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Spiro-fused Pyrrolidine, Piperidine, and Oxindole Scaffolds from Lactams

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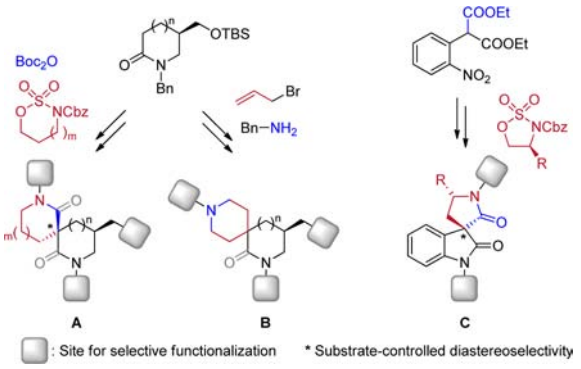
ABSTRACT



Expedient routes to three classes of novel spiro-fused pyrrolidine, piperidine, and indoline heterocycle scaffolds are described. These three-dimensional frameworks, which conform to the "rule of three", are suitably protected to allow for site-selective manipulation and functionalization. Different modes of substrate control were explored, which allow for good to excellent levels of diastereoselectivity and dispense with the need for additional chiral reagents or catalysts. The concepts developed were applied in short, formal syntheses of (±)-coerulescine and (±)-horsfiline.

The "rule of three" guides the design of library candidates for fragment-based drug discovery: this rule requires molecules with a molecular weight of ≤300 g/mol, a *C* log *P* ≤ 0.3, and a number of hydrogen bond donors and acceptors of ≤3.[1] Given our general interest in providing new routes to small, chiral, and "sp^3-rich" drug-like heterocycles, we have exploited the reactivity of cyclic sulfamidates[2] to generate a set of rigid heterocyclic scaffolds, which fit these requirements of molecular weight and hydrogen bond donor/acceptors. Key considerations were the generation of an effective three-dimensional environment, as well as the presence of orthogonally protected functional groups, that allows the ability to "evolve" eventual hits. Spirobased azacycles have found extensive application in medicinal chemistry,[3] and this motif is also present

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(1) Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discov. Today* **2003**, *8*, 876–877.

(2) (a) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727–4730. For reviews, see: (b) Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581–2616. (c) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505–1519.

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in a variety of biologically active natural products.[4] Consequently, spirocycles **A**, **B**, and **C** emerged as attractive targets incorporating sites (Figure 1) for functionalization/derivatization and for which efficient stereocontrol is available directly.

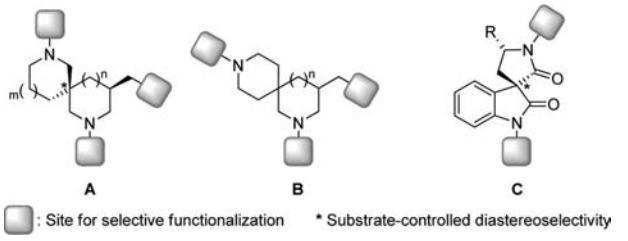
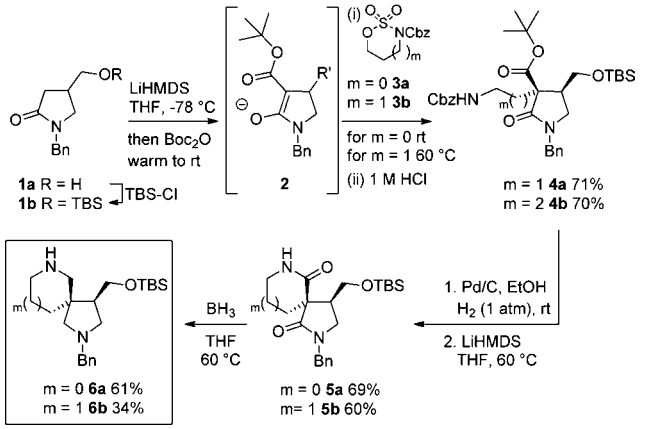


