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Expanding the Azaspiro[3.3]heptane Family: Synthesis of Novel Highly Functionalized Building Blocks

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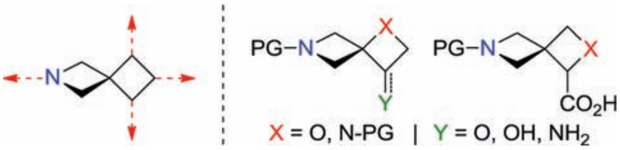
ABSTRACT



The preparation of versatile azaspiro[3.3]heptanes carrying multiple exit vectors is disclosed. Expedient synthetic routes enable the straightforward access to these novel modules that are expected to have significance in drug discovery and design.

In previous work we have shown that oxetanes and spirocyclic azetidines are versatile elements for the modulation and fine-tuning of pharmacokinetic properties.[1] In particular, linear azaspiro[3.3]heptanes were found to possess high aqueous solubilities and low metabolic clearance rates.[1c] These encouraging results prompted us to continue exploring the chemical space of spirocyclic systems (Figure 1). Accordingly, angular azaspirocycles have been prepared and structurally characterized.[2] While many of these spiro[3.3]heptanes can be considered structural surrogates for commonly employed saturated heterocycles, such as piperidines, piperazines, and morpholines, their inherent structural features and accompanying beneficial physicochemical properties can render these building blocks distinctive. Herein we describe a new generation of angular spirocycles that provide unique applications as novel scaffolds for medicinal chemistry.

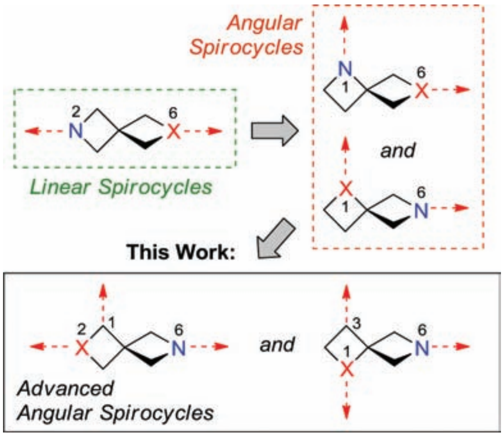


Figure 1. From linear to advanced angular azaspiro[3.3]heptanes. Red arrows denote vectors.

Most of the spirocycles we have previously documented can only be used as terminal fragments linked to the remaining pharmacophore through the azetidine nitrogen atom in analogy to morpholine and piperidine. The use of these novel spiro[3.3]heptanes as scaffolds requires at least two attachment points for the incorporation of a variety of substituents that define exit vectors from the central core.[3] We have thus embarked on the preparation of spirocyclic

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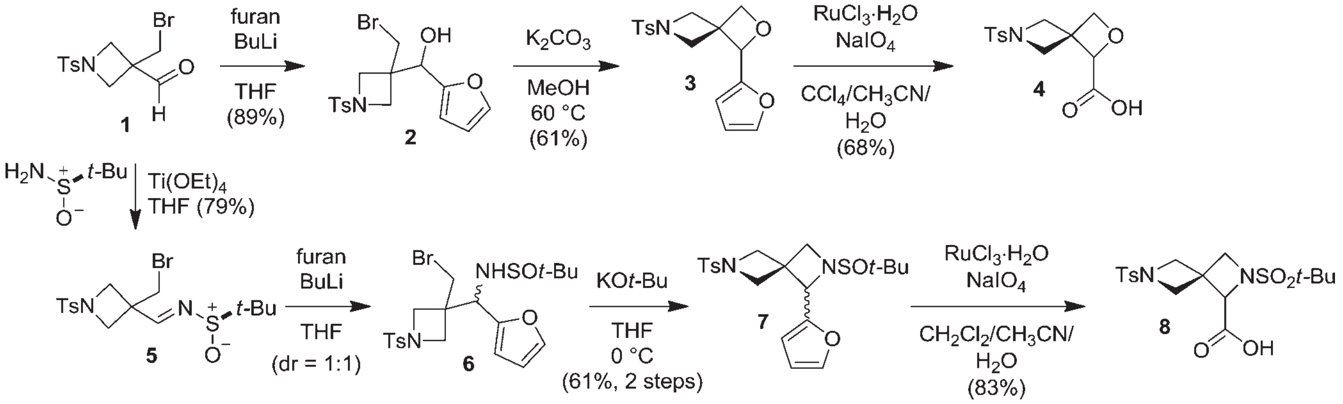
(1) Oxetanes, key references: (a) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227–3246. (b) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052–9067. Azetidines: (c) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524–3527.

(2) (a) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944–1947. (b) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780–783.

