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Synthesis of sp^3-rich scaffolds for molecular libraries through complexity-generating cascade reactions†

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An efficient strategy for the synthesis of complex small molecules from simple building blocks is presented. Key steps of the strategy include tandem Petasis and Diels–Alder reactions, and divergent complexity-generating cyclization cascades from a key dialdehyde intermediate. The methodology is validated through the synthesis of a representative compound set, which has been used in the production of 1617 molecules for the European Lead Factory.

Introduction

Small organic molecules are essential for the treatment of many diseases and constitute most medicines marketed today. The development of high-throughput screening (HTS) has enabled the extremely rapid biological evaluation of large collections of small organic molecules. However, despite advances in HTS technologies and general access to large molecular libraries, the annual number of approved small-molecule drugs has been declining for years.[1] Growing evidence now suggests that many existing compound collections are inadequate in the search for new molecular entities capable of interacting with complex biological targets.[2] Traditional compound collections are typically composed of flat molecules with a high degree of sp^2-hybridization and only few stereocenters.[3] These compound collections are commonly synthesized using classical combinatorial chemistry methods, powered by the development of effective sp^2–sp^2 coupling reactions, which have been widely exploited in the last decades. The routine synthesis of complex sp^3-rich molecules with control of stereochemistry remains elusive and poses a substantial challenge for library production.[4,5] Here, we report a strategy towards a screening library containing molecules with a relatively high degree of sp^3 hybridization. In general, contributions to the European Lead Factory from the public consortium have a significantly higher fraction of sp^3 compared to commercial compound collections.[4]

Results and discussion

In this work, we wish to present a strategy for the efficient formation of two novel scaffolds, each containing four stereogenic centers, including a quaternary center, applicable to molecular library production. The approach starts with a Petasis 3-component reaction[6] of salicylic aldehyde, allyl amine and 2-furyl boronic acid derivatives to form an aminophenol, which upon exposure to elevated temperatures undergoes an intramolecular Diels–Alder reaction[7,8] (Fig. 1). The Diels–Alder product may then undergo oxidative cleavage to

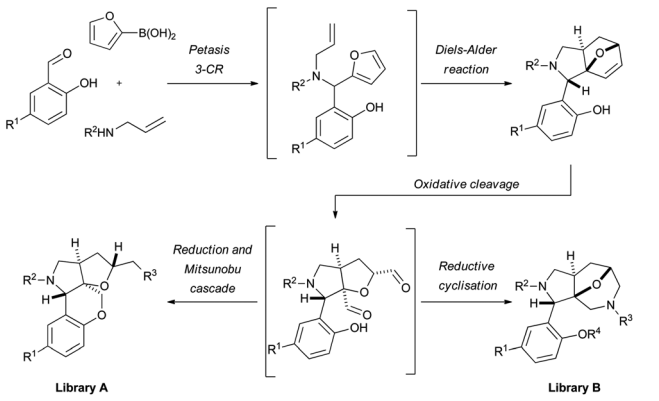

Fig. 1 Synthesis strategies for the generation of two distinct and complex sp^3-rich scaffolds (**A** and **B**), based on complexity-generating reactions from readily available starting materials.

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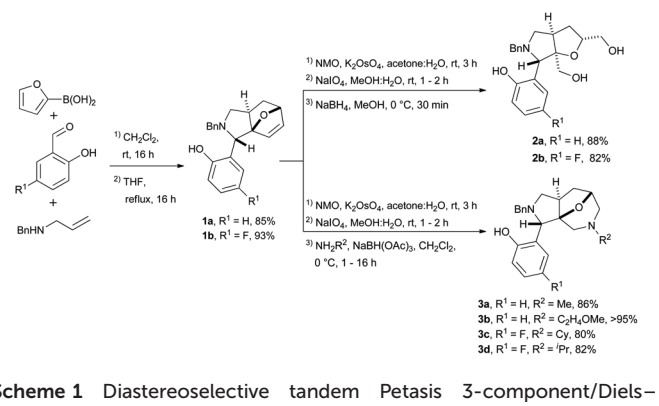
form a key dialdehyde intermediate, which can be reduced and used in a Mitsunobu[9] cascade reaction (library **A**), or participate in a reductive cyclisation with amines (library **B**).

