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Townley, C, McMurray, L, Marsden, SP orcid.org/0000-0002-2723-8954 et al. (1 more author) (2022) A unified "top-down" approach for the synthesis of diverse lead-like molecular scaffolds. Bioorganic and Medicinal Chemistry Letters, 62. 128631. ISSN 0960-894X

https://doi.org/10.1016/j.bmcl.2022.128631

A unified "top-down" approach for the synthesis of diverse lead-like molecular scaffolds

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Abstract

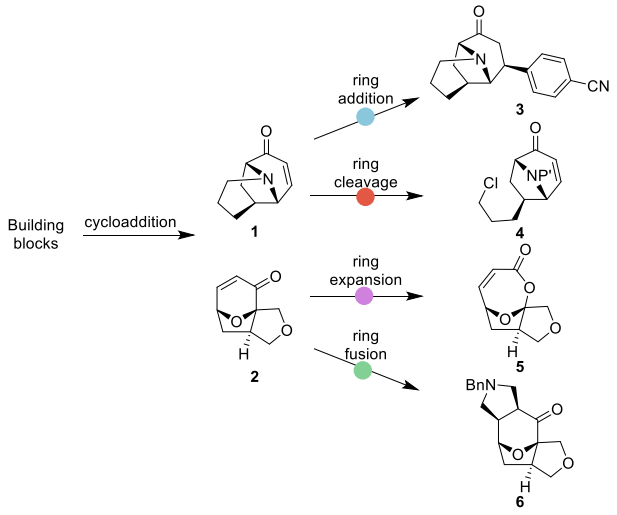
A "top-down" synthetic approach enabled the step-efficient synthesis of 21 diverse novel molecular scaffolds. The scaffolds were derived from four complex intermediates that had been prepared using cycloaddition chemistry. Scaffold-hopping of these intermediates was achieved through attachment of an additional ring, ring cleavage, ring expansion and/or ring fusion. It was shown that the resulting scaffolds could be decorated to yield diverse lead-like screening compounds.

Keywords

molecular diversity; molecular scaffolds; screening compounds

The control of molecular properties is intrinsic to the discovery of useful bioactive molecules such as drugs and chemical probes.[1] Yet, medicinal chemistry programmes have tended to focus increasingly on flatter and more lipophilic molecules,[2] despite the poor correlation of these features with successful translation into drugs.[3] This practice may stem from a narrow underpinning reaction toolkit[4] and the poor availability of sp^3-rich building blocks,[5] both of which have impacted on the diversity of exemplified scaffolds in medicinal chemistry.[6] Recently, unified synthetic approaches have been developed that can deliver many diverse sp^3-rich scaffolds that may provide distinctive starting points for bioactive molecular discovery.[7] As an example, a "top-down" approach enabled complex bridged intermediates to be converted into diverse sp^3-rich scaffolds with natural product-like features.[8]

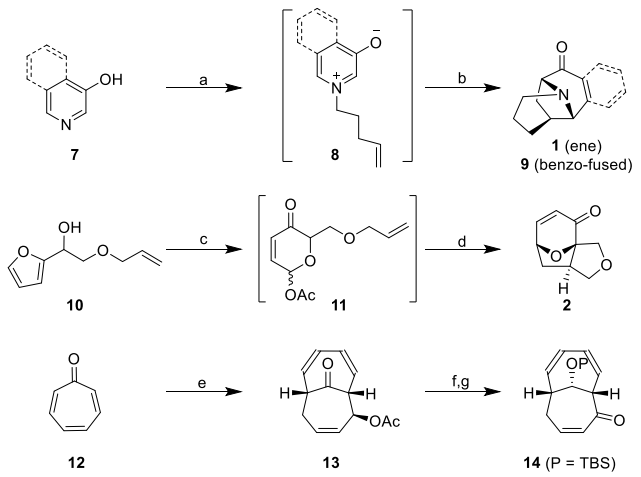
In this paper, we describe the development and application of a "top-down" synthetic approach to access diverse lead-like scaffolds (Scheme 1). Initially, key polyfunctional three-dimensional intermediates (such as **1** and **2**) would be prepared using complexity-generating cycloaddition chemistry. It was envisaged that these intermediates would then be converted into diverse molecular scaffolds through scaffold-hopping approaches: attachment of additional rings (e.g. **1** → **3**); ring cleavage (e.g. **1** → **4**); ring expansion (e.g. **2** → **5**); or annulation (e.g. **2** → **6**). It was hoped that an underpinning toolkit of reactions would enable the synthesis of many different lead-like molecular scaffolds from a small number of intermediate cycloadducts in an efficient manner.



