Densely functionalised spirocyclic oxetane-piperidine scaffolds for drug discovery

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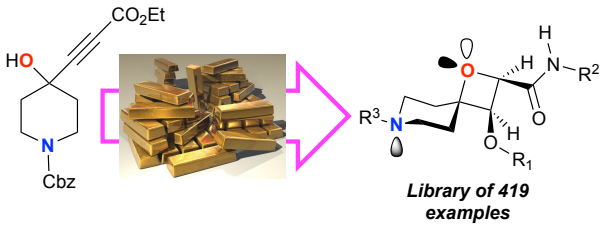


Abstract: A spirocyclic, *sp*^{3}-atom rich oxetane-containing scaffold was synthesised in just two steps via a gold catalysed propargylic alcohol rearrangement. The key gold cyclisation can be undertaken on a 40 g scale allowing the preparation of 419 lead-like compounds based on the scaffold for the 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 (Figure 1).[4]

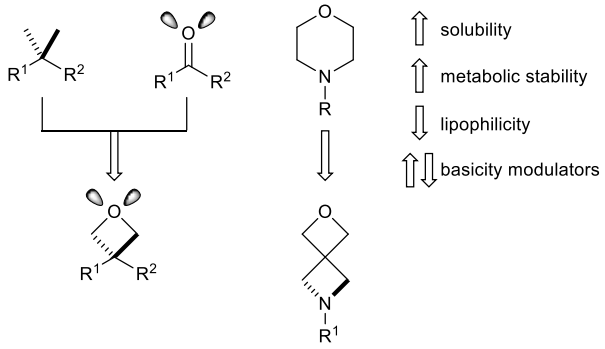


Figure 1: Bioisosteric roles of oxetanes in medicinal chemistry.

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

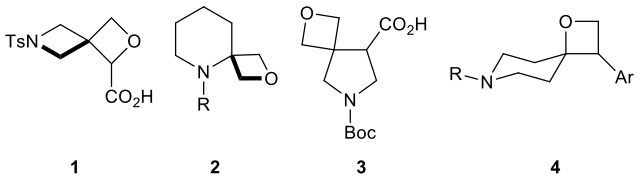


Figure 2: Recent examples of spirocyclic oxetane scaffolds.

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 (Figure 3).

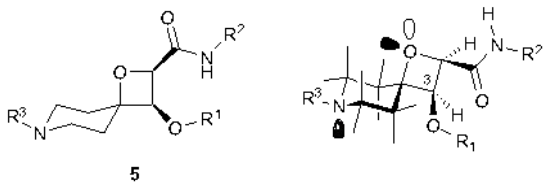


Figure 3: The 2-carboxyl-3-alkoxy-1-oxa-7-azaspiro[3,5]nonane ring system.

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 (Figure 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.

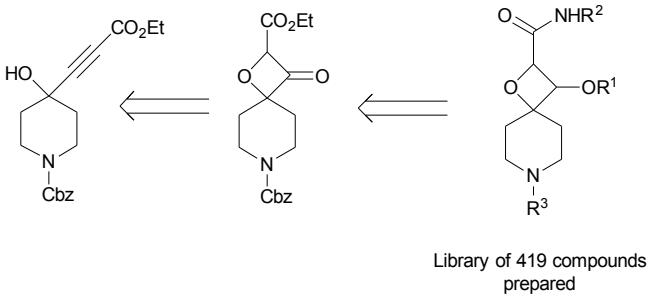
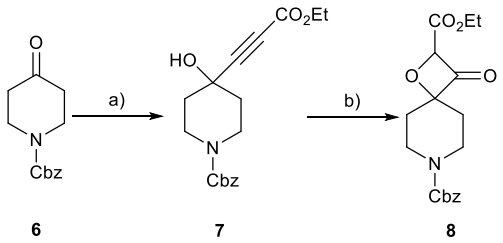


Figure 4 Synthesis of key spirocyclic oxetane and functionalisation via gold catalysed rearrangement.

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).



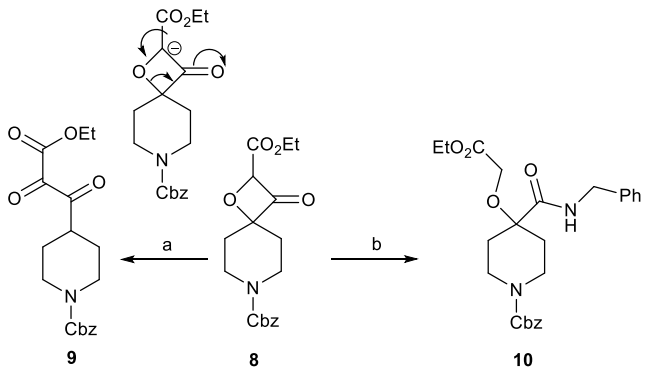
6 **7** **8**

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%.

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

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.

