Concise and diversity-oriented synthesis of novel scaffolds embedded with privileged benzopyran motif†

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Received (in Cambridge, UK) 4th May 2006, Accepted 25th May 2006
First published as an Advance Article on the web 13th June 2006
DOI: 10.1039/b606341a

A branching DOS strategy for an unbiased natural product-like library with embedded privileged benzopyran motif was established to provide complexity and diversity of resulting heterocycles with desired drug-likeness. The importance of skeletal diversity conducted on a privileged substructure was demonstrated through the biological evaluation of a small molecule library representing 22 unique core skeletons *via in vitro* cytotoxicity assay.

Privileged substructures from bioactive natural products have played and continue to play an invaluable role in the drug discovery process.[1] The diversification of these heterocyclic compounds using diversity-oriented synthesis (DOS) has been proven to be an essential tool to rapidly discover biologically active small molecules.[2] Therefore, the development of a concise and efficient strategy leading to skeletal and stereochemical diversity has gained much attention in scientific communities involved in drug discovery and biomedical research.[3] To achieve this goal, it is crucial to identify a new privileged substructure with the potential for chemical transformations toward novel key intermediate skeletons.

Benzopyran is a privileged structural motif observed in many biologically active natural products, and it plays an important role in binding with various biopolymers.[5] To date, syntheses of bioactive benzopyrans have been extensively studied, especially a combinatorial library based on a privileged benzopyran template has been reported by Nicolaou and coworkers.[6] However, previous reports focused on limited diversifications of appendices on the arene region of benzopyrans with a few core structures. Herein, we report our recent efforts to maximize skeletal diversity through the branching pathway for constructions of 22 discrete novel core skeletons (Ia–XIa, Ib–XIb) embedded with a privileged benzopyran substructure *via* various chemical transformations such as Diels–Alder reaction (A1 & B1), click chemistry (A2 & B2), and palladium mediated cross-coupling (A3 & B3) (Fig. 1A). In particular, a Diels–Alder adduct from pathway A1 was successfully transformed into four drastically different core skeletons using a library-from-library approach; high-yield chemical transformations of the scaffold with a high degree of diastereocontrol and atom efficiency.[7] The skeletal diversity was visualized (Fig. 1 B & C) by overlay of 11 unique skeletons (R = Me, Ia–XIa) for clarity. These representative compounds with the simplest appendices were energy-minimized and aligned with the arene region of the benzopyran substructure.[4] The resulting rigid polycycles with skeletal diversity may provide highly selective and specific interactions with biopolymers by taking advantage of the prepaid entropic penalty.

Under the goal of accessing the diverse core skeletons through the recombination of privileged substructures,[8] we initiated the development of a concise and efficient pathway by synthesizing two key intermediates—dimethylbenzopyran template **3a** and spiro(cyclopentyl)benzopyran template **3b**[9] (Scheme 1). The cyclization of 2,4-dihydroxyacetophenone **1a** with acetone in the presence of pyrrolidine afforded 2,2-dimethyl-7-hydroxy-4-chromanone **2a**.[10] The intrinsic limitation of less reactive cyclopentanone with **1a** was overcome by using electron-rich 2-hydroxy-4-methoxyacetophnone **1b** as a starting material followed by demethylation with dry pyridine·HCl at 210 °C which afforded the desired spiro compound **2b**. Subsequent series of reactions (protection & triflation) provided the starting materials **3a** and **3b** of pathway **A** with a high overall yield (86%–81%).

Palladium-mediated Stille coupling reaction[11] of **3a** or **3b**, followed by *in situ* Diels–Alder reaction, provided diastereochemically enriched complex steroid-like **4a** or **4b** (Scheme 1, Table 1). The *endo* favored cycloaddition yields polycycles **4a** and **4b** with

