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Densely functionalised spirocyclic oxetane-piperidine scaffolds for drug discovery

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ABSTRACT

A spirocyclic, sp^3-atom rich oxetane-containing scaffold was synthesised in just two steps via a gold catalysed propargylic alcohol rearrangement. The key gold cyclisation can be undertaken on a 40 g scale allowing the preparation of 419 lead-like compounds based on the scaffold for the European Lead Factory.

1. Introduction

Recent initiatives in drug discovery have focussed on the development of synthetic methodologies to low molecular weight, lead-like, sp^3-atom rich molecules; that have the potential for diverse functionalisation.[1–3] The oxetane motif has been explored in drug discovery due to its impact on the physicochemical properties of biologically active molecules.[4–6] Originally identified as isosteres for *gem*-dimethyl groups increasing steric bulk without increased lipophilicity,[5] oxetanes also act as bioiosteric replacements for carbonyls and morpholines (Fig. 1).[4]

In particular, spirocyclic oxetanes (Fig. 2) represent an interesting alternative scaffold due to their intrinsic high degree of three-dimensional character, rigidity and well defined vectors.[7–11]

Oxetanes can be prepared using a variety of methods including the intramolecular Williamson ether synthesis,[10,12,13] the Paterno-Buchi reaction,[14] intramolecular alkylation,[15] or by gold catalysed rearrangement of propargylic alcohols.[16] In keeping with our aim to prepare sp^3-atom rich scaffolds for drug discovery, as part of the European Lead Factory project,[10,17–19] we identified the spirocyclic oxetane scaffold **5** for inclusion in the Joint European Compound Library (Fig. 3).

We foresaw that the 2-carboxyl-1-oxa-7-azaspiro[3,5]nonane scaffold **5** should be accessible by the aforementioned gold catalysed rearrangement of a propargylic alcohol (Fig. 4), provided that the reaction was scalable and compatible with other functional groups. We now report the successful realisation of these goals that ultimately led to the synthesis of a library of 419 compounds in lead-like chemical space.

2. Results and discussion

The propargylic alcohol **7** was prepared easily from Cbz-protected piperidinone **6** in 73% yield (Scheme 1). Alcohol **7** was then subjected to the gold catalysed rearrangement conditions, based on the literature procedure.[16] Following these conditions we observed 58% conversion into the desired product (Entry 1, Table 1), with remaining starting material. Increasing the catalyst loading to 20 mol% had little effect on this ratio (Entry 2, Table 1). Increasing the temperature to 60 °C (Entry 3, Table 1) increased the yield to 74% with a significant reduction of remaining starting material. Pleasingly we also found that lowering the loading of the gold catalyst in this reaction from 5% (as in the literature procedure) to 2%, gave the key scaffold, oxetan-3-one **8**, in a 65% yield on a 17 mmol scale. On a 130 mmol scale (43 g), oxetan-3-one **8** was isolated in 76% yield. With the core scaffold **8** in hand, further diversification was attempted (Scheme 2).

Methylation at C-4 with caesium carbonate and iodomethane was unsuccessful and resulted in the cleavage of the strained oxetan-3-one ring to tricarbonyl compound **9**. This was based on observation of a new product formed with the same mass as the starting material,[20] and similar transformations in the literature.[21] Reductive amination of the ketone was attempted under a range of conditions, but only the opening of the oxetan-3-one ring to amide **10** or reduction to give alcohol **11** was observed (Scheme 2).

