Iodoetherification as a strategy towards sp^3-rich scaffolds for drug discovery

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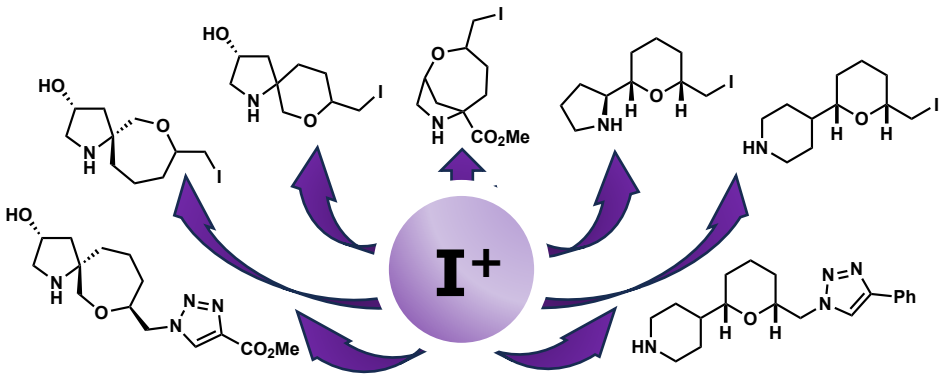
Abstract



Functionalised tetrahydropyran and spiro-oxepane scaffolds were prepared utilising an iodoetherification strategy and elaborated to demonstrate their potential use in library synthesis. The iodoetherification products could be readily transformed to the corresponding azides that could be further functionalised *via* copper-catalysed azide-alkyne cycloaddition or reduction to the amine. The lead-likeness and three-dimensionality of the scaffolds were examined and compared to commercial libraries.

Introduction

Oxygen-containing heterocycles are ubiquitous in molecules made by nature, and these natural products provide inspiration to medicinal chemists working in drug discovery.

Examples include centrolobine,[1,2] isolaurepan,[3] (5*S*,7*S*)-conophthorin[4] and aculeatin A (Figure 1).[5]

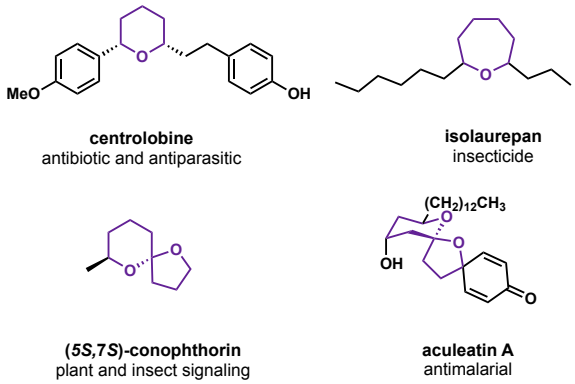


Figure 1. Oxygen-containing heterocycles from nature with diverse biological functions.

A study of FDA-approved small molecules revealed that 27% contained an oxygen heterocycle and that 89% of these were non-aromatic.[6] Hetero-aliphatic rings are associated with improved drug-like properties for solubility, decreased lipophilicity and reduced cytochrome P450 inhibition.[7–9] Pioneering work by Lovering has shown that increased Fsp^3 correlates with improved compound success from lead optimisation to market.[10,11]

The development of lead-like, sp^3-atom-rich and low molecular weight scaffolds, often with dense functionalisation has been a recent endeavour through strategies such as diversity-orientated, lead-orientated and biology-orientated synthesis. Screening libraries with an increased fraction of sp^3-hybridised atoms show improved binding selectivity and frequency,[12] specific binders tend to have more 3D character than promiscuous compounds.[13] Combined with fragment-based approaches to drug discovery, these represent a new paradigm for the development of new pharmaceuticals.[14,15] The expansion of this area of molecular space remains challenging due to the inherent difficulties in working in sp^3-rich space; an approach that utilises readily available, simple sp^3-rich monomers and introduces molecular complexity in a few steps is ideal.

A recent initiative, the European Lead Factory,[16,17] was established to develop compound libraries that fill this area of chemical space. Many of our contributions to this initiative have focussed on the development of oxygen-containing heterocycle libraries using a variety of approaches including reactive metallocarbenes from diazocarbonyls, gold catalysis, tethered Prins cyclisation, intramolecular reductive amination and tandem oxa-Michael/Dieckmann

cyclisation.[18–22] Herein we report another aspect of our work into sp^3-rich scaffolds using iodoetherification as the key step to form oxygen-containing heterocycles.

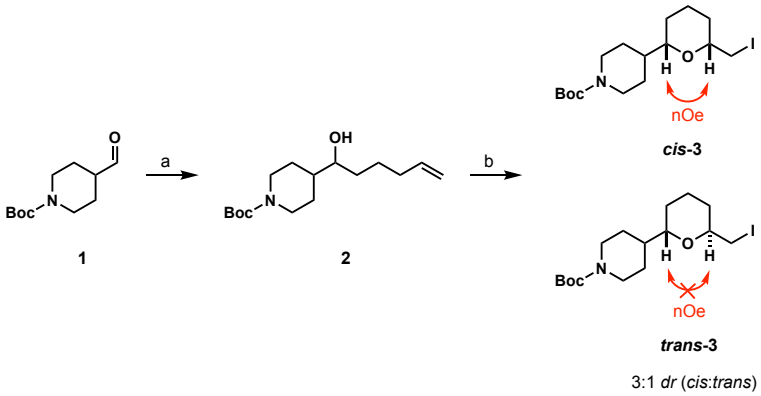
The electrophilic halocyclisation of olefins, where the halonium ions are generated from the olefin followed by an intramolecular opening from a neighbouring nucleophilic functional group has been utilised extensively in the synthesis of biologically active molecules, with halolactonisation being most reported.[23–25] Our strategy focussed on the synthesis of precursor olefins from readily available protected amino acids. By modifying the starting amino acid we identified that a range of oxygen-containing heterocycles could be prepared, including spirocycles.