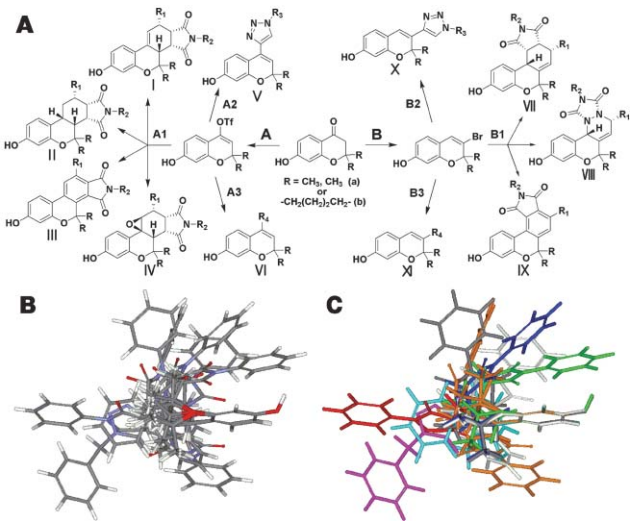

Fig. 1 **A**: Synthetic scheme of 22 unique heterocyclic skeletons (Ia–XIa, Ib–XIb) embedded with benzopyran substructure. **B**: 3-D structural difference of 11 distinct skeletons (Ia–XIa) through the alignment of energy minimized conformers with phenol.[4] R: Me, R_1 & R_2: H, R_3: Ph, R_4: Bn. **C**: individual skeletons were colour-coded to visualize the diverse 3-D orientation of appendices.

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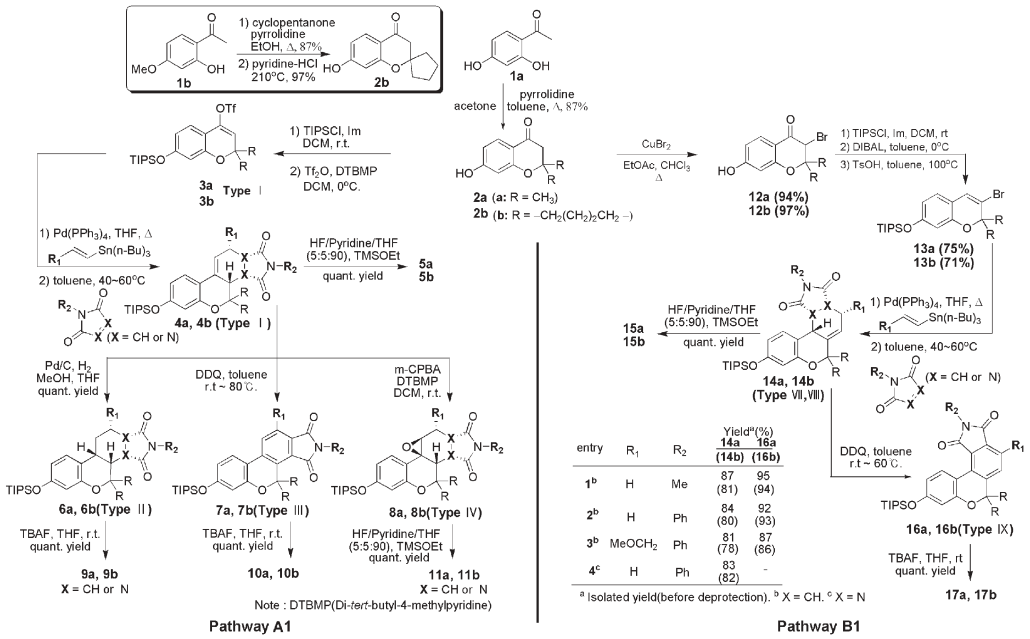
† Electronic supplementary information (ESI) available: experimental procedures and spectroscopic data for new compounds. See DOI: 10.1039/b606341a



Scheme 1 Pathways A1 and B1 (I–IV, VII–IX).