For library development, it was decided to use *N*-allylbenzylamine as the amine component to enable late stage functionalization of the resulting scaffolds through benzyl deprotection and appendage modification of the resulting secondary amine. Two 2-hydroxy benzaldehydes were used in the tandem Petasis/Diels–Alder sequence, which provided the desired products **1a** and **1b** as single diastereoisomers in high yield on a 90 gram scale (85% and 93%, respectively, Scheme 1).

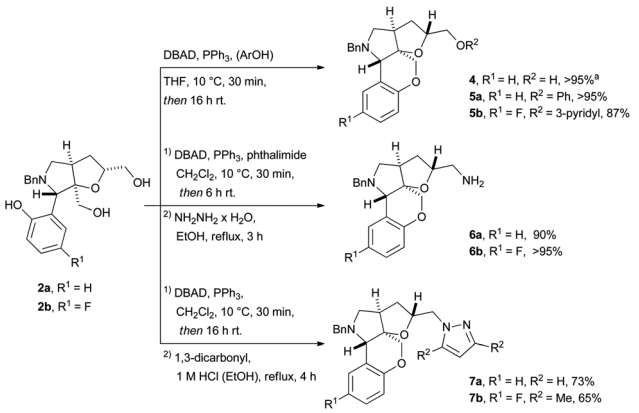
The Diels–Alder products **1a** and **1b** were oxidatively cleaved using catalytic K_2OsO_4 and NMO as oxidant,[10] followed by treatment with $NaIO_4$. The intermediate dialdehyde was then either reduced to give the diols **2a** and **2b** in excellent yields (88% and 82%, respectively over three steps), or used in a reductive cyclisation with variable primary amines to give the compounds **3a–3d** in high yields (80–95%, over three steps).

With the two diols **2a** and **2b** in hand, conditions for the Mitsunobu cascade sequence were investigated. By applying di-*tert*-butyl azodicarboxylate (DBAD) and PPh_3 in CH_2Cl_2 at 10 °C, full conversion to the cyclized product was observed after 15 min, and the product **4** was isolated in near quantitative yield (>95%) (Scheme 2). DBAD was used as the azo-reagent to facilitate easy removal of the hydrazine by-products *via* acid treatment, improving the application for large-scale production of screening libraries.[11]

Having established an efficient protocol for the intramolecular Mitsunobu reaction, we wanted to investigate the possibility of a tandem intramolecular–intermolecular Mitsunobu cascade, which would enable simultaneous creation of the core scaffold and functionalization of the remaining alcohol. The reactions were conducted using either phthalimide or phenol along with three equivalents of DBAD and PPh_3. The reactions with phthalimide as external nucleophile proceeded smoothly to give **6a** and **6b** in excellent yields (90% and >95%, respectively over two steps) after the deprotection



Scheme 1 Diastereoselective tandem Petasis 3-component/Diels–Alder cascade for the synthesis of tricyclic scaffold (**1a–b**); oxidative cleavage followed by reduction or reductive cyclization to bicyclic scaffold (**2a–b**) and tricyclic scaffold (**3a–d**).