Scheme 1. Overview of the unified approach in which a toolkit of reactions is applied to multiple complex intermediates. Colours indicate the approach used: ring addition (blue), ring cleavage (red), ring expansion (purple) and ring fusion (green).

The synthesis of the key complex synthetic intermediates is illustrated in Scheme 2. Initially, 3-hydroxypyridine and 3-hydroxyisoquinoline (**7a/b**) were *N*-alkylated by reaction with 5-bromopent-1-ene in the presence of base; the resulting betaines (**8a/b**) underwent intramolecular cycloaddition[9] at 160 °C under microwave irradiation in acetonitrile (→ **1** and **9** respectively). Alternatively, treatment of the 2-furyl alcohol 10 with NBS, followed by acetylation yielded **11**, which underwent intramolecular cycloaddition[10] on heating at 60 °C in NMP–MeCN to yield the bridged intermediate **2**. Finally, intermolecular cycloaddition[11] between tropone (**12**) and 1-acetoxybutadiene gave the bridged adduct **13**; reduction with $NaBH_4$, protecting group manipulation and oxidation gave the enone

14. The complex intermediates **1**, **2**, **9** and **14** are all bridged enones, which was expected to facilitate the subsequent conversion into diverse scaffolds using a common toolkit of transformations.

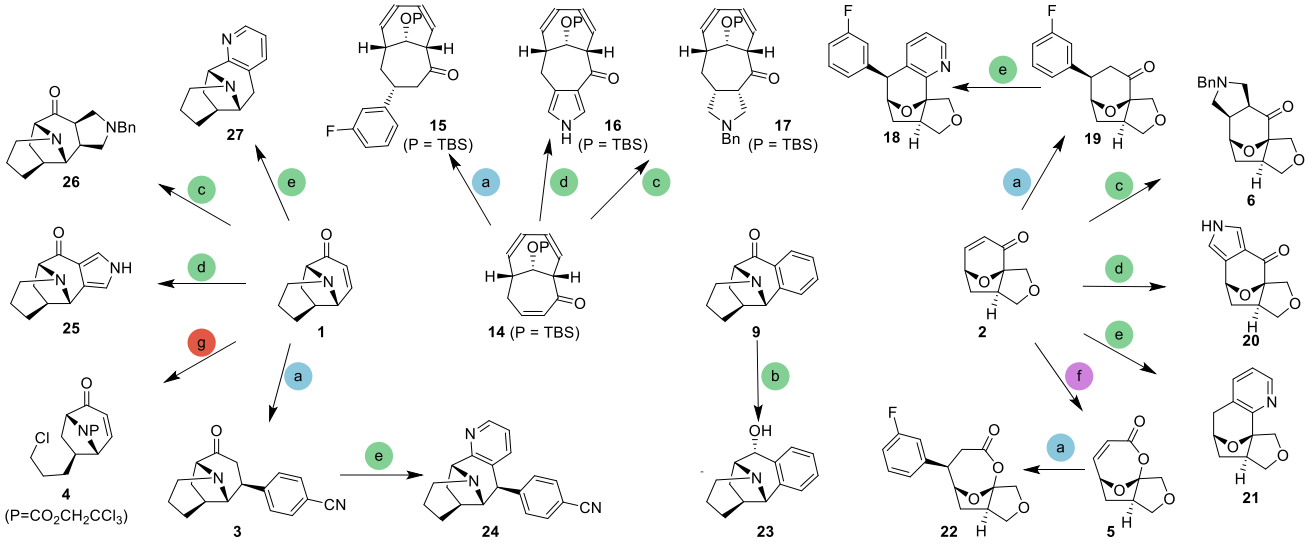


Scheme 2. Synthesis of complex intermediates. (a) 5-bromopent-1-ene, K_2CO_3, ^{i}PrOH, D; (c) μW, 160 °C, MeCN, 70% (**1**) and 45% (**9**) over 2 steps; (c) NBS, THF–water then Ac_2O, pyridine; (d) *N*-methylpyrrolidine, MeCN, 60 °C, 60%; (e) acetoxybutadiene, Δ, 57%; (f) $NaBH_4$, ^{i}PrOH, 39% (major isomer) (crude dr. 62:38); (g) TBSCl, imidazole, DMF then K_2CO_3, MeOH then DMP, CH_2Cl_2, 33% over 3 steps.

