Synthesis of Oxetane and Azetidine Containing Spirocycles Related to the 2,5-Diketopiperazine Framework

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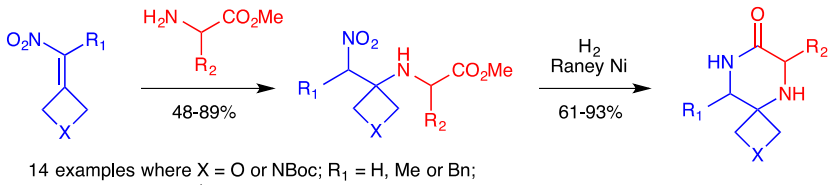
This article is dedicated to Professor Steven V. Ley CBE FRS on the occasion of his 70th Birthday.



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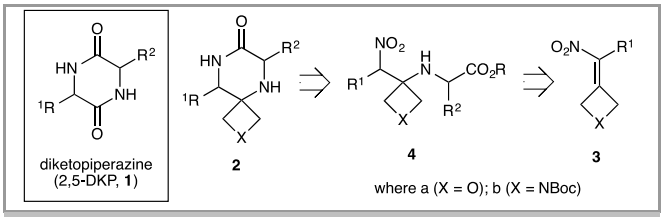
Abstract A simple two-step sequence is used to efficiently make novel spirocyclic analogues of the diketopiperazine nucleus. Conjugate addition of chiral α-amino esters to nitroalkenes, generated from oxetan-3-one or N-Boc-azetidin-3-one, followed by nitro group reduction provides, after spontaneous cyclization, the spirocycles in good overall yields. These rigid scaffolds can be functionalized by selective N-alkylations as well as by carbonyl reduction to the corresponding piperazines.

Key words oxetanes, diketopiperazines, spirocycles, peptidomimetics, piperazines

There is much interest in the preparation of spirocyclic heterocycles for use in medicinal chemistry.[1] Important properties of these scaffolds include their inherent rigidity, structural novelty, reduced lipophilicity and greatly increased potential for the precise presentation of pendant functional groups in three-dimensional space. Considerable progress has been made towards the development of general methods for the preparation of such spirocycles,[2,3] however efficient access to new scaffolds has the potential to open up further regions of chemical space for drug discovery.

The 2,5-diketopiperazine subunit (2,5-DKP, **1**) is found in many bioactive natural products and medicinal agents including in the marketed drug, Tadalafil (Scheme 1).[4,5] As part of an ongoing interest in the preparation of useful oxetane containing frameworks,[3h,6,7] we sought to examine the feasibility of preparing novel spirocyclic scaffolds related to 2,5-DKPs. Specifically, we targeted the synthesis of 2-hetero-5,8-diazaspiro[3.5]nonan-7-ones (**2**) wherein one of the C=O bonds is replaced by four-membered oxetane (**2a**) or azetidine (**2b**) rings.[8,9] This was inspired, in part, by the work of Carreira, Rogers-Evans and co-workers who have demonstrated the benefits of carbonyl to oxetane substitution in other common scaffolds used in drug discovery.[10] Moreover, **2** has much potential for derivatization via selective substitution at up to four carbon atoms and two nitrogen atoms (three nitrogens for the azetidine series) of the rigid framework. Thus, they should serve as excellent templates for the precise display of various biological receptor binding groups in three-dimensional space.

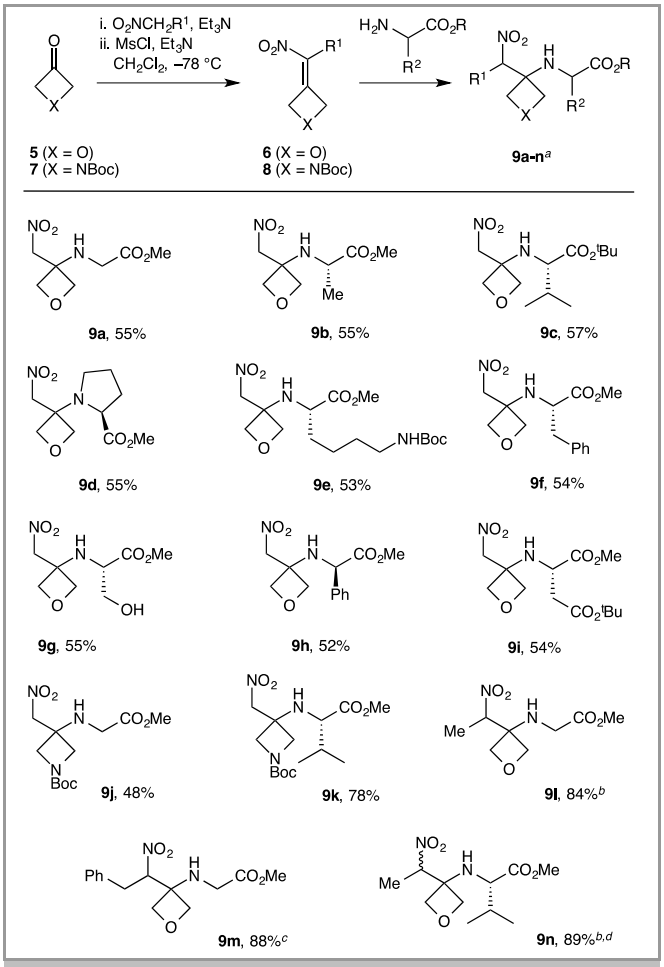
Our retrosynthetic strategy to **2** is outlined in Scheme 1. The route involves: conjugate addition of an α-amino ester to highly strained nitroolefin **3** followed by reduction of the resulting nitroalkane **4**, and cyclization to the target spirocycle. In this Letter, we report the development of an efficient and general strategy to these new spirocycles, and show how they can serve as useful intermediates en route to spirocyclic piperazines which are themselves of current interest.[3e]



