Tetrahedron Letters 52 (2011) 4204–4206

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A diversity-oriented-synthesis protocol for scaffold discovery based on a general synthetic route to spirocycles

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ARTICLE INFO

Article history:
Received 12 April 2011
Revised 29 May 2011
Accepted 4 June 2011
Available online 13 June 2011

Dedicated to Professor Yoshito Kishi on the occasion of his 75th birthday

Keywords:
Diversity-oriented synthesis
Scaffold discovery
Drug discovery
Library design
Spirocycle

ABSTRACT

A diversity-oriented synthesis (DOS) protocol for scaffold discovery is described. A general synthetic route is developed from a single lactam for the access to various multi-functionalized spirocyclic keto-lactams and their derived spirocyclic keto-amines. This work provides the foundation for a sequential DOS strategy from scaffold discovery to drug discovery.

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In modern drug discovery research, new molecular scaffold discovery plays a central role in lead generation and lead optimization.[1] A molecular 'scaffold' is also termed as 'core', 'template', 'chemotype', 'framework' and 'skeleton'. An ideal drug-like molecular scaffold should be small in size, rigid in shape and multi-functionalized for further chemical modifications. This type of new scaffolds is becoming extremely important for the discovery of novel therapeutic molecules as new molecular entities. In practice, they are the major driving force that supports the current two leading approaches in lead generation, fragment-based drug design (FBDD) and diversity-oriented synthesis (DOS).[2] DOS is a practical concept and an effective approach for the generation of many structurally diversified compounds based on unique molecular scaffolds for structure–activity relationship studies in drug discovery.[3] Current major strategies in DOS include: (1) generation of a common scaffold based on a certain chemical technology and its subsequent derivatization, using such reactions as multi-component reactions and macrocycle formations; (2) generation of several different scaffolds based on a few different chemical technologies from a common precursor and their subsequent derivatization, using the 'functional group pairing strategy'.[4]

In recent years, we have been interested in new molecular scaffold discovery for a number of our drug discovery programs, based on either heterocycles[5] (Biginelli-type pyrimidines) or natural products[6] (steroid hormones). These target-oriented synthesis and diversity-oriented synthesis have led to new synthetic methodology development[5,7] and identification of novel bioactive molecules[8] for certain therapeutic targets.

Spirocyclic compounds have recently attracted considerable attention from the synthetic and medicinal communities due to their unique structural features and associated properties.[9] Many bioactive natural products also contain the spirocycle units, such as Fredericamycin, Acorenone B, Spriofornabuxine, and Vetivone (Fig. 1). Besides pharmaceutical interests, spirocyclic compounds are also widely utilized in material science.[9] The synthesis of spirocycles is generally considered to be challenging due to the creation of a quaternary carbon center, whose formation is usually more difficult than other chemical bond formations. Spirocyclic keto-lactams **1** and **2** (Fig. 2) are interesting small multi-functionalized molecular scaffolds that are potentially useful for drug discovery research. Therefore, a number of synthetic methods have been developed for the preparation of these types of compounds.[10] While effective in many occasions, these methods generally require multi-step synthesis using either expensive reagents or advanced intermediates. Herein, we report a general synthetic route to the synthesis of the spirocyclic keto-lactams **1** and **2** and their derivatives using inexpensive starting materials by way of a DOS protocol for scaffold discovery. These spirocyclic scaffolds have been effectively incorporated into lead compounds in several of our drug discovery programs.

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doi:10.1016/j.tetlet.2011.06.020

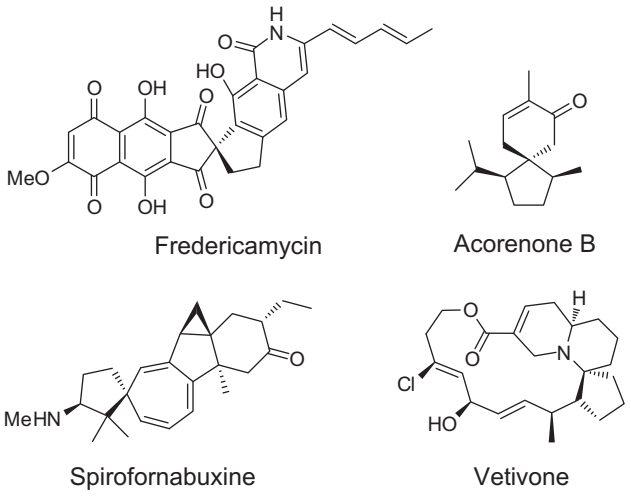


Figure 1. Natural products with spirocycles.