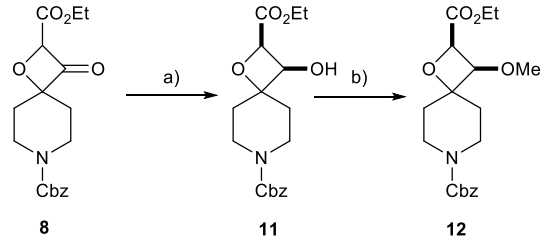
Methylation at C-4 with caesium carbonate and iodomethane was unsuccessful and resulted in the cleavage of the strained oxetan-3-one ring to tricarbonyl compound **9**. This was based on observation of a new product formed with the same mass as the starting material,[20] and similar transformations in 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).



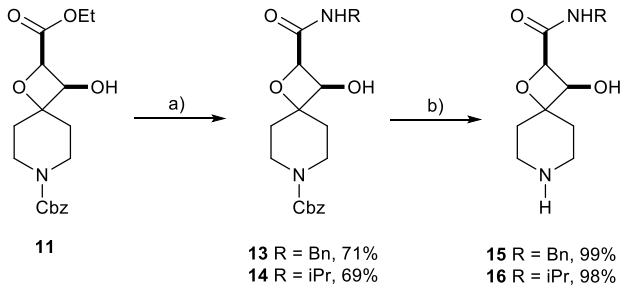
Scheme 2 Initial attempts at diversification of 1-oxa-7-azaspiro[3,5]nonane core **8**. *Reagents and conditions* a) MeI, Cs_2CO_3, DMF, 87% (mass recovery). B) $BnNH_2$, $Na(OAc)_3BH$, 1,2-DCE, 35%.

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



Scheme 3 Reduction and methylation of oxetan-3-one **8.** *Reagents and conditions***:** a) $Na(OAc)_3BH$ (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%.

