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A simple reaction to produce small structurally complex and diverse molecules ☆

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Abstract—In order to mimic the complexity of natural products, we designed and obtained with simple synthetic methods, building blocks with 'quaternary chiral centers'. These tricyclic lactams resulted from the reaction of a functional γ-keto-acid and various commercially available bi-nucleophiles.

1. Introduction

Nature has always provided valuable leads for the development of new drugs.[1] Since 1980, the development of combinatorial and parallel synthesis has led to the accumulation of chemical libraries, either diverse or focused. These libraries usually lack natural templates, whose complex synthesis cannot be achieved using simple automated reactions. In order to enhance the value of hit-seeking libraries for biological screening, many groups are developing strategies for parallel synthesis of 'natural privileged structures'.[2–6]

In our on-going interest to incorporate more value into chemical libraries made in parallel, we investigate the design and synthesis of complex, chiral and reactive building blocks. In particular, we focused on bi- and tricyclic lactams obtained from γ-keto-acid and bi-nucleophiles. The reaction proceeds in a condensation of various chiral β-amino-alcohols with a linear or cyclic nonchiral or racemic γ-keto-acid. Thanks to the deracemization of the tertiary carbon atom in α-position relative to the keto group, the reaction produces only one diastereoisomer, in a very stereoselective manner.[7] Meyers and other groups have extensively developed the use of bi-cyclic lactams as useful intermediates to generate highly stereoselective heterocycles, like chiral pyrrolidines.[7–12]

We used the commercially available chiral γ-keto-acid **1** (Fig. 1).[13] This precursor presents several advantages. (1) It displays three functional groups: ketone, carboxylic acid, nitromethyl; (2) it is a pure enantiomer available in bulk at low price; (3) it has a low molecular weight. To our knowledge, only one group has used chiral cyclic γ-keto-acids to obtain complex fused heterocycles.[14,15]

From compound **1**, we thus synthesized 7 nitromethyllactams and validated their conversion into amine

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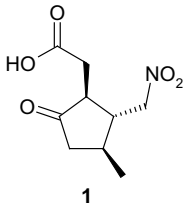

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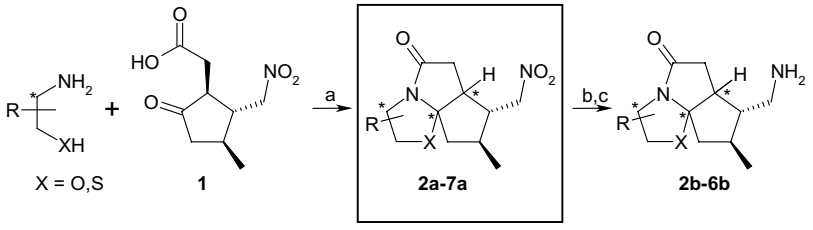
Figure 1.

building blocks. Central rigidity has been recognized as a key feature controlling the bioavailability of drug molecules.[16] In this series, the diverse substituents are projected in the three directions of space in a conformationally restricted manner around the rigid cyclopentane core. Moreover, the nitro group of the precursor can easily be reduced to yield a primary amine that can be reacted with diverse electrophiles. This makes them suitable building blocks for parallel synthesis of complex chemical libraries.

2. Synthesis of tri-cyclic lactams

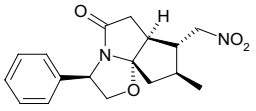
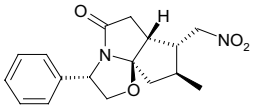
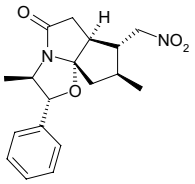
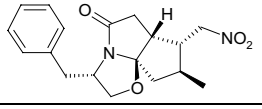
The complex lactams are synthesized in a one-step procedure as described in Scheme 1 (step a). Tables 1–3 summarize the results of syntheses achieved and attempted.