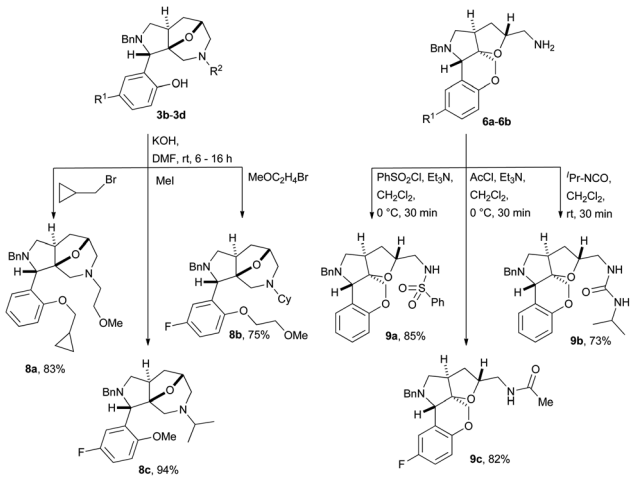


Scheme 2 Tandem Mitsunobu reactions for the synthesis of cyclic ethers (**5a–b**), primary amines (**6a–b**), and pyrazoles (**7a–b**). [a] Reaction performed in CH_2Cl_2.

with hydrazine. On the other hand, the use of phenol only gave 10% of the desired product, along with 90% of a di-Boc hydrazine side-product (from reaction with reduced DBAD).

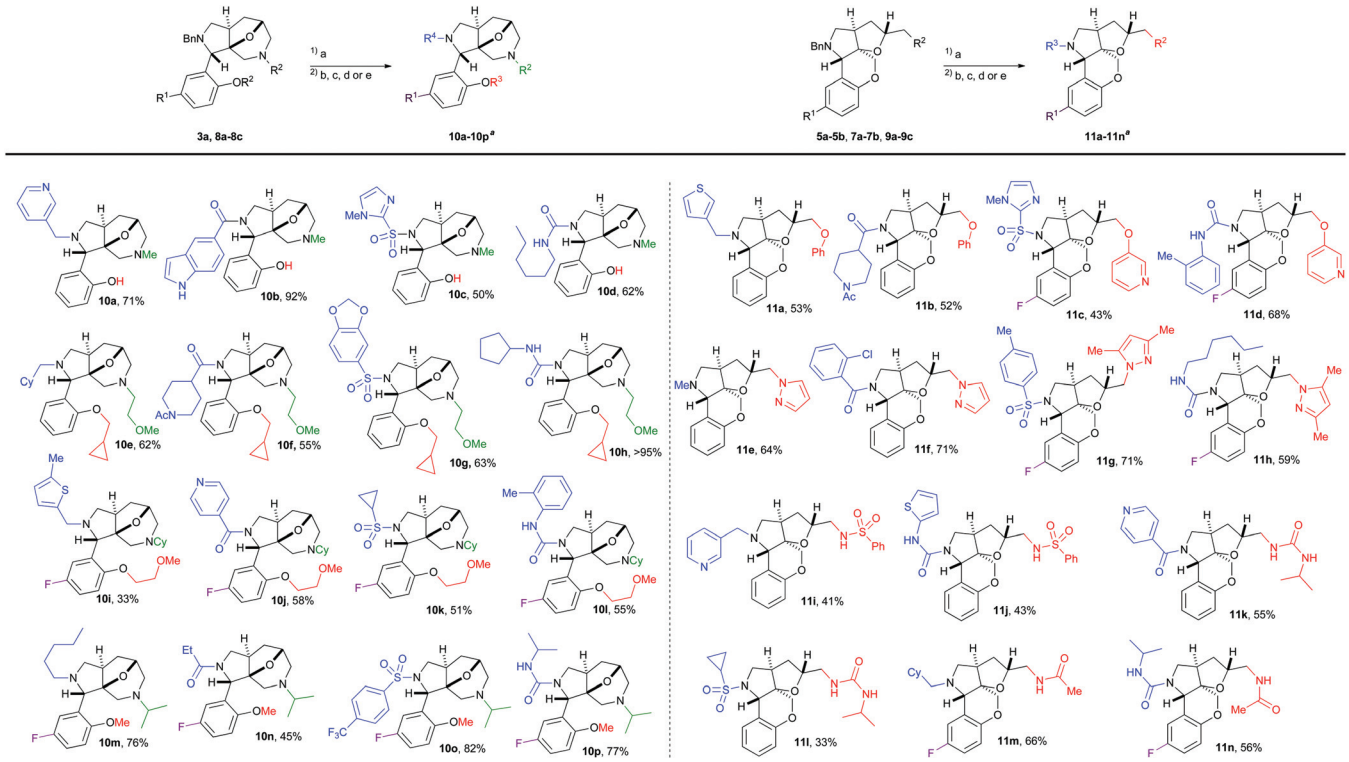
The low selectivity of the aromatic alcohol addition was solved by changing the solvent to THF and employing an excess of the nucleophile (3 equiv.), which gave the desired compounds **5a** and **5b** in excellent yields (>95% and 87%, respectively) using either phenol or 3-hydroxy pyridine as nucleophile (Scheme 2).

