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Synthesis of oxaspiropiperidines as a strategy for lowering log*D*

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ABSTRACT

The syntheses of four new spiropiperidines designed as polar analogs of methyl 2-(3-azaspiro[5.5]undecan-9-yl)acetate are described.

Spiropiperidines have emerged as valuable fragments for drug discovery and have demonstrated favorable biological properties in small molecule programs across multiple therapeutic areas.[1] Spiropiperidine frameworks are often described as privileged structures[2] because they have been successfully employed as ligands for a variety of targets including muscarinic,[3] δ-opioid,[4] melanocortin,[5] and CCR4 receptors,[6] as well as the proteins HDAC,[7] ACC,[8] and SCD.[9] At Merck, spirocyclic small molecules have been especially successful with an NPY inhibitor[10] and a growth hormone secretagogue[11] advancing to Phase II and Phase III clinical trials, respectively. During the course of a recent drug discovery program, we became interested in commercially available *tert*-butyl 9-(2-methoxy-2-oxoethyl)-3-azaspiro[5.5]undecane-3-carboxylate **1** (Chart 1) as a compact and rigid linker containing both amine and ester functional handles for elaboration. We were also drawn to analogs of **1** with decreased lipophilicity. Decreased lipophilicity, indicated by a lower value for distribution coefficient (log*D*), is commonly associated with favorable drug properties such as high solubility, low plasma protein binding, and decreased affinity for common off-target enzymes like ion channels and cytochrome P450's.[12] We therefore considered oxygen for carbon replacements in the spiropiperidine framework as a strategy for the reduction of log*D*.

As shown in Chart 1, incorporation of oxygen significantly increased the calculated polarity of the spiropiperidine.[13] Thus, spiropiperidine **1** has a calculated log*D* (*c*log*D*) of 4.34 while oxygenated variant **2** has a *c*log*D* of 1.94. To further explore chemical space in this area, we also considered truncated analog **3** (*c*log*D* = 2.05), tetrahydropyran regioisomer **4** (*c*log*D* = 1.94), and tetrahydrofuran analog **5** (*c*log*D* = 2.25). The synthesis of these oxygenated spiropiperidines in racemic form is described in this Letter.

We first targeted spiropiperidine **2** (Scheme 1). In this case, *N*-Boc-4-piperidone (**6**) was subjected to reaction with allylmagnesium bromide followed by O-alkylation with allyl bromide. Diene **8** was then treated with Grubbs first generation catalyst to effect ring

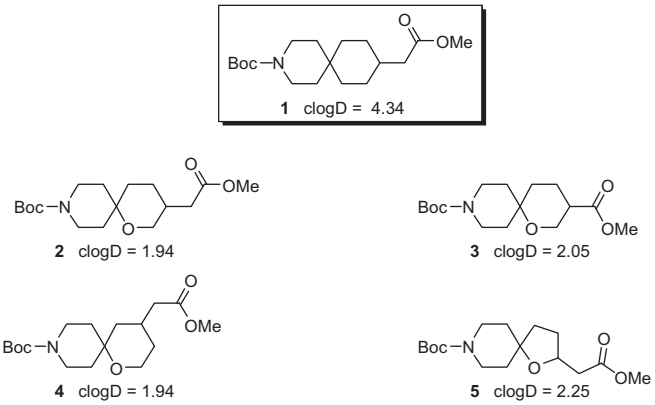

Chart 1. Oxaspiropiperidine targets and their calculated distribution coefficients (*c*log*D*).

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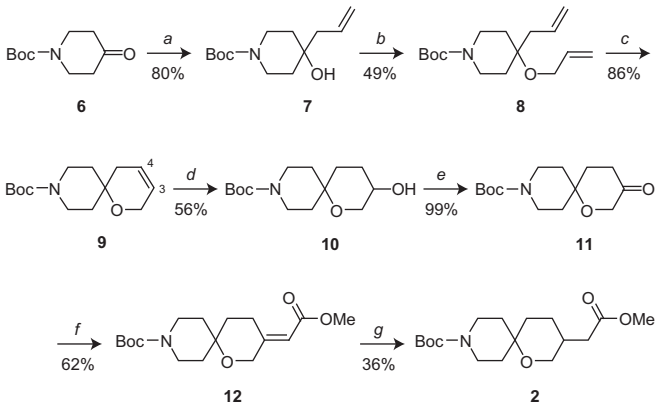


Scheme 1. Synthesis of spiropiperidine **2**. Reagents and conditions: (a) Allylmagnesium bromide in THF, Et_2O, 0–23 °C, 18 h; (b) allyl bromide, K_2CO_3, DMF, 0–23 °C, 18 h; (c) 10 mol % Grubbs I, CH_2Cl_2, 0–23 °C, 18 h; (d) BH_3·THF, THF, 0 °C, 18 h then NaOH, H_2O_2, 0–23 °C, 1 h, 3.5:1 mixture of regioisomers; (e) 1 mol % TPAP, NMO, THF, 23 °C, 40 min; (f) trimethyl phosphonoacetate, NaH, THF, 23 °C, 20 h; (g) H_2 (1 atm), 10 mol % Pd/C, EtOAc, 23 °C, 18 h.

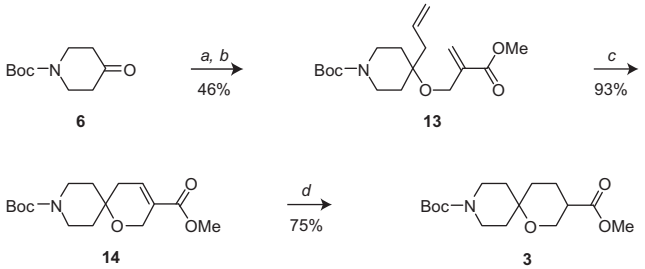
closure in 86% yield.[14] Hydroboration gave a separable mixture of regioisomeric alcohols in a 3.5:1 ratio favoring oxidation at position **3** as desired. Oxidation of the desired alcohol followed by Horner–Wadsworth–Emmons homologation and reduction produced the target spiropiperidine in 22% yield over three steps.