Compound **1** reacted with chiral amino-alcohols with good to high yields (68–85%) to give the desired tri-cyclic lactams (**2a**–**5a**, Table 1). The β-amino-alcohols were selected for (1) their availability and (2) the position and orientation of the aromatic group relative to both the semi-rigid lactam skeleton and the masked amino function (NO_2). Other β-amino-alcohols readily obtained from natural α-amino-acids could also be used, to access a chemically diverse platform. To further explore the scope of this reaction, we investigated other bi-nucleophiles that would allow the synthesis of analogues. In particular, two derivatives of α-amino-acids were tested, in order to introduce in the compounds another chemical function (here a methyl ester) for further derivatization (Table 2). While L-serine methyl



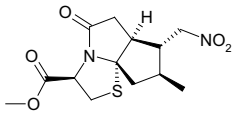
Scheme 1. (a) Molecular sieves, toluene, reflux, 2–6 h; (b) 5 eq Pd/C, ammonium formate, methanol, reflux, 2–4 h or Fe/HCl; (c) 5 eq HCl conc, THF, reflux 2–4 h.

Table 1. Tri-cyclic lactam and amine building blocks synthesized from chiral β-amino-alcohols

Entry	β-Amino-alcohol	Tri-cyclic lactam		Amine building block yield (%)
		Structure	Yield (%)	
1	(*R*)-Phenylglycinol	**2a** 	68	—
2	(*S*)-Phenylglycinol	**3a** 	84	**3b** 87[a]
3	(1*R*,2*S*) Norephedrine	**4a** 	80	**4b** 90[b]
4	L(-)-3-Phenyl-2-amino-propan-l-ol	**5a** 	85	—

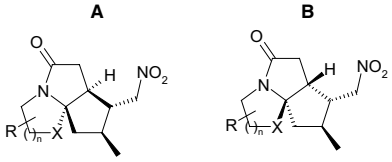
[a] As the chlorhydrate salt (two steps).
[b] As the free amine.

Table 2. Tri-cyclic lactam and amine building block synthesized from α-amino-acids

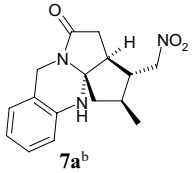
Entry	α-Amino-acid	Tri-cyclic lactam		Amine building block yield (%)
		Structure	Yield (%) (diastereoisomer ratio)	
1	L-Serine	—	35 (two diastereoisomers[a] (50:50))	
2	L-Cysteine	**6a** 	62 (one diastereoisomer)[b]	**6b** 98[c]

[a] In view of ^{1}H NMR spectrum.
[b] Absolute stereochemistry determined by X-ray crystal analysis.
[c] As the chlorhydrate salt (one step).

Table 3. Tri-cyclic lactam synthesized from other bi-nucleophiles



	Bi-nucleophile	Tri-cyclic lactams A:B ratio[a]	Yield (%)
1	(*R*)-2-Amino-1-phenylethanol	50:50	85
2	2-Amino-benzylalcohol	50:50	90
3	*o*-Amino-phenol	50:50	30
4	*o*-Phenylenediamine	50:50	20
5	*o*-Amino-thiophenol	90:10	32
6	2-Amino-benzylamine	100:0	38



7a[b]

[a] In view of ^{1}H NMR spectrum and/or LCMS.
[b] Relative stereochemistry determined by X-ray crystal analysis.

ester gave two diastereoisomers, the reaction of L-cysteine methyl ester with compound **1** gave only lactam **6a** in a good yield. We hypothesized that the Cα of the amino-acid function racemizes at different rates in serine and cysteine.

Experiments with other nonchiral bi-nucleophiles (Table 3) led most of the time to the expected mixture of diasteroisomers. Interestingly, the reaction with 2-amino-benzylamine is regioselective since the tri-cyclic lactam (**7a**) displays the benzylamine moiety involved in the lactam ring (Fig. 2). Noteworthy, this nucleophile leads to a single diastereoisomer (**7a**), as *o*-amino-thiophenol in a lesser extend.

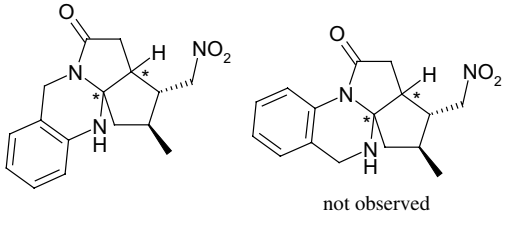


Figure 2. Possible regioisomers resulting for the reaction of **1** with 2-amino-benzylamine.