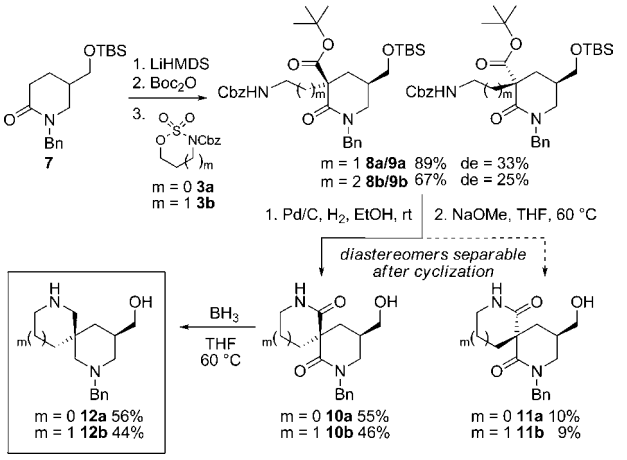
Figure 1. Target spirocycles of types **A**–**C**.

Scheme 1. Tandem Acylation–Alkylation and Spiro-Lactam Formation; Pyrrolidine-Based Targets **A** ($m = 0, 1$; $n = 0$)



Initial studies focused on readily available lactams **1b** (prepared from **1a** by silylation) and **7**.[5] Enolization of **1b** with an excess of LiHMDS and subsequent acylation with Boc_2O[6] delivered the stabilized enolate **2** which reacted with cyclic sulfamidates **3a** and **3b**, generating acylation/alkylation products of type **4** in one step and with high (essentially complete) diastereoselectivity (Scheme 1).[7] While alkylation of **2** with the five-membered cyclic sulfamidate **3a** proceeded efficiently at room temperature, reaction of **2** with homologue **3b** required heating at 60 °C for 13 h. Completion of the spirocyclic scaffold was achieved by Cbz cleavage and subsequent base-mediated cyclization. To facilitate lactamization onto the *tert*-butyl ester, strong bases were necessary: the crude product, after Cbz removal, was heated in THF at 60 °C with LiHMDS to afford spiro-lactams **5a** and **5b**, in 69% and 60% yield, respectively.[8] Borane reduction (carried out in THF at 60 °C) provided the target scaffolds (of type **A**) **6a** and **6b** in 61% and 34% yield, respectively, where the constituent N- and O-sites are differentiated.[9]

Scheme 2. Tandem Acylation–Alkylation and Spiro-Lactam Formation; Piperidine-Based Targets **A** ($m = 0, 1$; $n = 1$)



While diastereoselective acylation/alkylation of **1b** was clearly directed by the adjacent silyoxymethyl substituent, the effect of a more remote 1,3-interaction was more challenging and hence of interest. Acylation/alkylation of **7** with cyclic sulfamidates **3a** and **3b** each delivered an inseparable mixture of diastereomers **8** and **9** (Scheme 2). ^{1}H NMR indicated only a modest diastereomeric excess (de = 33% with **3a** at rt; 20% with **3b** at 60 °C). Based on subsequent conversions, it is likely that the formation of diastereomers **8a** and **8b** is favored over **9a** and **9b** respectively, but no conclusive stereochemical evidence was obtained at this stage. Amine deprotection and cyclization was performed on diastereomeric mixtures using sodium methoxide, with concomitant desilylation, which facilitated separation of diastereomers **10** and **11**[10] by chromatography. Interestingly, products **10** predominated and only

(4) For example: (Manzamines) (a) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201–6258. (Horsfiline) (b) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527–6530.

(5) Compounds derived from **1a** and **7** are racemic, and in Schemes 1 and 2 the relative stereochemistry is depicted. For preparation of **1a**, see: (a) Stanetty, P.; Turner, M.; Mihovilovic, M. *Molecules* **2005**, *10*, 367–375. (b) Gallagher, T.; Derrick, I.; Durkin, P. M.; Haseler, C. A.; Hirschhäuser, C.; Magrone, P. *J. Org. Chem.* **2010**, *75*, 3766–3774. For preparation of **7**, see: (c) Hirschhäuser, C.; Haseler, C. A.; Gallagher, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 5162–5165. For access to enantimerically pure precursors, see: (d) Lima, E. C.; Domingos, J. L. O.; Dias, A. G.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2008**, *19*, 1161–1165. (e) Galeazzi, R.; Martelli, G.Mobbili, G.; Orena, M.; Panagiotaki, M. *Heterocycles* **2003**, *60*, 2485–2498. (f) Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419–2423.