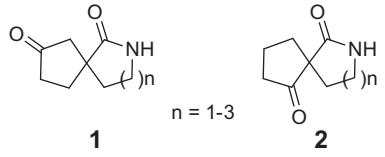
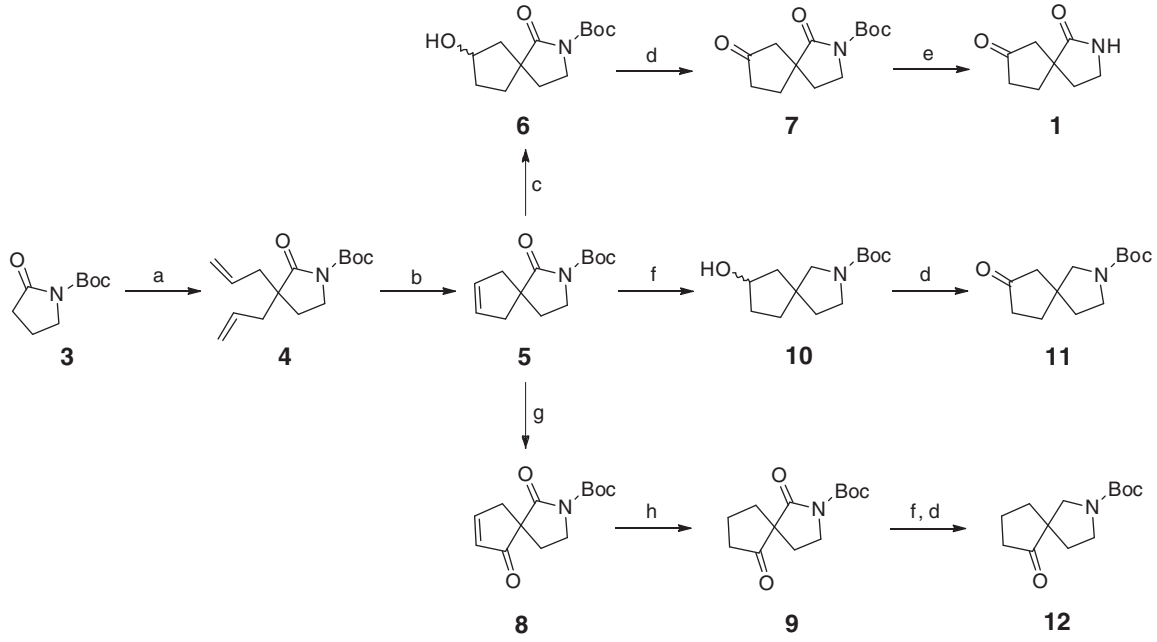


Figure 2. Spirocyclic keto-lactams as new molecular scaffolds.

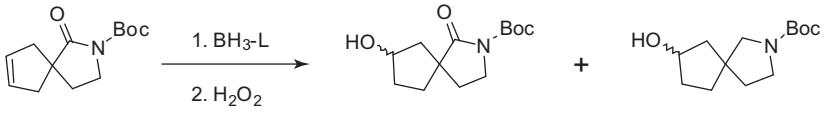
Our DOS protocol for scaffold discovery of spirocycles is based on an efficient and practical route to the spirocyclic keto-lactams **1**, **2** and their derivatives (Scheme 1). The key reactions of the synthesis include: (1) double allylation of the α-carbon of the lactam to generate the quaternary center, and (2) ring-closing metathesis of the allyl groups to form the spirocycle, which are used for the main synthetic pathway of compounds **3**–**5**; (3) hydroboration of the cyclopentene ring followed by oxidation to construct the spirocyclic β-keto-lactam system, which is used for the branch synthetic pathway of compounds **5**–**1**; (4) reduction of the spirocyclic β-keto-lactam system to produce the spirocyclic β-keto-amine system, which is used for the branch synthetic pathway of compounds **5**–**11**; and (5) allylic oxidation of the cyclopentene ring followed by hydrogenation to build the spirocyclic α-keto-lactam system, which is used for the branch synthetic pathway of compounds **5**–**12**.