These results demonstrate that it is possible to rapidly obtain related tri-cyclic lactams and expand the chemical and stereochemical diversity of this series.

3. Structure elucidation

The absolute stereochemistry of compound **6a** was determined using X-ray crystal analysis, thanks to the presence of the sulfur atom. The relative stereochemistry of compounds **2a**, **3a**, and **7a** was established by NMR-ROESY experiments and X-ray crystal analysis. In particular, the presence (dotted arrows) or absence of NOE cross-peaks from the hydrogen atoms at C1, C2, C3, and C8 (Fig. 3), have confirmed a relative stereochemistry in agreement with Meyers' observations for compounds **2a** and **3a**. Relative stereochemistry of compounds **4a** and **5a** (Table 1) were assigned from these preceding results.

4. Synthesis of the building blocks

The conversion of the nitromethyl group into a reactive aminomethyl group was validated for three tricyclic lactams (Scheme 1). The reduction proceeds easily with

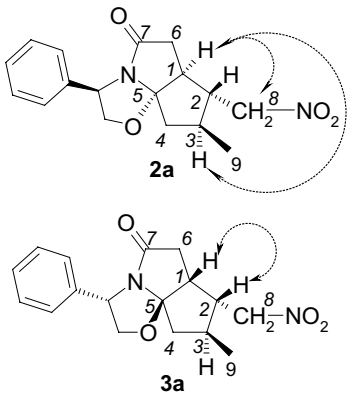


Figure 3.

Pd/C and ammonium formate, except for the sulfur-containing derivative **6a** for which, expectedly, the reaction is not complete. Compound **6b** was thus obtained via a reduction with Fe and HCl in methanol, yielding the desired compound as a HCl salt. Compound **4b** was stored as a free base, whereas compound **3b** was transformed into a HCl salt.

5. Conclusion

We developed a procedure to obtain complex tricylic building blocks useful as reactants in parallel synthesis of chemical libraries. The key precursor is the γ-keto-acid **1** that is accessible in large quantities. The synthesis is versatile enough to allow the use of a variety of β-amino-alcohols (symmetrical or chiral), as well as adequate derivatives of natural and other, non-chiral, bi-nucleophiles. We are now focusing on synthesizing β-amino-alcohols from chiral α-amino-acids to improve the diversity of the final building blocks. Compound **6a** is of particular interest since it displays two functional groups (amine and methyl ester), for a moderate molecular weight. We are currently investigating its incorporation into complex chemical libraries.

Material

Supplemental material contains the chemical procedures and the characterization of all the compounds synthesized. The crystallographic data for compounds **2a**, **3a**, **6a**, and **7a** is also given (.cif).

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References and notes

1. Young, R. N. *Pure Appl. Chem.* **1999**, *71*, 1655–1661.
2. Willand, N.; Beghyn, T.; Nowogrocki, G.; Gesquiere, J. C.; Deprez, B. *Tetrahedron Lett.* **2004**, *45*, 1051–1054.
3. Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284–289.
4. Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303–309.
5. Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565–8566.
6. Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656–5657.
7. Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57–70.
8. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296.
9. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1992**, *57*, 1656–1662.
10. Meyers, A. I.; Seefeld, M. A. *J. Org. Chem.* **1996**, *61*, 5712–5713.
11. Meyers, A. I.; Andres, C. J.; Resek, J. M.; Woodall, C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931–8952.
12. Kossenjans, M.; Soeberdt, M.; Wallbaum, S.; Harms, K.; Martens, J.; Aurich, H. G. *J. Chem. Soc., Perkin Trans.* **1999**, 2353–2365.
13. For synthesis of close analogues that are precursors of prostaglandines, see works at Hoffmann–La Roche: (a) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440–3442; (b) Coffen, D. L.; Holland, G. W.; Rosen, P.; Wong, F. U.S. Patent 4558140, 1985.
14. Sohár, P.; Stáger, G.; Szabó, A. E.; Bernáth, G. *J. Mol. Struct.* **1996**, *38*, 187–195.
15. Miklós, F.; Stáger, G.; Sohár, P.; Bernáth, G.; Sillanpää, R. *Heterocycles* **1998**, *48*, 1407–1414.
16. Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615–2623.