The synthesis of representative diverse scaffolds is shown in Scheme 3. The attachment of additional rings to the complex intermediates was largely achieved through Rh-catalysed conjugate additions[12] of aryl boronic acids. Thus, treatment of the enones **1**, **2** and **14** with an arylboronic acid and 2.5 mol% $[Rh(cod)Cl]_2$ at 80 °C in dioxane–water gave **3**, **19** and **15** respectively with high diasteroselectivity. The relative configurations of these products were determined by NMR spectroscopy (for **3** and **15**) and X-ray crystallography (for **19**; CCDC deposition number 2150924). In addition, the ketone **9** was reduced to yield the alcohol **23** with high diastereoselectivity.

The fusion of new rings to the complex intermediates was achieved with three different reactions. Saturated heterocycles were appended through 1,3-dipolar cycloaddition: thus, enones **1**, **2** and **14** were treated with $Me_3SiCH_2NBnCH_2OMe$ and LiF in MeCN at room temperature,[13] resulting in the diastereoselective fusion of pyrrolidine rings to these scaffolds (→ **26**, **17** and **6**). Alternatively, heteroaromatic annulation to the same enones was achieved by cyclocondensation with *p*-toluenesulfonylmethyl isocyanide and potassium tert-butoxide, yielding the corresponding pyrroles **25**, **20** and **16**.[14] Finally, hydrogenation of the enones **1** and **2** gave the corresponding

saturated ketones; treatment of these ketones with propargylamine and 2.5 mol% $NaAuCl_4$ enabled fusion[15] of a pyridine ring to give the scaffolds **27** and **21** respectively.



Scheme 3. Representative syntheses of diverse scaffolds. Scaffolds were prepared from cycloadducts by ring addition/substitution (blue), ring fusion (green), ring cleavage (red) or ring expansion (purple). Typical conditions (see ESI for full details): (a) $ArB(OH)_2$, 2.5 mol% $[Rh(cod)Cl]_2$, Et_3N, 6:1 dioxane-water, 80 °C (**3**: 24%, crude d.r >20:<1; **15**: 14%, crude d.r >20:<1; **19**: 49% crude d.r >20:<1; **22**: 33%, crude d.r 58:42); (b) H_2, $Pd(OH)_2/C$, MeOH (**23**: 93%); (c) $MeOCH_2NBnCH_2SiMe_3$, LiF, MeCN, rt (**6**: 74%, crude d.r >20:<1; **17**: 7%, crude d.r >20:<1; **26**: 40%, crude d.r >20:<1); (d) $TsCH_2NC$, KO^tBu, THF, rt (**16**: 11%; **20**: 34%; **25**: 24%); (e) (i) H_2, 10 wt% Pd/C, rt; (ii) $HC{\equiv}CCH_2NH_2$, 2.5 mol% $NaAuCl_4{\cdot}H_2O$, EtOH, 80 °C (**18**: only step (ii) 21%; **21**: 83% then 3%; **24**: only step (ii) 73%; **27**: 87% then 42%); (f); *m*-CPBA, CH_2Cl_2, (**5**: 28%); (g) Cl_3CCH_2OCOCl, K_2CO_3, toluene, Δ, (**4**: 8%).

Ring expansion of **2** was possible by *m*-CPBA-mediated Baeyer-Villiger reaction to give the corresponding α,β-unsaturated lactone **5**. Moreover, treatment of the enone **1** with 2,2,2-trichloroethyl chloroformate and K_2CO_3 resulted in the cleavage of one of its rings to yield the bicyclic enone **4**.

In addition, some of the prepared scaffolds were useful intermediates for the synthesis of further scaffolds. For example, Rh-catalysed conjugate addition of 3-fluorophenylboronic acid enabled the attachment of an additional ring to **5** to yield **22**. Furthermore, Au-catalysed annulation with propargylamine enabled the fusion of a pyridine ring to both **3** and **19** ($\rightarrow$ **24** and **18** respectively).

Overall, the unified approach enabled the synthesis of 21 distinct scaffolds. The diversity may be captured by formalising the hierarchical relationship[16] between the 16 distinct frameworks (obtained by removal of non-doubly bonded alpha atoms) (Figure 1). Systematic iterative simplification of these frameworks yielded nine parent monocycles, demonstrating significant diversity at each hierarchical level of the scaffold tree. The exploitation of four different complex intermediates (**1**, **2**, **9** and **14**) was critical to realising this scaffold diversity, for example by enabling variation of heteroatom identity and position (e.g. **21**/**27**; **3**/**15**/**19**) and the presence/absence of a fused benzene ring (e.g. **3**/**23**).