Results and Discussion.

Tetrahydropyran scaffold

The first scaffold prepared was based on the iodoetherfication of ene-alcohols derived from cyclic amino aldehydes. Reaction of the commercially available piperidine-4-carboxaldehyde **1** with freshly prepared 4-pentenyl magnesium bromide generated the desired ene-alcohol **2** in 67% yield (Scheme 1). The iodoetherification was initially attempted using iodine as the haloetherification source, however, the isolated yield of the two diastereomers of the reaction was 31%. Switching to *N*-iodosuccinimide as the haloetherification source, and running the reaction shielded from light, improved the yield to 97%, in a 3:1 diasteromeric ratio. This transformation could be undertaken on a multigram scale. The major diastereoisomer was confirmed as product *cis*-**3** by the use of nOe spectroscopy, this is expected based on the transition state of the reaction (Figure 2).[26] The corresponding reaction with L-prolinal **5**, prepared from L-prolinol **4** by Dess-Martin oxidation,[27] generated the 5-membered ene-alcohol **6** as a 1:1 mixture of diastereoisomers using the same conditions to prepare ene-alcohol **2** (Scheme 2). By reducing the temperature of addition of the Grignard reagent from -5 C to -78, the diastereomeric ratio could be improved to 2:1 in favour of the (*S*,*S*) diastereomer.[28] These were readily separated by silica gel column chromatography. The analogous reaction with the 5-membered ene-alcohol **6** provided the tetrahydropyrans *cis*-**7** and *trans*-**7** in 87% yield as a 1.3:1 mixture of diastereoisomers. Attempts to synthesise the

corresponding azetidine analogue were unsuccessful due to the competing beta-hydride reduction.



Scheme 1. Synthesis of tetrahydropyrans *cis*-3 and *trans*-3. *Reagents and conditions* a) i. Mg, I_2, 5-bromopentene, THF, 1 h, ii. piperidine-4-carboxaldehyde, THF - 5 °C to r.t., 5 h, 67%; b) *N*-iodosuccinimide, acetonitrile, 90 h, r.t., 97%.

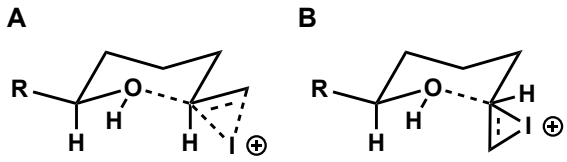
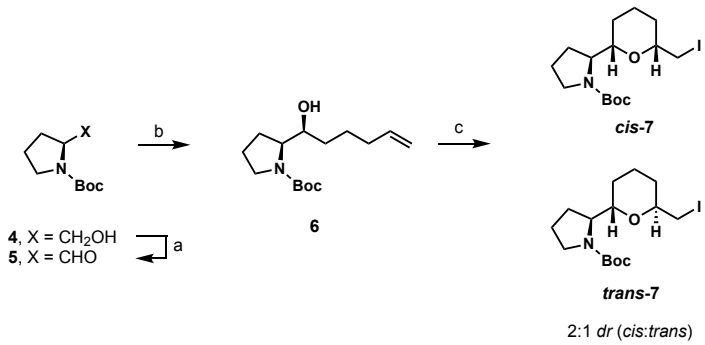


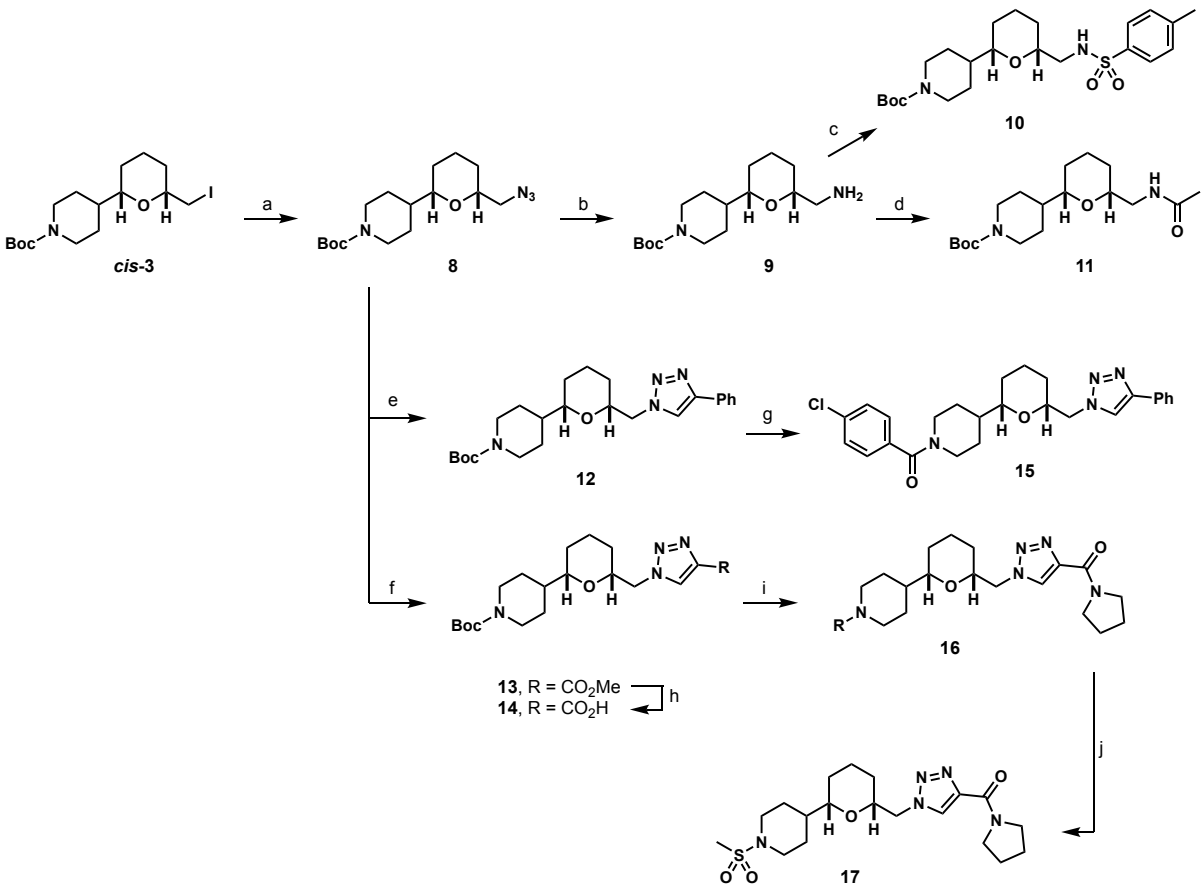
Figure 2. Transition states of iodoetherification.