the four newly generated stereocenters (see ESI†), and diastereochemically enriched skeletons were further diversified with various reaction conditions, such as hydrogenation, aromatization, and epoxidation. This resulted in the reconstruction of core skeletons **6**, **7**, and **8**, respectively, in completely different 3-D orientations. Further, the atom efficiency was maximized by quadrupling the size of the small molecule library without any changes in the substituent pattern. Both **6a** and **6b** were yielded as a single diastereomer by substrate-controlled asymmetric hydrogenation (see ESI†). The DDQ aromatization successfully converted the U-shaped core structures **4a–b** to flat aromatic skeletons, namely, **7a–b**. The initial attempt of the epoxidation with *m*-CPBA yielded some aromatization products, and several asymmetric epoxidation conditions provided desired products in low yield. However, in the presence of DTBMP as a proton sponge, *m*-CPBA epoxidation provided a facile means to access epoxide products **8a–b** as single diastereomers in high yield (see ESI†). To determine the efficiency profile, several commercially available building blocks listed in Table 1 were screened to evaluate the scope of this pathway.

Table 1 Synthesis of pathway A1 with some building blocks

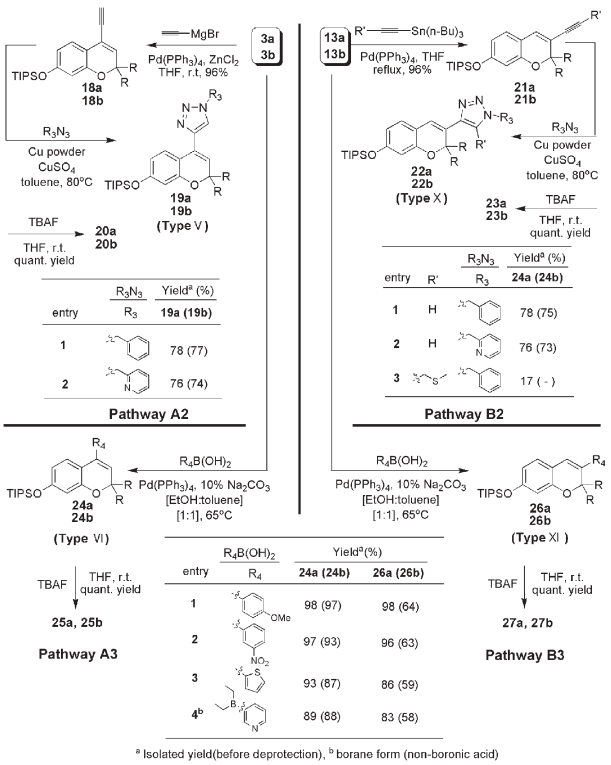
				Yield[b] (%)			
Entry	R_1	R_2	T/°C[a]	**4a** **4b**	**6a** **6b**	**7a** **7b**	**8a** **8b**
1[c]	H	Ph	40	84 82	98 97	88 86	76 74
2[c]	$MeOCH_2$	Ph	60	81 80	96 94	87 85	75 73
3[c]	Ph	Bn	40	83 82	95 95	87 85	77 75
4[d]	H	Ph	40	85 84	96 95	— —	— —

[a] Temperature (Diels–Alder reaction) [b] Isolated yield (before deprotection). [c] **X** = CH [d] **X** = N

The identical strategy was applied for pathway B by the synthesis of key intermediates (**13a–b**) for palladium-mediated coupling from compounds **2a-b** through subsequent series of reactions (bromination, protection, and dehydration), but the resulting skeleton from pathway B exhibited distinct differences in 3-D orientations. The substituted vinylation *via* Stille coupling followed by the *endo*-selective Diels–Alder reaction provided the tetracycles **14** with high diastereochemical enrichment. Although we tried to pursue the further diversification of **14** with optimized reaction conditions in pathway A1, hydrogenation and epoxidation did not proceed well and we conjecture the reason to be steric hindrance of dimethyl and spirocyclopentyl groups.

Further diversification of compounds **3** and **13** was carried out by alkynylation followed by click chemistry of the resulting **18** and **21** with azide reagents *via* Huisgen 1,3-dipolar cycloaddition through the copper–$CuSO_4$ catalyzed process.[12] It provided regiospecific 1,4-disubstituted 1,2,3-triazoles **19** and **22** in high yield (Scheme 2 Top, Pathway A2 & B2). However, disubstituted alkyne (Scheme 2 Top, Pathway B2, entry 3) provided regioisomeric mixtures of 1,4,5-trisubstituted 1,2,3-triazole in the case of dimethyl-benzopyran **21a-3**, and no desired product in the case of spirocyclopentyl-benzopyran **21b-3**; this did not fulfil the requirement for the DOS pathway. In pathway A3 and B3, an array of benzopyran derivatives was synthesized by the introduction of aromatic and heterocyclic compounds **24** and **26** *via* palladium-mediated Suzuki coupling reaction[13] in high yield (Scheme 2 Bottom), which gave a collection of diverse skeletons with a limited number of freely rotatable bonds.