Scheme 1 *Route to 2-hetero-5,8-diazaspiro[3.5]nonan-7-ones (**2**).*

We began by examining the conjugate addition of α-amino esters to nitroalkene **3**. This element of the work builds on recent communications by us[7] and by Carreira[11] that outline the use of this reaction for the synthesis of oxetane based peptidomimetics. Here, 14 new examples of this conjugate

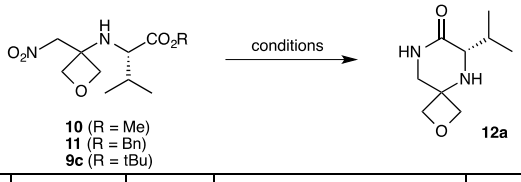
addition chemistry are reported providing **9a-n** in moderate to good yields (Scheme 2). For derivatives **9a-i**, 3-(nitromethylene)oxetane **6** (R^1 = H) was made in situ from oxetan-3-one (**5**) and nitromethane prior to addition of the amino ester. Using nucleophiles derived from a variety of proteinogenic amino acids, we are able to make products containing non-polar (Gly, Ala, Val), polar (Ser), aromatic (Phe), acidic (Asp) and basic (Lys) amino acid residues. The use of L-proline methyl ester allowed entry to tertiary amine **9d**, whilst access to aryl substitution as in **9h** was exemplified using (*R*)-phenyl glycine methyl ester. The chemistry was further extended to the synthesis of azetidines **9j** and **9k** through use of 3-(nitromethylene)azetidine **8** (R^1 = H), made in situ from commercially available N-Boc azetidin-3-one (**7**). Variation in R^1 was established through the preparation of **9l-n** derived from **6** (R^1 = Me[12] or Bn[13]) made from nitroethane and 2-phenylnitroethane respectively.



Scheme 2 Scope of the conjugate addition reaction. [a] Isolated yield after column chromatography. [b] made from isolated **6** (R^1 =Me). [c] made from isolated **6** (R^1 = Bn). [d] formed as a 1:1 mixture of diastereomers.

With access to a variety of oxetane and azetidine modified DKP precursors, we sought to identify suitable conditions for the reduction/cyclization. To explore the impact of the nature of the ester group on this chemistry, methyl ester **10**, benzyl ester **11** and *tert*-butyl ester **9c** possessing the same backbone substitution pattern were selected as a test substrates.[14] Controlled reduction of the nitro group of methyl ester **10** was explored under a variety of conditions (Table 1, entries 1-6). In each case, **12a** was isolated as a result of spontaneous cyclization of the resulting primary amine with loss of methanol. The use of Raney Ni under an atmosphere of hydrogen proved most effective (Table 1 entry 6). Under these conditions, the DKP analogue **12a** was produced in 81% over the two steps. Much lower yields were observed using the corresponding benzyl and *tert*-butyl esters under these optimized conditions (Table 1, entries 7-8).