10.1021/ol2028459

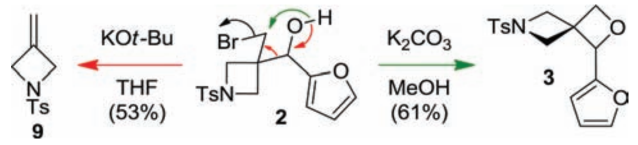
Scheme 1. Synthesis of C1-Functionalized Linear Spirocycles



structures that incorporate two heteroatoms within the framework and include versatile functionality as a branching substituent.

The first targets were based on linear spirocycles containing a carboxylic acid at C1 (Scheme 1). Aldehyde **1**[4] was identified as the starting material, and addition of 2-furyllithium at −78 °C afforded carbinol **2** in 89% yield. Upon treatment with potassium carbonate (5 equiv) in hot MeOH,[5] this material cleanly converted to oxetane **3**, which was isolated in 61% yield. It is worth noting that the choice of base and solvent is crucial to the successful execution of ring closure. Thus, for example, treatment of **2** with KO*t*-Bu in THF at 0 °C did not afford oxetane **2**, instead furnishing 3-methylene azetidine **9** (53% yield) (Scheme 2). This Grob-type fragmentation is a known side reaction in oxetane syntheses from 3-bromopropanols.[6] Finally, the desired carboxylic acid (**4**) was obtained in 68% yield following oxidation of furan **3** using $RuCl_3{\bullet}H_2O/NaIO_4$.

Scheme 2. Fragmentation vs Oxetane Formation



The same strategy was then employed for the synthesis of a *homospiropiperazine*[7] having a carboxylic acid at C1.

Thus, *tert*-butylsulfinyl imine **5** (prepared from aldehyde **1**)[1c] was reacted with lithiated furan to afford the adduct **6** in excellent yield as an inconsequential 1:1 mixture of diastereomers. Subsequently, the unpurified mixture was subjected to KO*t*-Bu in THF to afford azetidines **7** in 61% yield over the two steps. In analogy to the final step in the synthesis sequence to **4**, RuO_4-mediated oxidative fission of the furan unveiled the targeted amino acid **8** in 83% yield.[8] Under the reaction conditions, the *tert*-butylsulfinyl group was concomitantly oxidized to a *tert*-butylsulfonyl (Bus) group.[9]

Next we turned our attention to substituted members of angular azaspiro[3.3]heptanes. The first set of targets were 1-oxa-6-azaspiro[3.3]heptanes bearing a C3 substituent, and their preparation was envisaged to commence from a protected azetidin-3-one.[10] Accordingly, *N*-Boc and *N*-Ts protected azetidinones **10** and **11** were converted to the corresponding propargylic alcohols **12** and **13** following standard protocols (TMSC≡CLi and then desilylation with Bu_4NF in THF, Scheme 3). We have found that Zhang's method for the preparation of azetidin-3-ones from propargylic amines[11] can be implemented for the cyclization of **12** and **13**. The use of 5 mol % [BrettPhosAuNTf$_2$], 8-ethylquinoline-*N*-oxide (2 equiv), and methanesulfonic acid (1.5 equiv) with **12** in dichloroethane at room temperature afforded key oxetanone **14** in 53% yield. However, somewhat more pressing conditions (8 mol % [Au], 40 °C) were necessary to generate **15**. The ketones

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(3) For an insightful account on unusual molecular scaffolds in drug design, see: Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514–5533.

(4) Prepared in three steps from tribromopentaerythritol. For details, see ref 1c and Burkhard, J.; Carreira, E. M. *Org. Lett.* **2008**, *10*, 3525–3526.

(5) Couladouros, E. A.; Vidali, V. P. *Chem.—Eur. J.* **2004**, *10*, 3822–3835.

(6) Searles, S.; Nickerson, R. G.; Witsiepe, W. K. *J. Org. Chem.* **1960**, *24*, 1839–1844.

(7) Due to their resemblance to piperazines, we refer to 2,6-diazaspiro[3.3]heptanes as homospiropiperazines.

(8) For similar protocols, see: (a) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433–1435. (b) Luo, Y.-C.; Zhang, H.-H.; Xu, P.-F. *Synlett* **2009**, 833–837. (c) Luo, Y.-C.; Zhang, H.-H.; Liu, Y.-Z.; Cheng, R.-L.; Xu, P.-F. *Tetrahedron: Asymmetry* **2009**, *20*, 1174–1180.