Scheme 2. Synthesis of tetrahydropyrans *cis*-7 and *trans*-7. *Reagents and conditions* a) i. Dess-Martin periodinane, CH_2Cl_2, 0 °C, 2 h, 64%, b) i. Mg, I_2, 5-bromopentene, THF, 1 h, ii. **5**, THF - 5 °C to r.t., 5 h, 60%; c) *N*-iodosuccinimide, acetonitrile, 22 h, r.t., 87%.

The synthetic utility of these scaffolds was exemplified using iodide *cis*-**3** (Scheme 3). Substitution of iodide *cis*-**3** with sodium azide provided the azidomethyltetrahydropyran **8** in 94% yield. Azide **8** was efficiently reduced to the corresponding amine **9** under Staudinger conditions in 70% yield. With azide **8** and amine **9** in hand, our attention turned to

diversifying the scaffold for potential library synthesis. Amine **9** was converted into tosylate **10** and acetamide **11** under standard conditions. Azide **8** was used in copper-catalysed azide-alkyne cycloaddition reactions to give triazoles **12** and **13** in 45% and 59% yield, respectively. Utilising triazole **12**, the Boc group was deprotected using TFA and converted to amide **15** with 4-chlorobenzoyl chloride. Saponification of methyl ester **13** provided carboxylic acid **14** in excellent yield, that was transformed into amide **16** under standard conditions. Amide **16** was deprotected under the same conditions and converted to sulfonamide **17**. All synthesised library compounds were found to be chemically stable in DMSO. This was determined by ^{1}H NMR spectroscopy of 10 mM samples in d_6-DMSO of the library compounds at one-week intervals with the sample stored at ambient temperature and sunlight in the interim, thus validating the tetrahydropyran scaffold as a viable scaffold for library production.

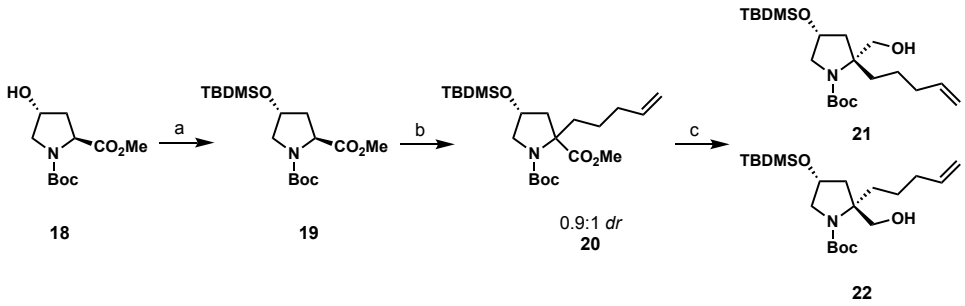


Scheme 3. Diversification of tetrahydropyran *cis*-3. *Reagents and conditions* a) NaN_3, DMF, 90 °C, 20 h, 94%; b) PPh_3, THF, water, 50 °C, 27 h, 70%; c) TsCl, pyridine, Et_3N, CH_2Cl_2, 0 °C to r.t., 90 h, 46%; d) Ac_2O, pyridine, CH_2Cl_2, 0 °C to r.t., 85 h, 73%; e) phenyl acetylene, $CuSO_4$•$5H_2O$, sodium ascorbate, *t*-BuOH:H_2O (1:1), r.t., 20 h, 45%; f) methyl propiolate,

$CuSO_4 \bullet 5H_2O$, sodium ascorbate, *t*-BuOH:H_2O (1:1), r.t., 20 h, 59%; g) i. TFA, CH_2Cl_2, r.t., 3 h., ii. 4-chlorobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C to r.t., 16 h, 67%; h) LiOH, THF:MeOH:H_2O (4:1:1), r.t., 18 h, 87%; i.) pyrrolidine, HATU *i*-Pr_2NEt, DMF, 0 °C to r.t., 21 h, 81%; %; j) i. TFA, CH_2Cl_2, r.t., 3 h., ii. methanesulfonyl chloride, pyridine, Et_3N, CH_2Cl_2 0 °C to r.t., 19 h, 58%.

