOAc/light petroleum): *R*_F = 0.46 (UV or phosphomolybdic acid stain). IR: *ν* = 2979, 1748, 1715, 1322, 1131, 1025, 754, 698, 512 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.41–7.31 (m, 4H), 7.29–7.21 (m, 1H), 5.00 (s, 1H), 3.55–3.50 (m, 1H), 3.32–3.12 (m, 3H), 3.00 (s, 3H), 2.74–2.55 (m, 4H), 2.49–2.38 (m, 2H), 2.14–2.06 (m, 1H), 1.92 (s, 3H), 1.49 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ = 207.9, 169.2, 142.3, 128.3, 127.2, 126.1, 81.5, 68.1, 65.5, 62.2, 56.3, 48.2, 47.0, 41.4, 40.7, 38.9, 38.8, 28.0, 22.4. HRMS (ES⁺): calcd. for C₂₃H₃₃N₂O₅S [M+H]⁺ 449.2105, found 449.2107.

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Conflict of interest

Two authors (HVA and DH) are employees of Sygnature Discovery Ltd.

Keywords: aza-Michael addition • bridged compounds • drug discovery • heterocycles • reductive amination

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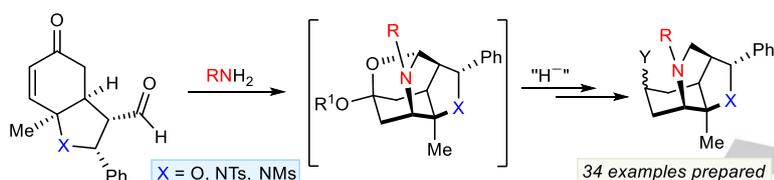
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- [22] In a control experiment, **8b** was re-subjected to the standard conditions (PMBNH₂, NaBH₃CN, MeOH/AcOH, rt, 6 h) resulting in no reaction and complete recovery of **8b**. This confirmed that the ketone of **8** was inert to direct hydride reduction by NaBH₃CN and/or a second reductive amination with the excess amine present.
- [23] The higher yield reported previously for **8a** (89%, Scheme 1, reference 16) compared to the structurally similar analogue **8b** (59%, Scheme 3) is possibly a result of the activating effect of the 2-chloro-substituted phenyl ring in **8a**, and that precursor **7** was used as a single diastereomer in that case. The reaction scales also differed significantly: 0.4 mmol scale for **8a** versus 4.6 mmol scale for **8b**.
- [24] Attempts to unmask the nitrogen of the PMB-protected compounds (**8b-d** and **16a**) by either hydrogenolysis with H₂/Pd/C, oxidation with DDQ or exchange with 1-chloroethyl chloroformate were unsuccessful. These reactions typically proceeded to completion but resulted in decomposition and/or complex mixtures.
- [25] The addition of an internal standard to the crude mixture analysed by NMR spectroscopy showed that the overall yield of **9** was essentially unchanged after purification, confirming that **9a** was (partially) converted to **9b** during silica gel chromatography. This acetal-hemiacetal exchange could be essentially avoided using NEt₃ as an additive in the eluent, however, this compromised the separation of **9a** from other minor reaction products.
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Aza-bridged, densely functionalised, tricyclic scaffolds based on octahydrobenzofurans and octahydroindoles have been prepared and decorated. These heterocycle-rich/sp³-rich frameworks were assembled by a one-pot, two-step bridge-forming reductive amination process, which was shown to proceed via caged, heteroadamantane intermediates that thermodynamically drive an *exo-endo* epimerisation, enabling intramolecular aza-Michael addition over the concave face of the fused bicyclic precursors.



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Nitrogen-Bridged, Natural Product-Like Octahydrobenzofurans and Octahydroindoles: Scope and Mechanism of Bridge-Forming Reductive Amination via Caged Heteroadamantanes