(6) Attempts to substitute Boc_2O in this type of sequence with dimethyl carbonate did not allow for conducting a subsequent alkylation in the same pot. Since the latter reagent releases 1 equiv of highly nucleophilic methoxide, side reactions that consume the cyclic sulfamidate are likely involved (cf. Supporting Information, p 10).

(7) For a reagent-controlled aproach, see: Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2009**, *49*, 568–571.

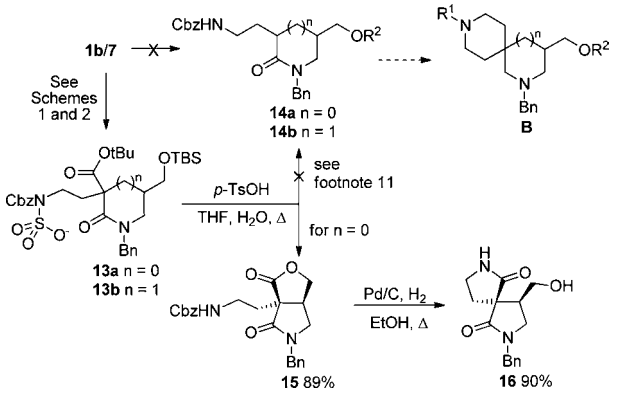
(8) When conducted with NaOMe, the reaction was cleaner and slightly more efficient; however partial cleavage of the TBS-ether also occurred.

(9) The relative configurations of **5a** and **6b** were confirmed by NOE.

(10) The relative configurations of **10a**, **11a**, and **10b** were established unambiguously by X-ray crystallography. The relative configuration of **11b** was confirmed by NOE.

small amounts of the corresponding diastereomers **11** were isolated (**10/11** dr ≈ 5:1; de ≈ 66%). The question then arises as to whether products of type **11** epimerize under the reaction conditions. This was examined by heating **11a** with sodium methoxide (10 equiv, THF 60 °C, 3 d), but no conversion to **10a** was observed by TLC. Instead, slow decomposition of **11a** occurred, both of which observations were confirmed by ^{1}H NMR. These results suggest that although products of type **11** do not epimerize (to **10**), these intermediates nevertheless decompose at a faster rate, thereby providing a mechanism for diastereomer enrichment. Since these spirolactams are generally highly crystalline and compounds of type **10** are significantly less soluble in chloroform than the epimers (i.e., **11**), chromatography-free purification should be possible for purposes of scale-up. Finally, borane reduction of **10a** and **10b** furnished scaffolds **12a** and **12b** in 56% and 44% yield, respectively.

Scheme 3. Attempted Extension into Scaffolds of Type **B**



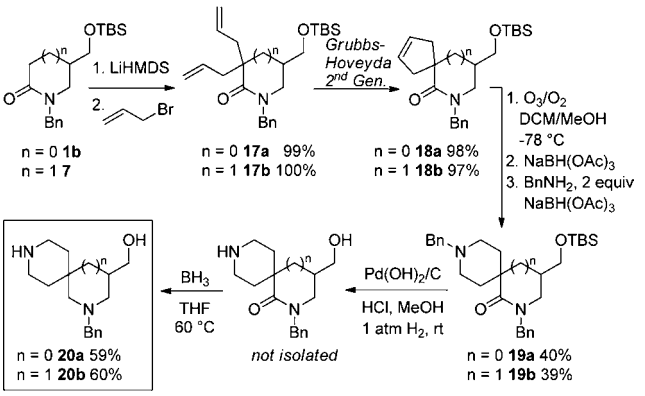
An effort to apply this chemistry in the synthesis of target scaffolds of type **B** is outlined in Scheme 3 with alkylated lactams **14a/b** as the focus. Initial attempts to alkylate directly lactam enolates (generated from **1b** or **7** and LiHMDS in THF at −78 °C) with cyclic sulfamidate **3a**, at either rt or 60 °C, did not deliver the desired products **14a/b**. We also examined the feasibility of direct (in situ) decarboxylation of the initial alkylation adducts (i.e., N-sulfated **13a/b**) derived by the carboxyl-directed alkylation exploited in Schemes 1 and 2. However, this led to desilylation without decarboxylation, after heating at 60 °C for 5 h.[11] In the case of the pyrrolidine variant **13a**, desilylation was followed by lactonization to give **15** in 89% yield. After amine deprotection, in situ lactone-to-lactam conversion provided **16** (the desilylated variant of **5a**) in 90% yield.