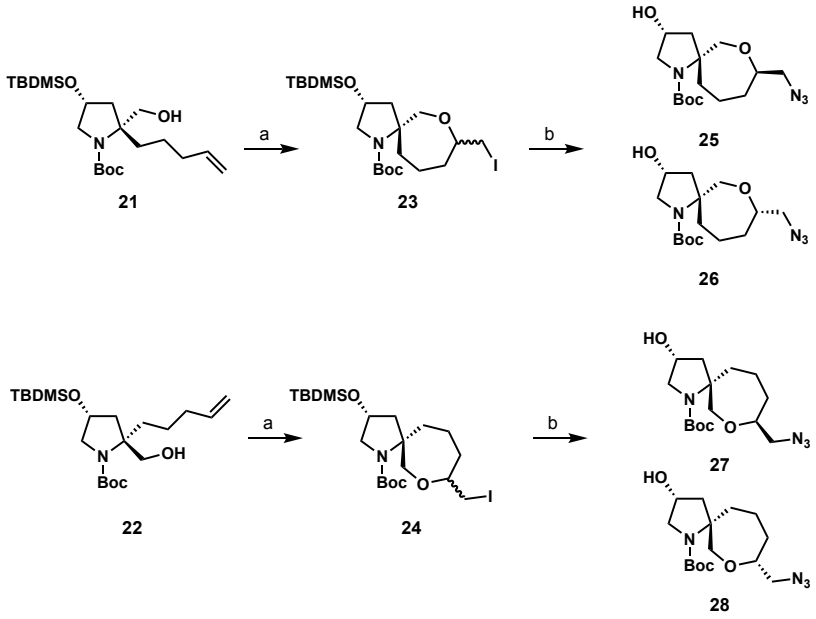
Spirocycle scaffold

The second scaffold was derived from Boc-L-hydroxyproline **18**, with the desired ene-alcohol derived from *C*-alkylation of the 2-position. Boc-L-hydroxyproline **18** was silyl protected before *C*-alkylation with LiHMDS and 5-bromopentene to give a 0.9:1 mixture of diastereomers **20** that were challenging to separate at this stage, (Scheme 4) . Reduction of the ester was accomplished with di*iso*butylaluminium hydride (DiBAl-H) to give the pair of ene-alcohols **21** and **22** in 41% and 46% yield respectively.



Scheme 4. Synthesis of iodoetherification precursors 21 and 22. *Reagents and conditions* a) TBDMSCl, imidazole, DMF, r.t., 24 h, 97%; b) i. LiHMDS, THF, -20 ºC, 0.5 h, ii. 5-bromopentene, r.t., 48 h, 76%; c) DiBAl-H, CH_2CH_2, 0 ºC, 5 h, **21** = 97%, **22** = 46%.

With the ene-alcohols **21** and **22** in hand, we turned our attention to the iodoetherification. Following a screening of conditions, we found that the use of *bis*(collidine)iodine(I) hexafluorophosphate was an effective reagent for the cyclisation to the oxepanes **23** and **24**,[29] albeit in a 1:1 mixture of diastereomers at the newly formed stereocentre for both enantiomeric ene-alcohols. Conveniently, following substitution of the iodide to the azide and methanolysis of the silyl group with *p*-TsOH, the azidoalcohols **25**-**28** were separated and isolated in excellent yield. The structures of azidoalcohols **26** and **27** were unambiguously determined by X-ray crystallography (Figure 2). This allowed for the determination of the absolute stereochemistry of the ene-alcohols **21** and **22** used in the iodoetherification *vide supra*.



Scheme 5. Synthesis of azidoalcohols 25-28. *Reagents and conditions* a) *bis*(collidine)iodine(I) hexafluorophosphate, CH_2Cl_2, r.t., 3 h, **23** = 50%, **24** = 44%; b) i. NaN_3, DMF, 65 °C, 10 h, 94%; ii. *p*-TsOH, MeOH, r.t., 24 h, **25** = 50%, **26** = 39%, **27** = 42%, **28** = 38%.