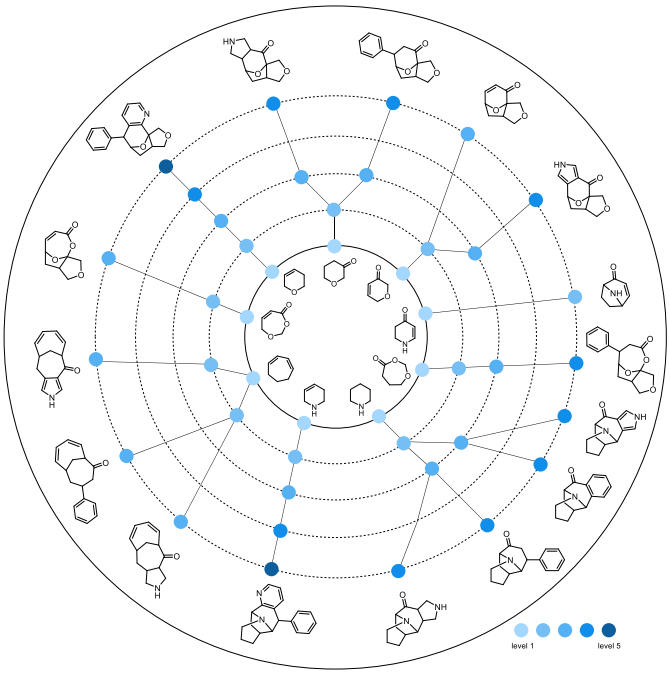
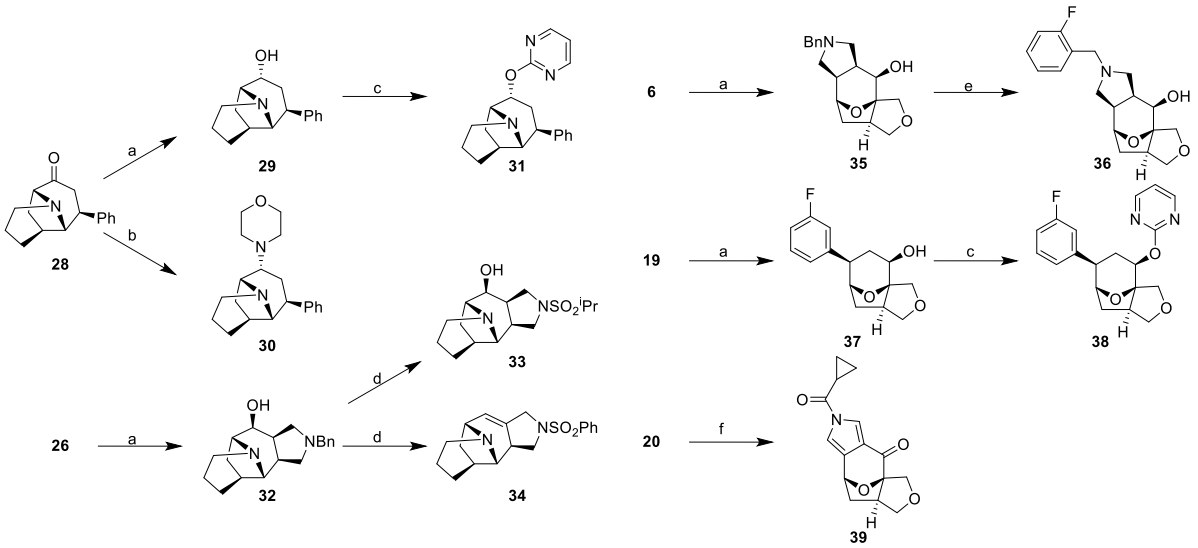


Figure 1: Hierarchical scaffolds tree. The circles represent frameworks (frameworks in the 21 scaffolds prepared, outer ring; simplified frameworks, other circles). The frameworks are related to nine parent (monocyclic) frameworks.

The novelty of the 21 (deprotected) scaffolds was assessed using the open-access computational tool LLAMA.[17] Only one of the scaffolds (**4**) was found as a substructure of a random 2% of the ZINC database[18] of commercially-available compounds.