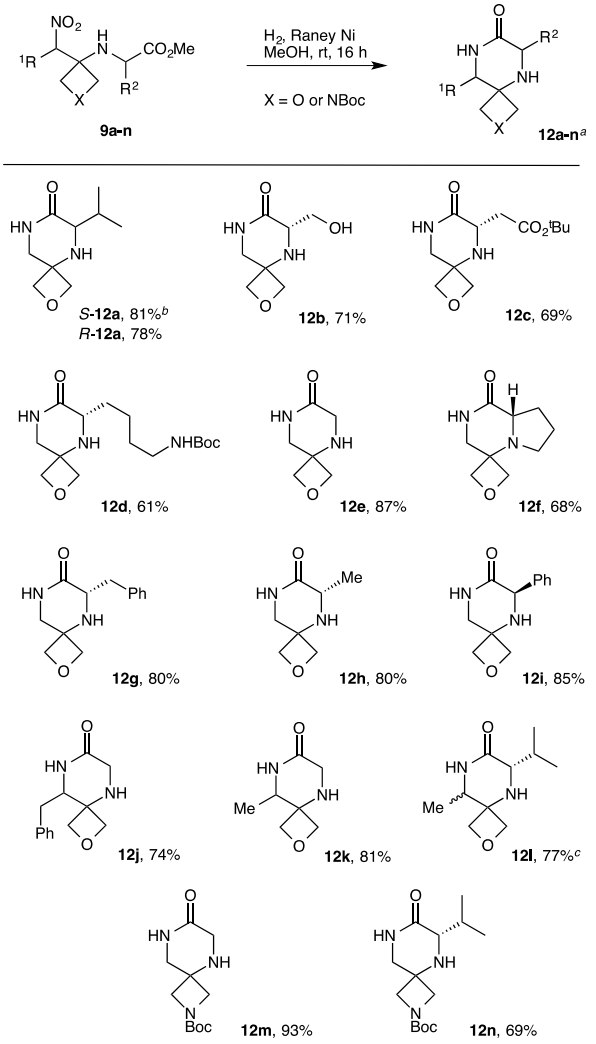
Table 1 *Optimization of cyclization conditions to* **12a**.



Entry	Substrate	R	Conditions[a]	Yield (%)[b]
1	**10**	Me	Zn, AcOH, THF	22
2	**10**	Me	Zn, aq. NH_4Cl, EtOH[c]	26
3	**10**	Me	In, HCl, THF/H_2O (1:3)	25
4	**10**	Me	10% Pd/C, H_2, MeOH	50
5	**10**	Me	10% Pt/C, H_2, MeOH	23
6	**10**	Me	Raney Ni, H_2, MeOH	81
7	**11**	Bn	Raney Ni, H_2, MeOH	17
8	**9c**	^{t}Bu	Raney Ni, H_2, MeOH	0[d]

[a] Conducted at RT unless otherwise stated. [b] Isolated yield after chromatography. [c] Reduction at 30 °C, then heated at reflux for 24 h. [d] Major product was the primary amine from reduction of nitro group without concomitant cyclization.

With conditions for the reduction/ring closure optimized, the substrate scope of the chemistry was explored (Scheme 3).[15] A wide variety of 2,5-DKP analogues **12a-n** were produced in good yields and the reaction tolerates a wide variety of substitution patterns. The structures of (*S*)-**12a** and **12j** were verified by X-ray crystallography.[16] Unlike 2,5-DKPs which typically adopt flat or puckered boat conformations,[4] **12a** adopts a envelope-type structure with the spiro-ring atom projecting out of the plane with the adjacent nitrogen sp^3-hybridized (Figure 1). Similar behaviour was seen for **12j** in which the carbon substitutent is located on the opposite side of the six-membered ring (see Supporting Information). Both enantiomers of **12a** were made, and we were able to confirm that no detectable racemization occurs during the reduction/cyclization sequence (see Supporting Information). Disubstituted derivatives such as **12l** can be produced in high yield as a diastereomeric mixture.



Scheme 3 Scope of reductive cyclization for the synthesis of spirocycles **12a-n**. [a] Isolated yield after column chromatography. [b] >95% ee as determined by ^{1}H NMR analysis in the presence of Pirkle's reagent (see Supporting Information). [c] Obtained as a 1:1 mixture of diastereomers

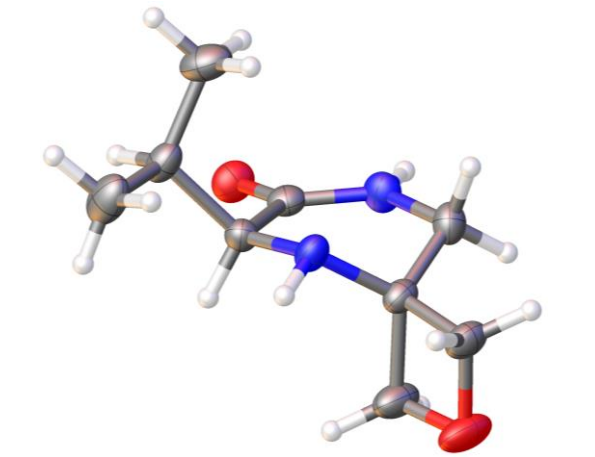
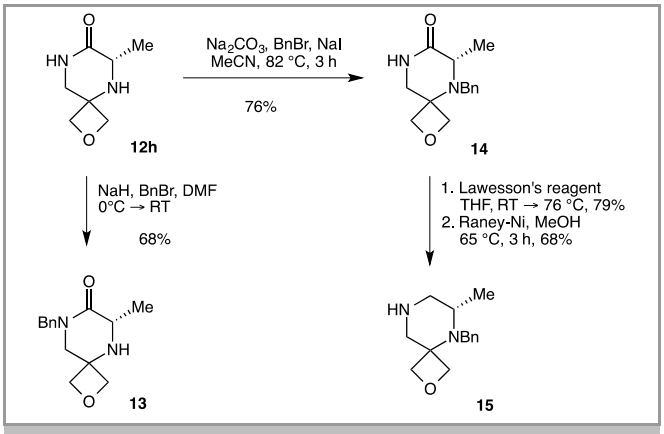