The synthesis of scaffolds of type **B** was achieved using an alternative solution, albeit still based on lactam enolate reactivity (Scheme 4).[12] Bisallylation of **1b** and **7** provided

(11) Refluxing **8a**/**9a** (but following isolation) with *p*-TsOH·H_2O in THF for 14 h (as opposed to 5 h) did deliver **14b** in 55% yield, but given the facile formation of **15** from **1b** (via **13a**) this approach was discarded in favor of the more general strategy illustrated in Scheme 4.

(12) For a related aproach, also see ref 3e.

Scheme 4. Synthesis of Scaffolds of Type **B**



alkenes **17a** and **17b**, respectively, which underwent ring closing metathesis to give **18a/b**.[13] Piperidine formation was achieved with the ozonolysis/reductive amination conditions recently published by Dussault,[14] which delivered **19a** and **19b** in 40% and 39% yield. Chemoselective amine N-debenzylation and subsequent lactam reduction completed the desired scaffolds **20a** and **20b** in 59% and 60% overall yield, respectively.[15]

Spiro-fused oxindoles have previously been approached using in situ generated α-acylated lactam enolates as vehicles for nucleophilic aromatic substitution (S_NAr).[16] However, our attempt to apply this strategy to the synthesis of scaffolds of type **C** failed as the less activated 2-fluoro-1-nitrobenzene did not react with enolate **2** at rt or 60 °C. Consequently, malonate **21** was chosen as an alternative starting material.

Alkylation of the enolate of **21** with 1,2-cyclic sulfamidates **3a** and **3c** at 60 °C produced **22a** and **22c** in 72% and 68% yield, respectively (Scheme 5). In the case of **22c**, unidentified byproducts were formed, which were inseparable from the product (purity of **22c** ≈ 90%), but these were easily removed at a later stage. The less reactive 1,3-cyclic sulfamidate **3b** (six-membered and less strained) and

(13) While this reaction worked well with the Grubbs–Hoveyda second generation catalyst in DCM, significant amounts of byproducts resulting from olefin migration were observed when Grubbs' second generation catalyst was employed.

(14) Kyasa, S.; Fisher, T.; Dussault, P. *Synthesis* **2011**, 3475–3481.

(15) Dialdehyde derivatives obtained from **17a**, **17b**, **18a**, and **18b** (by either ozonolysis or bishydroxylation and subsequent diol cleavage) proved to be unstable and were best transformed into the corresponding piperidines (**19**) by immediate reductive amination with benzylamine. Unfortunately, this sequence was capricious, and although a variety of conditions were explored, yields remained low and the reaction was plagued by several unidentified byproducts.