We then pursued truncated analog **3** (Scheme 2). Thus, *N*-Boc-4-piperidone was subjected to reaction with allylmagnesium bromide followed by O-alkylation with bromomethyl methacrylate. Diene **13** was then treated with Grubbs second generation catalyst and heated at 85 °C in 1,2-dichloroethane for 18 h to provide the desired spirodihydropyran in 93% yield. Palladium catalyzed hydrogenation of **14** on an H-Cube flow hydrogenation reactor[15] provided the target spiropiperidine (**3**).

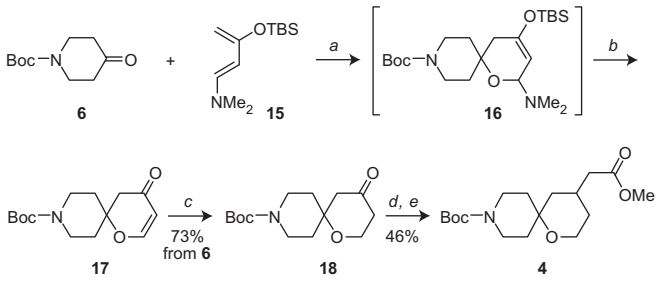
Next, we targeted regioisomer **4** (Scheme 3). Cycloaddition of Rawal's diene (**15**) across 4-piperidone occurred cleanly in 2-butanol to give cycloadduct (**16**) that was converted to dihydropyranone **17** following deaminative workup with acetyl chloride.[16] The crude cycloadduct thus obtained was subjected to hydrogenation then purified to give spirotetrahydropyranone **18** in 73% overall yield from **6**. Next, Horner–Wadsworth–Emmons homologation occurred in 80% yield followed by enone hydrogenation in 65% yield to give spiropiperidine target **4**.

Finally, we targeted spirotetrahydrofuran **5** which was synthesized from spirolactone **19**[17] (Scheme 4). Thus, DIBAL-H reduction of the lactone to lactol **20** occurred in 81% yield. Subsequent treatment with the potassium salt of trimethylphosphonoacetate gave **5** in 63% yield.

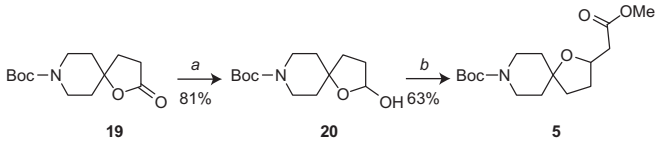
We next measured the distribution coefficients for spirocycles **1–5** using Haky and Young's HPLC method.[18] Data are shown in Table 1.



Scheme 2. Synthesis of spiropiperidine **3**. Reagents and conditions: (a) Allylmagnesium bromide, Et_2O, 0–23 °C, 18 h; (b) bromomethyl methacrylate, NaH, DMF, 0–23 °C, 18 h; (c) 10 mol % Grubbs II, 1,2-DCE, 85 °C, 18 h; (d) H_2 (50 barr, H-Cube), cat. $Pd(OH)_2$, EtOH, 23 °C.

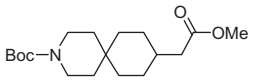
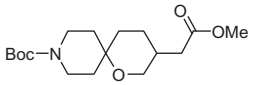
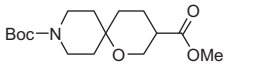
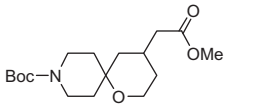
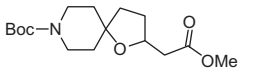


Scheme 3. Synthesis of spiropiperidine **4**. Reagents and conditions: (a) Compound **15**, 2-butanol, 23 °C, 2.5 h; (b) AcCl, Et_2O, −78 °C, 10 min; (c) H_2 (1 atm), 10 mol % Pd/C, 23 °C, 4 h; (d) trimethyl phosphonoacetate, NaH, THF, 0–23 °C, 4 h; (e) H_2 (1 atm), 30 mol % $Pd(OH)_2$, EtOH, 23 °C, 6 h.



Scheme 4. Synthesis of spiropiperidine **5**. Reagents and conditions : (a) DIBAL-H, CH_2Cl_2, −30 °C to 23 °C, 4 h; (b) trimethyl phosphonoacetate, ^{t}BuOK, THF, 0–23 °C, 16 h.

Table 1
Calculated and experimental log*D*'s for spiropiperidines **1–5**

Compound	Structure	*c*log*D*	HPLClog*D*
1		4.34	4.83
2		1.94	3.70
3		2.05	3.51
4		1.94	3.59
5		2.25	3.43

The experimental data indicated a log*D* lowering of 1.1–1.4 log units on incorporation of oxygen compared with a predicted lowering of 2.1–2.4 log units. Thus the calculated log*D*'s were overestimated but the trends in log*D* reduction were accurately predicted. The experimental data therefore confirmed that oxygenated spiropiperidines **2–5** are indeed considerably more polar than spiropiperidine **1**.

The oxaspiropiperidines presented in this Letter are compactly functionalized and rigid frameworks with lower log*D* than their carbogenic parent **1**. They possess both amine and ester functionality for synthetic elaboration and are each accessible from commercially available reagents in seven or fewer steps. We suggest that these fragments may be useful in drug discovery programs where increased polarity is desired.

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