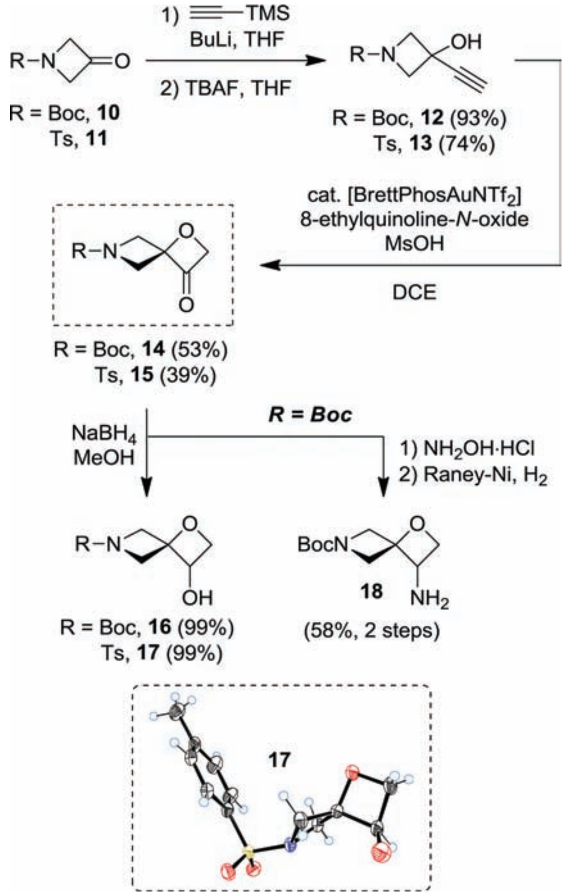
(9) The Bus protecting group is commonly removed using TfOH in CH_2Cl_2: Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604–8608.

(10) For the chemistry of azetidin-3-ones, see: (a) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29–60. (b) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988–4035.

(11) (a) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236–3239. The conditions described for the preparation of substituted oxetan-3-ones gave the desired products in marginal yields only. For the conditions, see:(b) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551.

were elaborated to the corresponding alcohols **16** and **17** (NaBH$_4$; 99% yield), as well as to amine **18** (NH$_2$OH•HCl, then Raney-Ni/H$_2$; 58% yield).

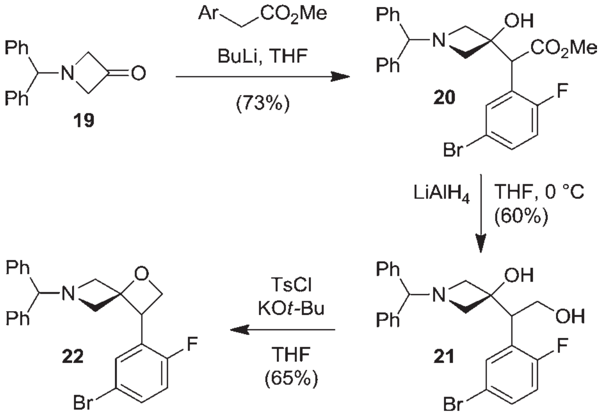
Scheme 3. Synthesis of C3-Functionalized Angular Spirocyclic Oxetanes



We were fortunate to obtain suitable crystals of oxetanol **17** for an X-ray diffraction analysis. The resulting solid-state structure is visualized in Scheme 3 (ORTEP format with ellipsoids at 50% probability). Two characteristics are worth noting: (1) the azetidine ring is puckered, and (2) the arene and oxetane oxygen are both found on the same side of the plane roughly defined by the azetidine, while the hydroxyl group is pointing outward on the opposite side of this plane. This structural information should be valuable when considering the use of this building block as a scaffold.

An alternative approach to C3-substituted 1-oxa-6-azaspiro[3.3]heptanes is delineated in Scheme 4. *N*-Benzhydryl-protected azetidin-3-one (**19**) was treated with the lithium enolate of methyl 2-(5-bromo-2-fluorophenyl)-acetate to afford β-hydroxy ester **20** in 73% yield.[12] Reduction of the ester group using LiAlH$_4$ at 0 °C afforded diol **21** (60% yield), which was cyclized to the corresponding oxetane **22** using TsCl and KO*t*-Bu in THF (65% yield).

Scheme 4. Synthesis of Angular Spirocyclic Aryl Oxetane



This and other similar bromoarenes serve as novel building blocks for further derivatization using transition-metal-mediated coupling reactions.

To complete the series, we were interested in the preparation of azetidine-azetidine spirocycles that would have an additional exit vector at C3. These novel modules containing three vectors in total will render the highly functionalized, but slim, scaffold exceedingly attractive. Since Au-catalyzed azetidin-3-one formation delivered the desired product in a trace amount only, we focused on an alternative strategy (Scheme 5). Previously reported β-lactam **23**[13] was subjected to enolization using KHMDS in THF, and subsequent treatment of the enolate with the Davis oxaziridine **24** led to the isolation of α-hydroxy lactam **25** in 63% yield. The β-lactam was successfully reduced using chlorohydroalane,[14] and azetidin-3-ol **26** was subsequently obtained in 67% yield. Its conversion to the corresponding ketone **27** was effected under Swern oxidation conditions (82% yield). This differentially protected trifunctional scaffold crystallized to give suitable single crystals for X-ray analysis. Similar to the situation noted in **17**, the tosyl group is positioned on the same side as the nitrogen of the adjacent ring. This leads to a situation, where both aromatic rings point in the same surrounding hemisphere, with arene ring centroids separated by 5.7 Å.