Double allylation[11] of the lithium enolate of lactam **3** in THF at −78 °C using LiHMDS (2.2 equiv) and allyl bromide (2.4 equiv) followed by warming to room temperature gave compound **4** in 60% yield. Ring-closing metathesis of compound **4** in DCM at room temperature using the first generation Grubbs catalyst[12] (2 mol %) afforded compound **5** in 95% yield. Hydroboration of compound **5** using BH_3–THF (1 equiv) in THF at 0 °C followed by oxidative workup furnished compound **6** in 93% yield. Oxidation of compound **6** in DCM–MeCN using TPAP–NMO[13] produced compound **7** in 95% yield. Removal of the Boc group using TFA in DCM provided compound **1** in nearly quantitative yield. Allylic oxidation of compound **5** in DCM using Pd/C-*t*-BuOOH[14] resulted in compound **8** in 80% yield. Hydrogenation of compound **8** in EtOAc–EtOH using Pd/C led to compound **9** in nearly quantitative yield. A one-pot hydroboration–reduction of compound **5** in DCM using BH_3–Me_2S (5 equiv) at 40 °C generated compound **10** in 90% yield. Similar transformations of compounds **9** and **10** yielded compounds **11** and **12**. The straightforward chemistry using inexpensive materials allowed the practical synthesis of these compounds in gram scales.[15]

It is interesting to note that the chemoselectivity between hydroboration of the olefin group and the reduction of the amide group of compound **5** could be controlled by the choice of the borane reagents and the reaction conditions (Scheme 2). The selective hydroboration of the olefin group using BH_3-THF (1 equiv) at 0 °C gave compound **6** exclusively. The non-selective simultaneous olefin-hydroboration and amide-reduction of compound **5** using BH_3–Me_2S (5 equiv) at 20 °C led to a mixture of compounds **6**



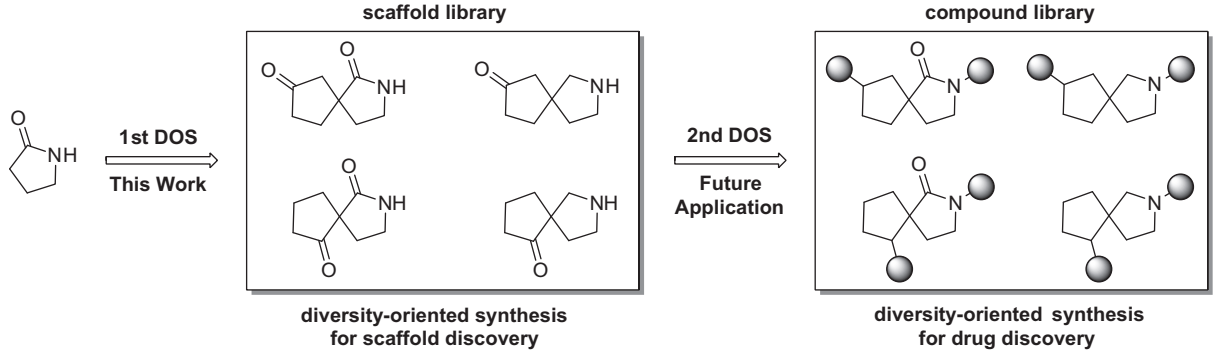
Scheme 1. A general synthetic route to the spirocyclic keto-lactams and keto-amines. Reagents and conditions: (a) LiHMDS (2.2 equiv), ally bromide (2.4 equiv), THF, −78 °C to rt, 60%; (b) Grubbs I (2 mol %), DCM (0.4 M), rt, 95%; (c) (1) BH_3–THF (1.1 equiv), THF, 0 °C, (2) H_2O_2, $NaHCO_3$, H_2O, rt, 93%; (d) TPAP (5 mol %), NMO (3 equiv), MS 4 Å, DCM–MeCN, 0 °C to rt, 95%; (e) TFA, DCM, rt, 99%; (f) (1) BH_3–DMS (5 equiv), THF, 40 °C; (2) H_2O_2, $NaHCO_3$, H_2O, 90%; (g) 10% Pd/C (10 mol %), Bu^tOOH (25 equiv), K_2CO_3 (1 equiv), DCM, 0 °C to rt, 70%; (h) H_2, 10% Pd/C, EtOAc–EtOH, 99%.