The main objective of our work was to merge two different concepts, being privileged structural motifs merging with unbiased structural diversity, into a single entity and to elucidate how structural diversity conducted on a privileged scaffold affects biological activity. After realization of the branching DOS pathway, the collection of small molecules which represents the 22 unique core skeletons with limited variations of appendices was



Scheme 2 Pathways A2 & 3 and B2 & 3.

subjected to *in vitro* cytotoxicity assay against human cancer cell line (A549 lung carcinoma cell)[14] to emphasize the structure–activity relationship based on skeletal diversity (see ESI†). Cell viability assay demonstrated interesting results (Table 2); the compounds exhibited a wide range of IC_{50} values. For instance, **9b-3** demonstrated excellent *in vitro* cytotoxicity (IC_{50} = 1.0 μM) which is 30–60 fold more potent than **10a-3**, **10b-3**, and **11b-3**, a set of molecules with same appendices and different core skeletons. These examples show the importance of core skeletons, not appendices for their biological activities. The ultimate aim of this study was to emphasize the importance of well-designed diverse core skeletons in small molecule collections, and dramatic differences in *in vitro* cytotoxicity assay results demonstrated the high correlation of core skeletons with their biological activities. Thus, DOS with unbiased skeletal diversity embedded with privileged structural motif might provide a systematic strategy to facilitate the discovery of novel chemical entities through extensive biological evaluations.

Table 2 Cell viability test of representative compounds

Compound ID	Core Type	R_1	R_2	R_3	R_4	IC_{50}/μM (A549)
9b-3	**II**b	Ph	Bn	—	—	1.0
10a-3	**III**a	Ph	Bn	—	—	33.5
10b-3	**III**b	Ph	Bn	—	—	63.9
11b-3	**IV**b	Ph	Bn	—	—	28.6
15a-2	**VII**a	H	Ph	—	—	7.0
15b-2	**VII**b	H	Ph	—	—	11.1
15a-3	**VII**a	$MeOCH_2$	Ph	—	—	30.0
15b-3	**VII**b	$MeOCH_2$	Ph	—	—	6.5
15b-4	**VIII**b	H	Ph	—	—	39.2
20b-1	**V**b	—	—	Bn	—	157.2
23b-1	**X**b	—	—	Bn	—	25.9
25b-2	**VI**b	—	—	—	NO_2-Ph	53.4

In conclusion, we have developed a branching DOS pathway leading to the synthesis of a natural product-like small molecule library embedded with a privileged benzopyran motif. The *endo*-selectivity in a Diels–Alder reaction yielded compounds with complex and diverse core skeletons. The resulting heterocycles were further diversified by simple transformation in order to quadruple the number of compounds using a single set of building blocks, which maximizes the atom efficiency in library construction and the drastic differentiation in the 3-D orientations of appendices on diverse polyheterocycles as biopolymer-binding elements. At the same time, these pathways furnished substrate-controlled diastereochemical enrichment. The preliminary biological evaluation of these core skeletons with a benzopyran substructure provided fruitful results, and the construction of the full-scale small molecule library through these pathways on solid support is currently underway. We envision that these molecules will provide valuable tools for the drug discovery process as well as for the exploration of biological space.

This work is supported by (1) MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea (MOMAF), (2) Center for Biological Modulators (CBM) of the 21st Century Frontier R&D Program, the Ministry of Science and Technology, Korea (MOST), and (3) Korean Science and Engineering Foundation (KOSEF). K.S.K., H.J.J. and K.E. are grateful for the award of a BK21 fellowship.

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