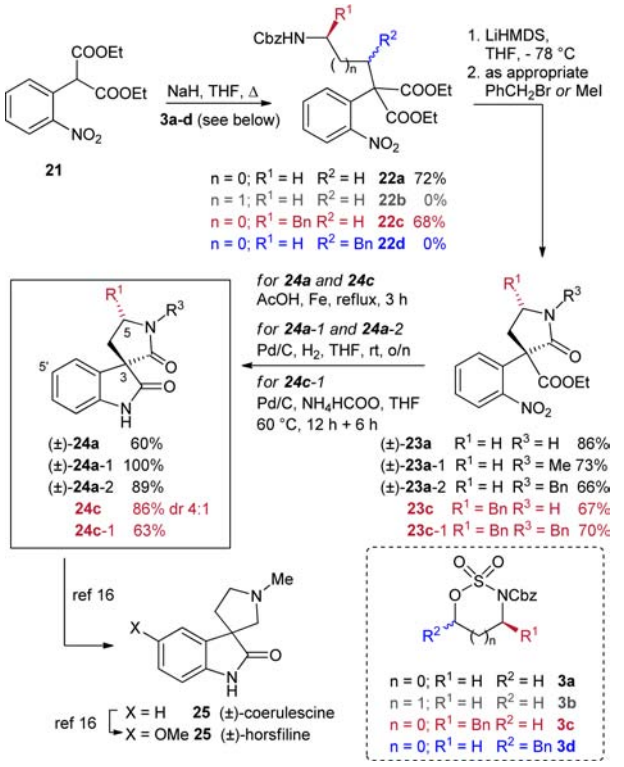
(16) (a) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670–3671. (b) Cowley, A. R.; Hill, T. J.; Kocis, P.; Moloney, M. G.; Stevenson, R. D.; Thompson, A. L. *Org. Biomol. Chem.* **2011**, *9*, 7042. (c) Sen, S.; Potti, V. R.; Surakanti, R.; Murthy, Y. L. N.; Pallepogu, R. *Org. Biomol. Chem.* **2011**, *9*, 358. (d) Kobbelgaard, S.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980–4987.

(17) Kulkarni, M. G.; Dhondge, A. P.; Chavhan, S. W.; Borhade, A. S.; Shaikh, Y. B.; Birhade, D. R.; Desai, M. P.; Dhatrak, N. R. *Beilstein J. Org. Chem.* **2010**, *6*, 876–879.

(18) An attempt to reduce and cyclize lactam **23a** under standard conditions (Pd/C, H_2, THF, rt, o/n) was not successful. Judging by ^{1}H NMR no cyclization had occurred, although the nitro group had been (at least partially) reduced.

the 5-substituted variant **3d** did not react with **21** at rt and underwent decomposition at 60 °C; this may reflect the extensive delocalization/lower reactivity of the enolate of **21**. Cyclization of **22a** and **22c** proceeded readily under basic conditions (LiHMDS, THF, −78 °C to rt), delivering lactams **23a/c**. Since Cbz cleavage occurred under these conditions, quenching with reactive alkyl halides (BnBr or MeI) provided a convenient means of further N-substitution.

Scheme 5. Synthesis of Scaffolds of Type **C** Including Formal Syntheses of (±)-Coerulescine and (±)-Horsfiline



Cyclization of **22c** was of particular interest since diastereoselectivity is dependent on the preference for one of two diastereotopic esters, induced by the relatively remote substituent R^1, and diastereomer **23c** was formed exclusively in 67% yield.

Scaffolds of type **C** were completed by nitro group reduction of **23** and lactamization. The N-substituted derivatives **23a**-1 and **23a**-2 cyclized readily upon reduction (Pd/C, THF, H_2, 1 atm, rt), delivering **24a**-1 and **24a**-2 in 100% and 89% yield, respectively. Selective reduction of the N-substituted lactam of **24a**-1 to deliver (±)-coerulescine and subsequent functionalization at C-5′ of the aromatic ring to complete (±)-horsfiline have been described previously.[17] Formation of the spirocycle from the pyrrolidone **23a** was best achieved by nitro group reduction with iron in acetic acid.[18] The 5-benzyl substituted congener **23c** formed a 4:1 mixture of **24c** and its C-3 epimer under these conditions, indicating lactam opening and reclosure. Reduction and cyclization of **23c**-1 were conducted in THF with Pd/C and ammonium formate at 60 °C.[16c] This reaction initially delivered the corresponding lactam *N*-hydroxide (which was isolated and characterized), and resubmission of this material to the reaction conditions delivered desired lactam **24c**-1 in 63% yield from **23c**-1.

In conclusion, three types of lead-like, spiro-fused scaffolds have been synthesized with core structures which are in agreement with the "rule of three". These frameworks also incorporate residues that are equipped with functionality suitable for selective further manipulation. By exploiting the inherent chirality of a range of different starting materials (i.e., cyclic sulfamidates), additional chiral reagents and catalysts were avoided. Finally, short, formal syntheses of (±)-coerulescine and (±)-horsfiline have been achieved.

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Supporting Information Available. Experimental procedures; crystallographic details for **10a/b**, **11a**, and **24a**-1; and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.