A two-step procedure, starting from β-lactam **23**, was developed for the synthesis of a protected triamine spiro compound. As outlined in Scheme 6, **23** was subjected to enolization, and the enolate was treated with isoamyl nitrite.[15] The intermediate nitroso compound smoothly isomerized to oxime **28**, which was isolated in 70% yield (12:1 ratio of oxime isomers according to ^{1}H NMR of

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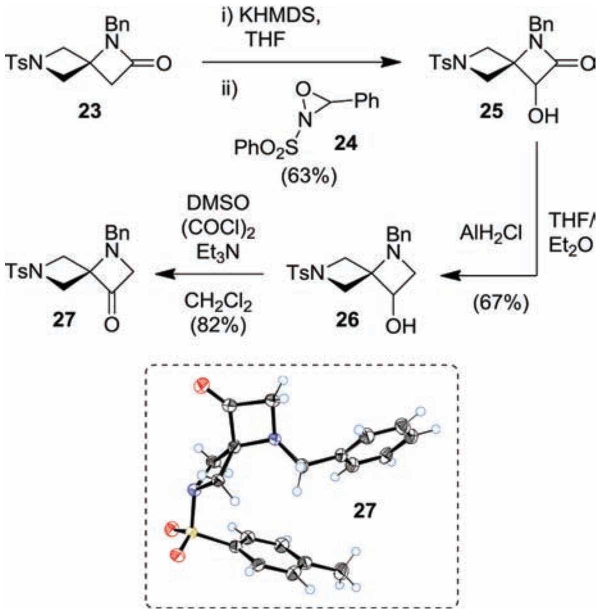
[12] Baker, R. K.; Bao, J.; Miao, S.; Rupprecht, K. M. (Merck & Co., Inc.), WO 2005/000809, 2005.

[13] Prepared in three steps from *N*-Ts-azetidin-3-one; see ref 2b.

[14] (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263–5277. Seminal work on the reduction of β-lactams: (b) Jackson, M.; Mander, L.; Spotswood, T. *Aust. J. Chem.* **1983**, *36*, 779–788.

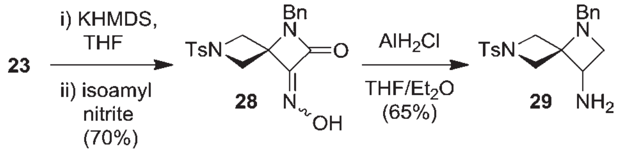
[15] Related work on β-lactams: (a) Takahashi, Y.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 2732–2742. (b) Yamashita, H.; Minami, N.; Sakakibara, K.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1988**, *36*, 469–480. (c) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170–8182.

Scheme 5. Synthesis of C3 Functionalized Angular Spirocyclic Azetidines



unpurified reaction product). Its treatment with AlH_2Cl concomitantly led to reduction of the lactam unit and the oxime to give 1,6-diazaspiro[3.3]heptan-3-amine **29** in 65% yield.

Scheme 6. Synthesis of Angular Spirocyclic Triamine



In conclusion, we have developed efficient access to a series of advanced angular azaspiro[3.3]heptanes. Azetidines substituted at C3 served as starting materials for the synthesis of these novel building blocks, which were prepared in two to five steps from commercially available or previously reported compounds. The ability to attach vectors at multiple positions in an array of orientations makes these compound scaffolds attractive in drug discovery programs, and they should be considered in the context of scaffold hopping.[16,17] Owing to their remarkable chemical stability, their unique structural characteristics, and their possibility to populate uncharted chemical space, we expect these modules to find wide applications in drug discovery and design.

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Supporting Information Available. Experimental procedures and characterization for all new compounds. Crystallographic information files (CIF) for **17** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a seminal publication, see: (a) Schneider, G.; Neidhart, W.; Giller, T.; Schmid, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 2894–2896. Reviews on the topic:(b) Schneider, G.; Schneider, P.; Renner, S. *QSAR Comb. Sci.* **2006**, *25*, 1162–1171. (c) Schneider, G.; Fechner, U. *Nat. Rev. Drug Discov.* **2005**, *4*, 649–663.

(17) The compounds that are the subject of this communication are produced as racemates. This is a desirable situation as it maximizes the potential for their use in drug discovery. Typically in the process, when an optically active compound is necessary it is easiest and most practical to effect resolution by chiral chromatography. In our experience, the identification of a promising structure in the context of a specific project then provides incentive for the development of an enantioselective route.