Having observed the efficient addition of di-Boc hydrazine in the Mitsunobu reaction, we investigated if this could be exploited as an entry to create more structural diversity in the resulting library. When the reaction was conducted in CH_2Cl_2, notably without the addition of an external nucleophile, full conversion to the hydrazine product was observed. The crude reaction mixture was subsequently treated with 1 M HCl in EtOH and a 1,3-dicarbonyl electrophile, thus giving 1,2-diazole



Scheme 3 Alkylation of phenols **3b–3d** and functionalization of amines **6a** and **6b** with sulfonyl chloride, acid chloride, and an isocyanate.

Table 1 Benzyl deprotection followed by library production



[a] All library compounds were purified by preparative HPLC to simulate large library production. Reagents and conditions. (a) 2.5–10 mol% Pd/C, $HCOONH_4$, MeOH or EtOH, reflux, 1–6 h. (b) RCHO, $NaBH(OAc)_3$, DMF, rt, 8–16 h. (c) RCOOH, TBTU, DIPEA, DMF, rt, 1–16 h. (d) RSO_2Cl, DIPEA, DMF, 1–16 h. (e) RNCO, DMF, 1–16 h.

substituted compounds **7a** and **7b** in good yields (73% and 65%, respectively over two steps).

The two scaffolds, containing either a free phenol (**3b–3d**) or a primary amine (**6a–6b**) were subsequently functionalized. The phenols **3b–3d** were alkylated with various alkyl halides in DMF using KOH as base to give ethers **8a–8c** in high yields (75–94%) (Scheme 3). The primary amines **6a** and **6b** were functionalized using either a sulphonyl chloride, acid chloride or isocyanate to give derivatives **9a–9c** in high yields (73–85%).[12]

By using the benzyl protected building blocks, a small library was synthesized to validate the strategy for library production. Rewardingly, the benzyl group was smoothly removed using catalytic Pd/C with $HCOONH_4$ as the hydrogen source. The resulting secondary amines were subsequently decorated with a variety of appendage functionalities using either reductive amination, amide couplings, sulfonylation or urea formation (Table 1). This process readily provided 30 compounds from the two scaffolds based on appendages using the 3–4 diversity points. The compounds were purified using preparative HPLC to simulate a large library production, and the compounds were generally isolated in good yields (33–95%, over two steps).

The validated chemistry was subsequently used to produce a total of 1617 screening compounds for the European Lead Factory. Library **A** (826 compounds) and library **B** (791 compounds) were both produced with a success rate of 90% in the final functionalization step. All compounds were purified by mass-directed preparative HPLC and obtained in purities exceeding 95%.

Conclusions

In conclusion, we have developed an efficient strategy for the synthesis of two complex and sp^3-rich scaffolds (Fsp^3 = 0.57), with excellent potential for appendage diversification reactions at three or four reactive sites. The benzyl protected building blocks for library production were obtained in 3–4 synthetic steps in high-yielding reactions amenable to large-scale synthesis. The chemistry was validated, first through production of thirty screening compounds (Table 1), and subsequently through large-scale production of 1617 compounds for the European Lead Factory.

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