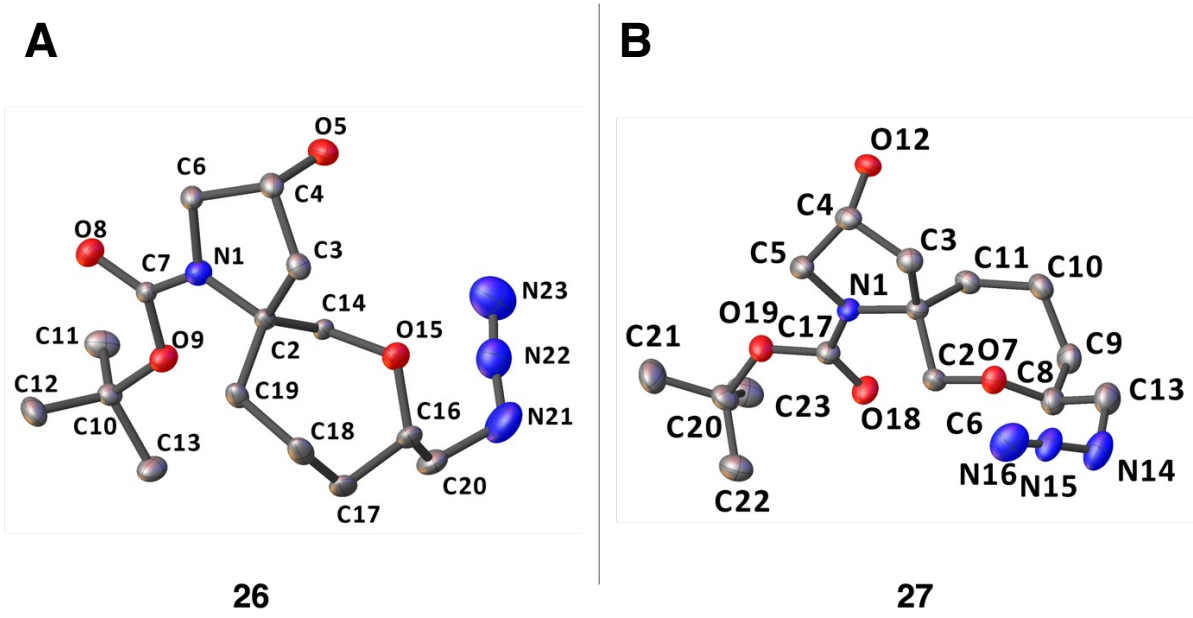
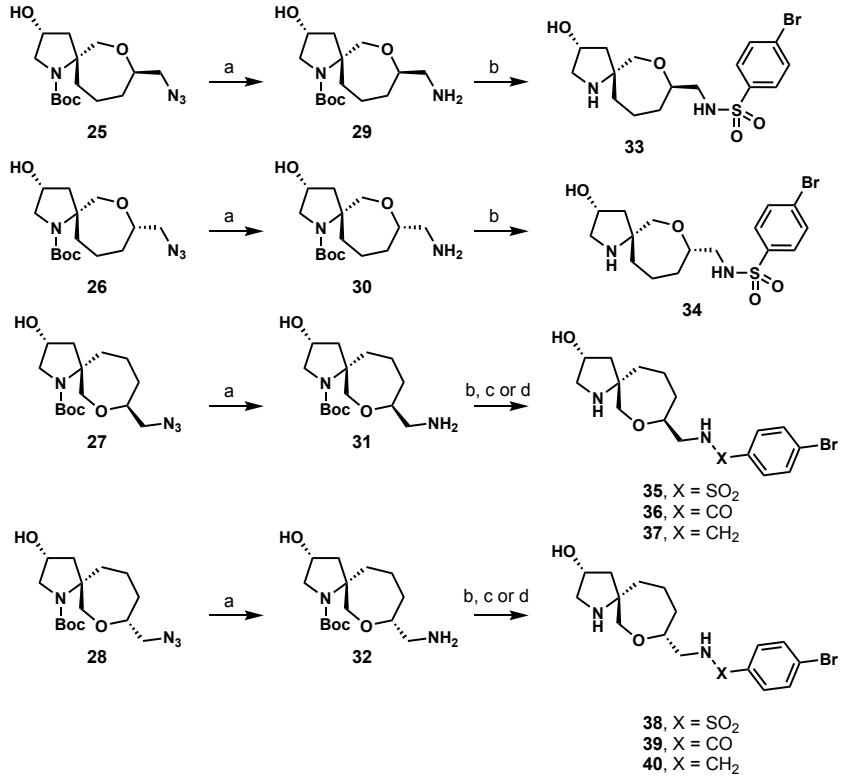


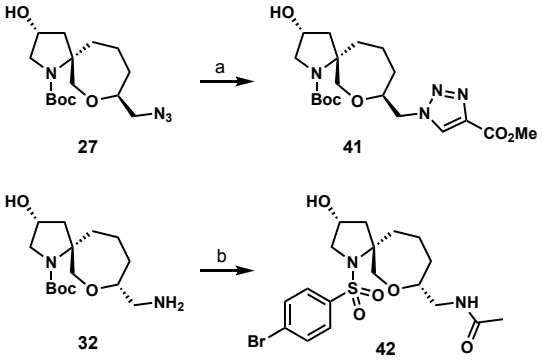
Figure 2: A. X-ray crystal structures of azide **26** (CCDC number 2290119; **B**. X-ray crystal structures of azide **26** **27** (CCDC number 2290120). Thermal ellipsoids set to 50% and hydrogen atoms omitted for clarity.

Azidoalcohols **25-28** were effectively reduced to the corresponding amines **29-32** by catalytic hydrogenation (Scheme 6). Each diastereomer was then further functionalised to the sulfonamide, amide or by reductive amination to give **33-40** to demonstrate the utility of the scaffold in potential library synthesis, (Scheme 6). Azide **27** could also be transformed by

copper-catalysed azide-alkyne cycloaddition to triazole **41** in modest yield (Scheme 7). Bis-functionalisation of spirocycle **32** could be achieved by acetylation under standard conditions, followed by Boc-deprotection and subsequent brosylation to give sulfonamide **42**. All synthesised library compounds were found to be chemically stable in DMSO, as previously detailed, validating the tetrahydropyran scaffold as a viable scaffold for library production.

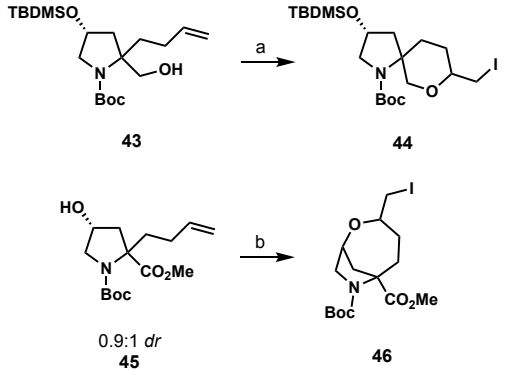


Scheme 6. Synthesis of azidoalcohols 25-28. *Reagents and conditions* a) H_2, Pd/C, EtOH, r.t., 18 h, **29** = 95%, **30** = quant., **31** = 97%, **32** = quant.; b) i. 4-bromobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, r.t., 18 h, ii. TFA, CH_2Cl_2, r.t., 20 h, **33** = 60% over two steps, **34** = 76% over two steps, **35** = 42% over two steps, **38** = 78% over two steps,; c) i. 4-bromobenzoic acid, HATU, *i*PrNEt$_2$, CH_2Cl_2, r.t., 18 h, ii. TFA, CH_2Cl_2, r.t., 16 h, **36** = 79% over two steps, **39** = 45% over two steps; d) i. 4-bromobenzaldehyde, $Na(OAc)_3BH$, CH_2Cl_2, r.t., 18 h, ii. TFA, CH_2Cl_2, r.t., 16 h, **37** = 20% over two steps, **40** = 24% over two steps



Scheme 7. Further diversification of spirocyclic scaffolds. *Reagents and conditions* a) methyl propiolate, $CuSO_4 \bullet 5H_2O$, sodium ascorbate, *t*-BuOH:H_2O (1:1), r.t., 20 h, 49%; b) i. Ac_2O, Et_3N, CH_2Cl_2, 5 h, ii. TMSCl, MeOH, r.t., 48 h, iii. 4-bromobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, r.t., 18 h, 27% over 3 steps.