5 **6** **10**

BH_3-L (amt, temp, time)	NMR Yield	NMR Yield
BH_3-THF (1 eq, 0'C, 18h)	100%	0%
BH_3-Me_2S (5 eq, 20'C, 18h)	65%	35%
BH_3-Me_2S (5 eq, 40'C, 18h)	0%	100%

Scheme 2. Control of chemoselectivity.



Scheme 3. A sequential DOS strategy from scaffold discovery to drug discovery.

and **10**, while the same reaction at 40 °C resulted in compound **10** exclusively.

This DOS protocol generated a scaffold library of the multi-functionalized small spirocycles **7**, **9**, **11**, and **12**. Besides the 5,5-spirocyclic system starting from the γ-lactam described herein, this general synthetic route can also be adapted to the 5,6- and 5,7-spirocyclic systems (compounds **1** and **2**, where $n = 2$ and 3, respectively) by starting from the corresponding δ- and ε-lactams. More importantly, this work provides the foundation for a sequential DOS strategy from scaffold discovery to drug discovery (Scheme 3). The scaffold library generated by the first DOS protocol will be useful in the second DOS protocol which is a process of two successive parallel syntheses involving the conversion of the scaffold library to the intermediate library and the conversion of the intermediate library to the target compound library. Consequently, this sequential DOS strategy will enable the generation of a large compound library of multi-functionalized structurally diversified spirocycles for drug discovery.

In summary, a DOS protocol for scaffold discovery of spirocycles is described. It is based on a general synthetic route to various spirocyclic keto-lactams and keto-amines involving one main synthetic pathway and three branch synthetic pathways. The practical synthesis of spirocycles in the scaffold discovery from a single lactam includes double allylation, ring-closing metathesis, olefin hydroboration and allylic oxidation. This work provides the foundation for a sequential DOS strategy from scaffold discovery to drug discovery.

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15. Characterization data for selected compounds in Scheme 1. *Compound* ***4***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (m, 2H), 5.15 (s, 2H), 5.11 (m, 2H), 3.61 (t, $J = 8$ Hz, 2H), 2.36 (m, 2H), 2.26 (m, 2H), 1.90 (t, $J = 8$ Hz, 2H), 1.54 (s, 9H). *Compound* ***5***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.56 (s, 2H), 3.70 (t, $J = 8$ Hz, 2H), 2.88 (d, $J = 16$ Hz, 2H), 2.33 (d, $J = 12$ Hz), 1.98 (t, $J = 8$ Hz, 2H), 1.56 (s, 9H). *Compound* ***7***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (t, $J = 6.9$ Hz, 2H), 2.73 (d, $J = 18.2$ Hz, 1H), 2.57 (m, 1H), 2.34 (m, 2H), 2.21 (d, $J = 18.2$ Hz, 1H), 2.03 (m, 3H), 1.57 (s, 9H). *Compound* ***11***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.44 (m, 2 H), 3.32 (s, 1H), 3.26 (s, 1H), 2.35 (m, 2 H), 2.22 (m, 2 H), 1.99 (m, 2 H), 1.86 (m, 2 H), 1.47 (s, 9H).