Reduction of the ketone was more successful and the *syn* diastereomer of alcohol **11** was obtained with an excellent diastereoselectivity (>20:1 by ^{1}H NMR spectroscopy) using sodium triacetoxyborohydride with the addition of acetic acid (Scheme 3). The major diastereomer was isolated by chromatography and the *syn* stereochemistry was assigned based on ^{1}H NMR coupling constants. The *syn* diastereomer was found to have a $^3J_{HH}$ coupling

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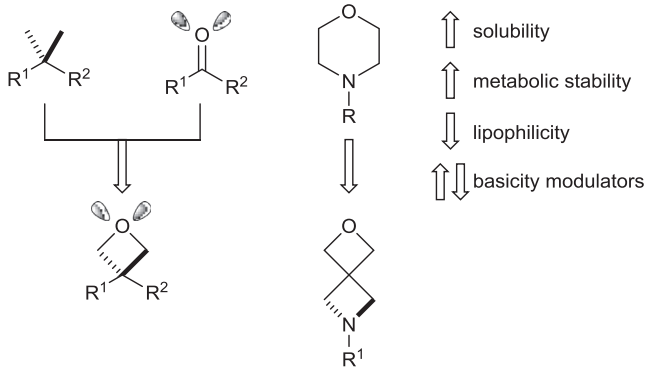


Fig. 1. Bioisosteric roles of oxetanes in medicinal chemistry.

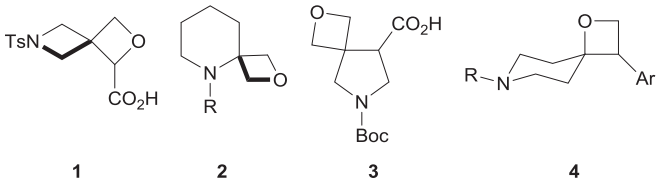


Fig. 2. Recent examples of spirocyclic oxetane scaffolds.

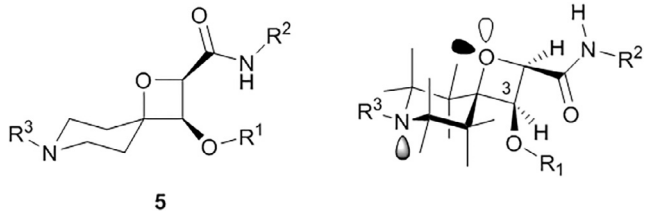


Fig. 3. The 2-carboxyl-3-alkoxy-1-oxa-7-azaspiro[3,5]nonane ring system.

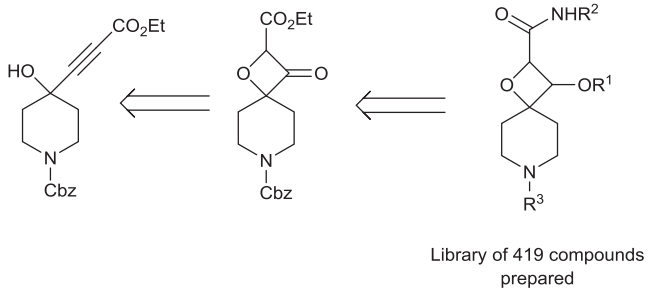
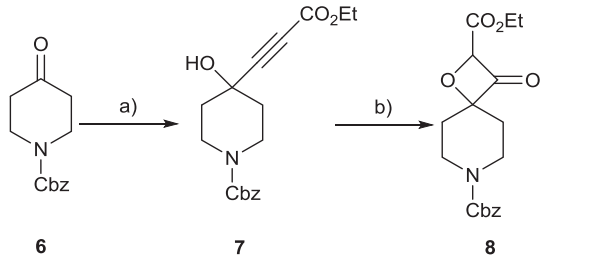


Fig. 4. Synthesis of key spirocyclic oxetane and functionalisation via gold catalysed rearrangement.