Structural diversity within the scaffolds could be accomplished by alkylation with a shorter carbon chain. Iodoetherification of 4-carbon chain TBDMS-protected ene-alcohol **43** provided the corresponding spirocyclic tetrahydropyran **45**. Intramolecular iodoetherification of this ester ene-alcohol provided the bridged oxepane **47** in 35% yield. It was not possible to determine the relative stereochemistry of these derivatives.



Scheme 8. Synthesis of scaffolds 44 and 46. *Reagents and conditions* a) *bis*(collidine)iodine(I) hexafluorophosphate, CH_2Cl_2, r.t., 16 h, 50%; b) *bis*(collidine)iodine(I) hexafluorophosphate, CH_2Cl_2, r.t., 4 h, 35%.

Library enumeration

Using the scaffolds prepared herein two virtual libraries were prepared based on the general tetrahydropyran (THP) and spirocyclic scaffolds. Library enumeration was accomplished using DataWarrior with a series of common reactions used in library synthesis (SI).[30] RDKit was used to calculate the molecular properties of the enumerated library.[31] The library was designed to consider the LogP and molecular weight of the compounds, ensure maximum diversity and to avoid undesirable functional groups in the final library. A total of 1906 and 1016 compounds were enumerated for the tetrahydropyran and spirocyclic libraries respectively (Supporting Information). The molecular weights of the compounds in the libraries were in the range 226-609 and 242-611 Da (Figure 3). With 93 and 87% of compounds in the two libraries being within Lipinski-compliant space.

The enumerated libraries were compared to two commercial libraries; Maybridge HitCreator and Maybridge HitFinder that consist of diverse, drug-like compounds for screening (Table 1). When considering the cLogP vs molecular weight of the enumerated libraries there is a narrower range of lipophilicity values compared to the commercial libraries (Figure 4). The average molecular weight of the enumerated THP and spirocycle libraries remains within "Lipinski-space" for drug-likeness, albeit slightly higher than the commercial libraries. This higher molecular weight average is matched with a lower calculated lipophilicity than the commercial libraries. The core structure of each scaffold is composed of entirely sp3 carbon atoms, as such the enumerated libraries are high in Fsp3 content, averaging 0.69 and 0.72 (Figure 5). The Fsp3 content can be exquisitely modulated by the choice of reagents allowing for optimisation of the Fsp3 for drug-likeness. As the Fsp3 tends to decrease during lead optimisation, the scaffolds in this study present an improved starting point compared to molecular libraries with a lower Fsp3 content. For example, comparing these enumerated libraries to the commercial Maybridge HitFinder and HitCreator libraries (Table 1), the enumerated libraries have a significantly increased mean Fsp3.

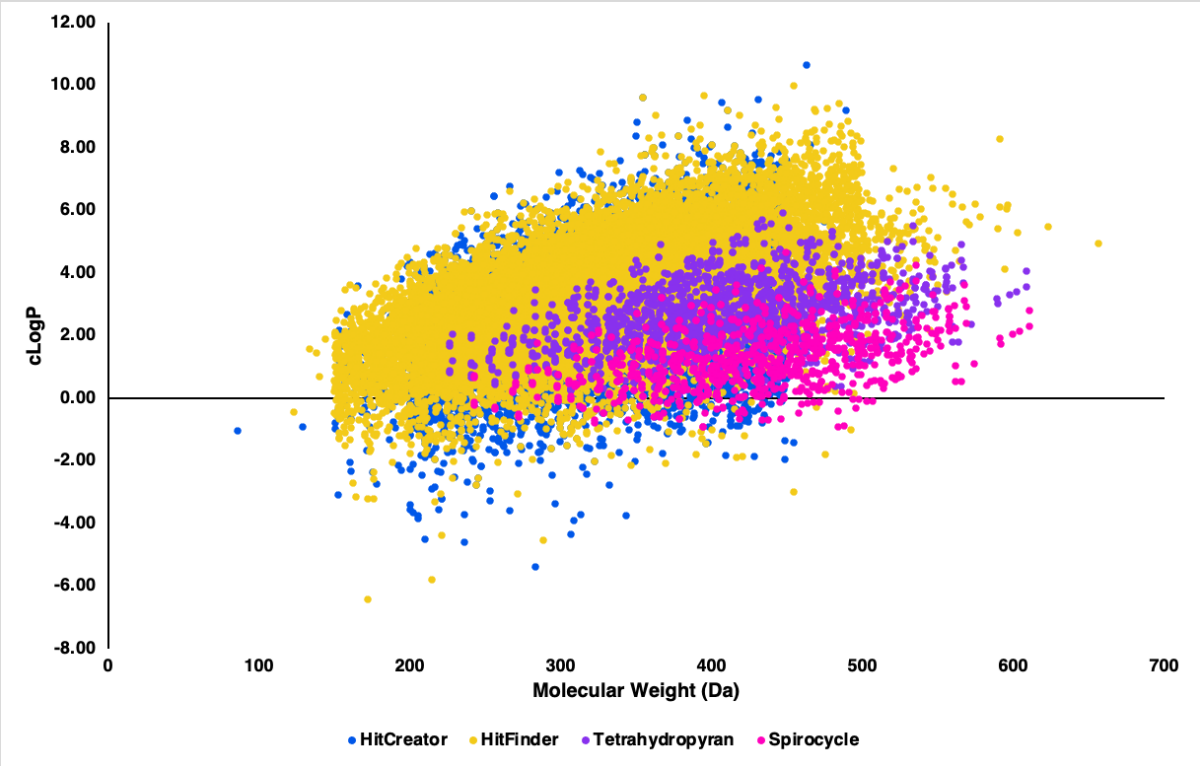


Figure 3: Plot of molecular weight vs clogP for the enumerated libraries and two commercial libraries.