Figure 1 *X-ray structure of* **12a** *with thermal ellipsoids drawn at 50% probability level.*

To explore the utility of these novel building blocks, further manipulations of a representative compound, namely **12h**, have been undertaken (Scheme 4). For example, selective benzylation of the amide and amine nitrogens of this spirocycle can be achieved by exploiting differences in the nucleophilicity/ basicity of these centers. Thus, **13** and **14** could be separately produced in good yields. Reduction of the amide carbonyl to afford the corresponding spirocyclic piperazine **15** was also established. This was best achieved in two steps *via* the corresponding thioamide as direct hydride reduction using reagents such as $LiAlH_4$ led to partial opening of the oxetane ring.



Scheme 4 *Illustrative manipulations of oxetane containing spirocycle* **12h**.

In conclusion, we have developed a general and efficient route to new spirocycles related to the medicinally important 2,5-DKP nucleus. Future work will focus on the application of these new scaffolds in drug discovery programmes.

Acknowledgment

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Supporting Information

Experimental procedures and characterization data for all new compounds, copies of ^{1}H and ^{13}C NMR spectra of compounds **9a-n, 12a-n, 13-15** and chiral Pirkle analysis of **12a**.

References and Notes

(1) For a review on the use of spirocyclic scaffolds in drug discovery, see Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673.

(2) For reviews on spirocyclic systems containing four membered heterocycles, see (a) Carreira E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257. (b) Undheim, K. *Synthesis*, **2014**, *46*, 1957.

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(8) We have previously reported the isolation of **12g** as an unwanted by-product in the synthesis of oxetane based peptidomimetics, see ref 7.

(9) For other recent work on piperazinone synthesis, see Treder, A. P.; Tremblay, M.-C.; Yudin, A. K.; Marsault, E. *Org. Lett.* **2014**, *16*, 4674.

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(14) The synthesis of **10** and **11** was realized as previously reported, see ref 7.

(15) *General procedure for nitro reduction and cyclization to **12**:* The substrate (1 eq) and Raney Ni (1.0 mL, slurry in H_2O) in MeOH (10 mL/mmol) were stirred at room temperature under an atmosphere of H_2 (balloon) for 16 h. The reaction mixture was filtered through a plug of Celite® eluting with EtOAc. The eluent was concentrated under reduced pressure and the crude product purified by column chromatography. Using this method, (*S*)-**10** (325 mg, 1.32 mmol) gave, after column chromatography (0-10% MeOH in EtOAc), (*S*)-**12a** (197 mg, 81%) as white solid. R_f (10% MeOH in EtOAc) 0.31; m.p. 153-158 °C; $[\alpha]_D^{25}$ –118.1 (c 0.10, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.36 (1H, bs, NHCO), 4.62 (2H, s, OCH_2), 4.50 (1H, d, *J* = 7.1 Hz, OCHH), 4.45 (1H, d, *J* = 7.1 Hz, OCHH), 3.65 (1H, dd, *J* = 11.5, 4.6 Hz, NHCHH), 3.51-3.40 (2H, m, NHCHH, CH^iPr), 2.50-2.34 (1H, m, $CHMe_2$), 1.80 (1H, bs, NH), 0.99 (3H, d, *J* = 7.3 Hz, CH_3), 0.91 (3H, d, *J* = 6.8 Hz, CH_3) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 81.5 (CH_2), 79.3 (CH_2), 59.3 (CH), 54.7 (C), 48.4 (CH_2), 29.5 (CH), 18.5 (CH_3), 15.6 (CH_3) ppm; IR (film) 3253, 2965, 2869, 1649, 1321, 980 cm^{-1}; MS *m/z* (ES^+) 185 $[M+H]^+$, 207 $[M+Na]^+$; HRMS (ES^+) Calcd for $C_9H_{17}N_2O_2$ $[M+H]^+$: 185.1285, found 185.1284.

(16) CCDC 1430502 (**12j**) and 1430503 (**12a**) contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.