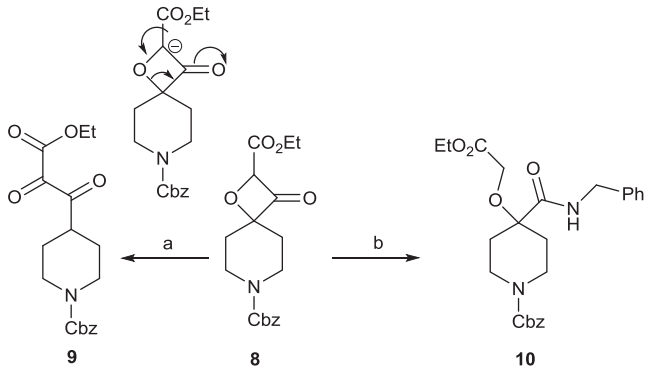
constant of 7.1 Hz, corresponding to the expected 0° dihedral angle. In contrast, the minor diastereomer was found to have a $^3J_{HH}$ coupling constant of 5.5 Hz corresponding to the expected 60° dihedral angle.[22] *O*-Methylation of alcohol **11** could be achieved using iodomethane in the presence of silver oxide and a 72% yield of **12** was obtained on a small scale (200 mg). This reaction, however, was not compatible with scale up conditions and on a 2.7 g scale, the yield dropped dramatically to just 23%. For this reason, further diversification of ether **12** was not attempted. It was found that the ester functionality in **11** could be directly converted into an amide by treatment with an amine and DABAL-Me_3 (Scheme 4).[23] In this way, benzyl amide **13** and isopropyl amide **14** were prepared in 71% and 69% yields respectively. Deprotection of



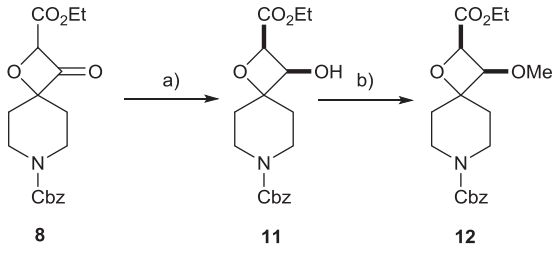
Scheme 1. Preparation of oxetan-3-one **8**. *Reagents and conditions*: a) *n*-BuLi (3.0 eq.), ethyl propiolate (3.4 eq.), THF, -70 °C, 2 h, 43 mmol scale: 73%, 168 mmol scale, 77%; b) *i*PrAuNTf$_2$ (2.1 mol%), Tf$_2$NH (1.2 eq.), 4-acetylpyridine *N*-oxide (2 eq.), 1,2-DCE, 60 °C, 24 h, 17 mmol scale: 65%, 130 mmol scale: 76%.

Table 1
Optimisation of gold cyclisation. [a]Reactions were conducted on a 0.15 mmol scale with 1.2 eq. Tf$_2$NH, 2 eq. 4-acetylpyridine *N*-oxide in anhydrous 1,2-DCE, [b]0.075 mmol scale, [c]17 mmol scale.

Entry[a]	Time/h	Temp/°C	iPrAuNTf$_2$/mol%	SM **7**/%[a]	Product **8**/%[a]
1	20	40	5	37	58
2	20	40	20	27	62
3	20	60	5	7	74
4[b]	72	60	5	0	0
5[c]	24	60	2	0	65



Scheme 2. Initial attempts at diversification of 1-oxa-7-azaspiro[3,5]nonane core **8**. *Reagents and conditions* a) MeI, Cs_2CO_3, DMF, 87% (mass recovery). b) $BnNH_2$, Na(OAc)$_3$BH, 1,2-DCE, 35%.



Scheme 3. Reduction and methylation of oxetan-3-one **8**. *Reagents and conditions*: a) Na(OAc)$_3$BH (2 eq.), AcOH (1.7 eq.), 1,2-DCE, rt, 18 h, 77%. b) Ag_2O (5 eq.), MeI (150 eq.), 45 °C, 48 h, 200 mg scale: 72% 2.7 g scale: 23%.

the Cbz protecting group by hydrogenolysis (H_2, Pd/C) gave the amine scaffolds **15** and **16** ready for library synthesis.

2.1. Library synthesis

The synthetic tractability of the amine cores **15** and **16** in library synthesis was tested on a small scale at Sygnature Discovery (Not-