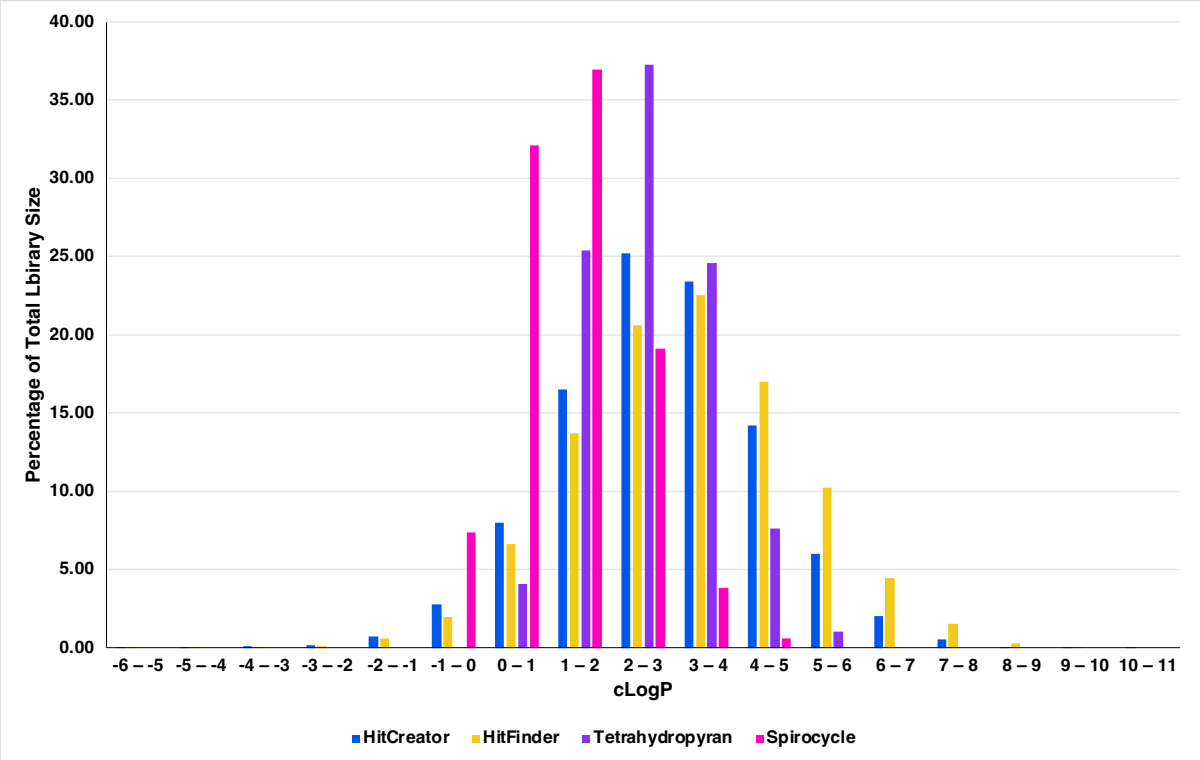


Figure 4: Comparison of cLogP for the tetrahydropyran and spirocycle enumerated libraries and two commercial libraries

Table 1: Comparison of key molecular properties for the enumerated THP and spirocyle library and two commercial libraries.

Library	Mean molecular weight (Da)	Mean clogP	Mean Fsp3
THP library	405	2.60	0.72
Spirocycle	427	1.30	0.69
Maybridge HitFinder	326	3.30	0.24
MayBridge HitCreator	340	2.87	0.31