To demonstrate potential to generate lead-like screening compounds, nine scaffolds were decorated with medicinally-relevant capping groups. Exemplar syntheses of these 29 screening compounds are shown in Scheme

4. The ketones **28**, **26**, **6** and **19** were treated with L-Selectride at −78 °C, and the corresponding alcohols **29**, **32**, **35** and **37** were obtained with moderate to high diastereoselectivity. Reductive amination of the ketone **28** using morpholine ($Ti(OiPr)_4$, $NaBH_4$) gave **30** and its epimer in 22% and 11% yield respectively. A range of reaction types were harnessed for decoration, for example of the intermediates **29**, **37** and **39** and, after debenzylation, **32** and **20**: *O*-hetarylation (→ **31** and **38**), sulfonamide formation (→ **33** and **34**), reductive amination (→ **36**) and amide formation (→ **39**). The products were typically purified by mass-directed HPLC and, in most cases,[‡] the designed products were obtained. The molecular properties and shape diversity of the synthesised compounds are shown in Figure 2. Pleasingly, the majority of the compounds fall within lead-like chemical space,[1b] with significant shape diversity covered by the collection.



Scheme 4. Synthesis of representative screening compounds. Typical conditions (see ESI for full details): (a) L-selectride, THF, −78 °C (**29**: 22%; **32**: 77%, crude d.r >20:<1; **35**: 86%, crude d.r >20:<1; **37**: 38% and 15%); (b) morpholine, $Ti(OiPr)_4$, EtOH then $NaBH_4$ (**30**: 22% and 11%); (c) 2-chloro pyrimidine, NaH, DMF (**31**: 48%; **38**: 35%); (d) H_2, $Pd(OH)_2$/C then sulfonyl chloride, pyridine, THF (**33**: 70% then 34%; **34**: 70% then 7%); (e) H_2, $Pd(OH)_2$/C then *o*-fluorobenzaldehyde, $NaBH_4$, DMF 97% then 13%; (f) cyclopropane carbonyl chloride, pyridine then LiOH, H_2O (**39**: 8%).

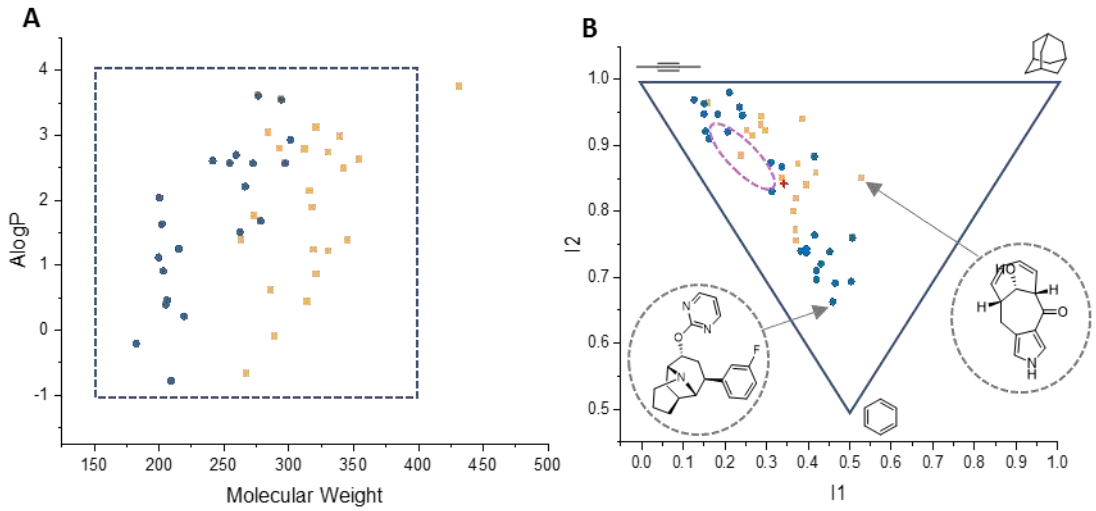


Figure 2. Molecular properties (Panel A) and shape diversity (Panel B) of the deprotected scaffolds (blue) and screening compounds (yellow). In Panel A, lead-like chemical space is indicated (dotted rectangle). In Panel B, the mean PMI of the compounds (red cross) and the most populated region for lead-like compounds in the chemical universe database of molecules with up to 17 non-hydrogen atoms,[19] GDB17 (pink oval) is indicated.

In conclusion, a "top-down" synthetic approach was developed that enabled 21 diverse molecular scaffolds to be prepared by scaffold-hopping from four intermediate cycloadducts. These 21 scaffolds were formed in a total of just 24 synthetic steps from the four intermediates. It was demonstrated that these scaffolds could be decorated to yield lead-like screening compounds. The assessment of the biological relevance of these screening compounds will be reported in due course.

Acknowledgments

We thank EPSRC (EP/N025652/1) and AstraZeneca for funding.

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‡In the case of **34**, the obtained product stemmed from an elimination reaction in addition to the expected sulfonylation.

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