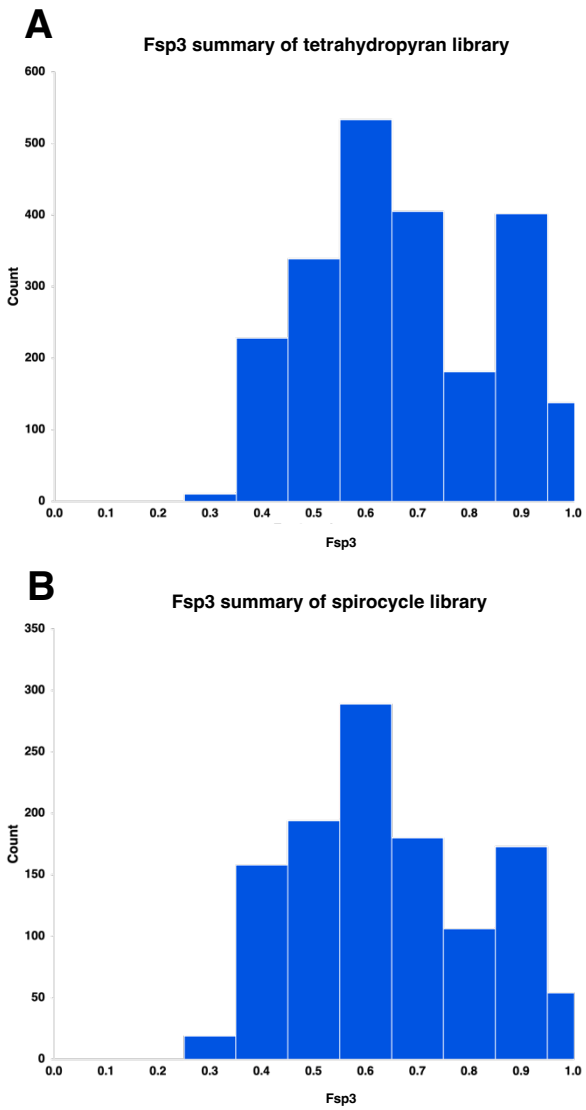


Figure 5: **A**, Plot of fraction Fsp3 atoms versus count for the enumerated tetrahydropyran library; **B**, Plot of fraction Fsp3 atoms versus count for the enumerated spirocycle library.

The three-dimensionality of the enumerated library was examined using principal moment of inertia (PMI) analysis. Normalised ratios of principal moments of inertia were calculated using RDKit and plotted to assess the molecular shape (Figure 6). The virtual library enumerated for both scaffolds occupy a similar area of molecular space, rod-like, this is based on the main contribution to the molecular shape coming from the core scaffolds. The majority of compounds in the THP library (approximately 99%) and the spirocycle library (about 91%) adhere to Veber's rules for oral bioavailability, with a tPSA less than 140 Å^2.[32]

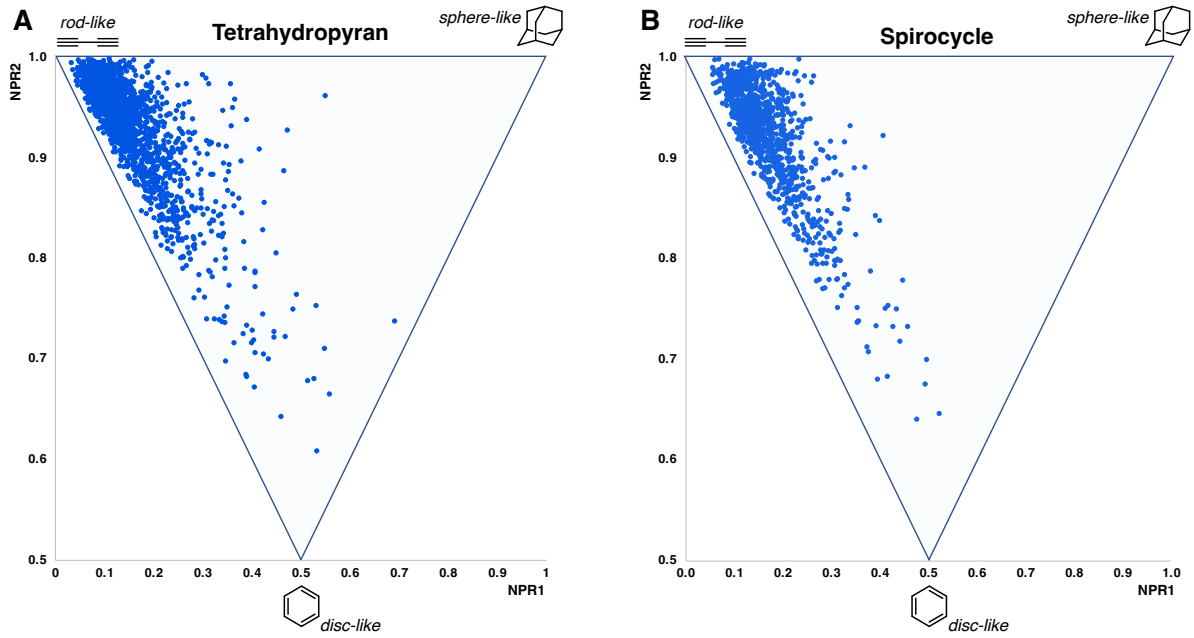


Figure 6: **A**, Principal moment of inertia diagram for the enumerated THP library; **B**, Principal moment of inertia diagram for enumerated spirocycle library..

Conclusions

We have applied iodoetherification of ene-alcohols to the synthesis of functionalised tetrahydropyran and spirocyclic oxepane-pyrrolidines. The key ring-forming reactions can be undertaken on a multigram scale generating orthogonally functionalisable scaffolds for use in medicinal chemistry. Both scaffolds are constructed entirely of sp3 hybridised carbon atoms, resulted in libraries that have high Fsp3, making them desirable molecules for medicinal chemistry. The scaffold can be further elaborated to prepare compound libraries that are of

importance to medicinal chemistry due to their rod-like structures and natural product-like architectures.

Abbreviations

cLogP – calculated partition coefficient
DiBAl-H – di*iso*butylaluminium hydride
Fsp3 – fraction of sp^3 carbon atoms
HATU – Hexafluorophosphate azabenzotriazole tetramethyl uronium
LiHMDS – Lithium bis(trimethylsilyl)amide
NPR1 – First Normalised PMI (i.e. I_1 / I_3)
NPR2 – Second Normalised PMI (i.e. I_2 / I_3)
TFA – Trifluoroacetic acid
THP – Tetrahydropyran
TMSCl – Trimethylsilyl chloride

Author contributions

AN conceived the projects. TB carried out the synthesis and analysis of the spirocyclic structures, overseen by CJM; LB and AJS carried out the synthesis and analysis of the tetrahydropyran structures, overseen by AN; AN enumerated the virtual libraries and OSB determined the molecular properties with RDKit. SPA, LB and WL conducted x-ray crystallography and analysis. AN wrote the paper with contributions LB.

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