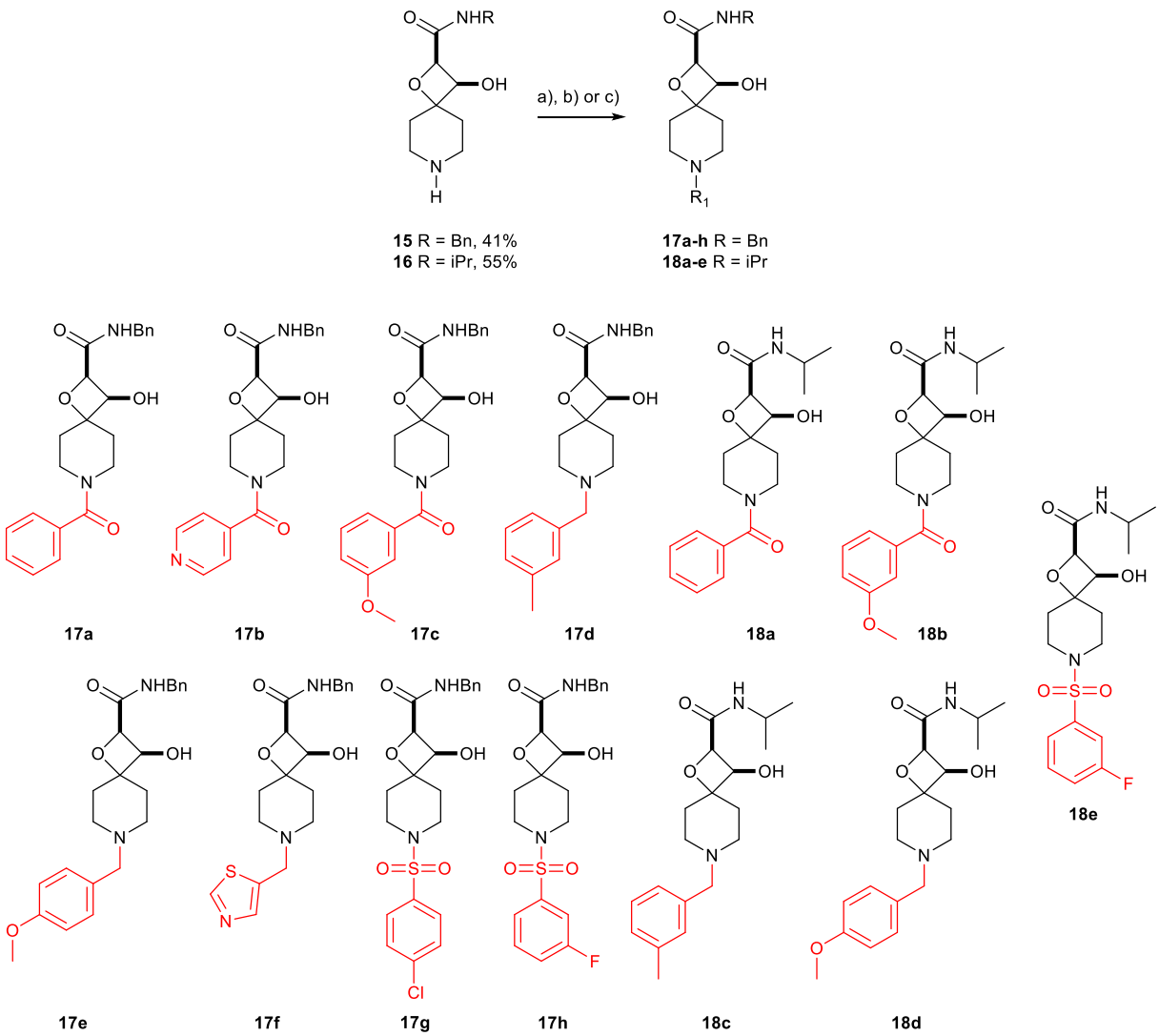


Scheme 4 Functionalising oxetan-3-ol **11.** *Reagents and conditions* a) 1. DABAL-Me_3 (1.5 eq.), RNH_2 (1.5 eq.), THF, 40 °C, 1 h. 2. 11, THF, 65 °C, 18 h. b) H_2, Pd/C (10 wt%), CF_3CH_2OH, rt, 15 h.

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 (Nottingham, UK) using high-throughput methods. A small library of 13 compounds

was prepared by HATU mediated amide coupling to give amides **17a**-**c** and **18a**-**b**, reductive amination to give tertiary amines **17d**-**f** and **18c**-**d**, and reaction with sulfonyl chlorides to give sulfonamides **17g**-**h** and **18e** (Scheme 5).



Scheme 5 Library compounds synthesised by high-throughput methods**.** *Reagents and conditions*: a) carboxylic acid, *i*-Pr_2NEt, HATU, DMF, 18 h, rt.; b) aldehyde, AcOH, $NMe_4(OAc)_3BH$, DMF, 18 h, rt.; c) sulfonyl chloride, pyridine, DMF, 18 h, rt.

The scaffolds prepared in this paper were developed for inclusion in the Joint European Compound Library (JECL) for the European Lead Factory, and therefore following the small-scale library synthesis, a

full library of 419 compounds was prepared. The design of the library was chosen to consider the molecular properties of the compounds, including logP and molecular weight and to avoid any potentially undesirable groups. The molecular weights of the compounds within the library were between 324 and 445 Da (Figure 5). The molecular weight of the core unfunctionalised scaffold is 202. When compared to two commercial libraries; Maybridge HitCreator and Maybridge HitFinder we can see that the oxetane library is more densely clustered in lead-like space compared to the commercial libraries (Figure 5).[24] The compounds have a high fraction of sp^3 hybridised atoms with the majority between 60 and 70% with an average of 57%; compared to 24% and 31% for the commercial HitFinder and HitCreator libraries respectively (Figure 6 and Table 2). Thus our oxetane library provides a focused set of compounds with more desirable "lead-like" lipophilicity with an f^{sp3} expected of a candidate drug molecule.

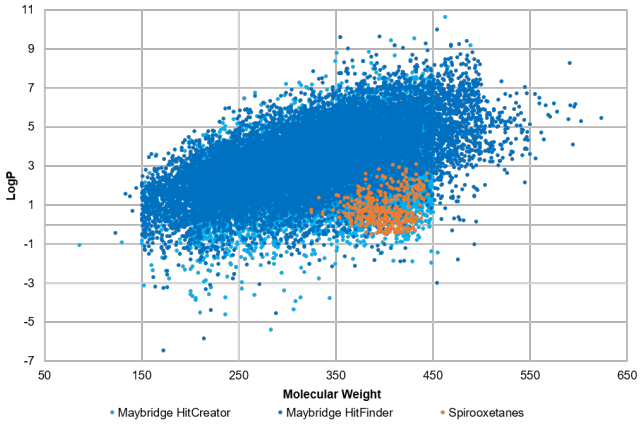


Figure 5 Plot of molecular weight versus cLogP for the prepared oxetane library and commercial libraries.

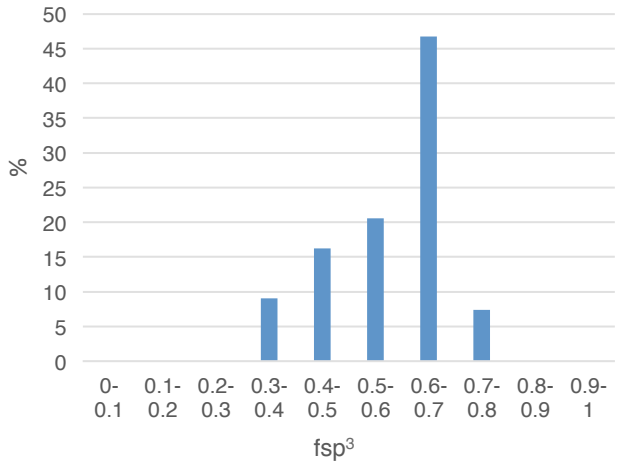


Figure 6 Plot showing fraction of sp^3 hybridised carbons.

Library	Mean MW (Da)	Mean cLogP	Mean *F*sp3
Oxetane Library	399.40	0.89	57%
Maybridge HitFinder	325.56	3.30	23%
Maybridge HitCreator	340.17	2.87	30%

Table 3: Comparison of key molecular properties for the oxetane library and two commercial libraries.

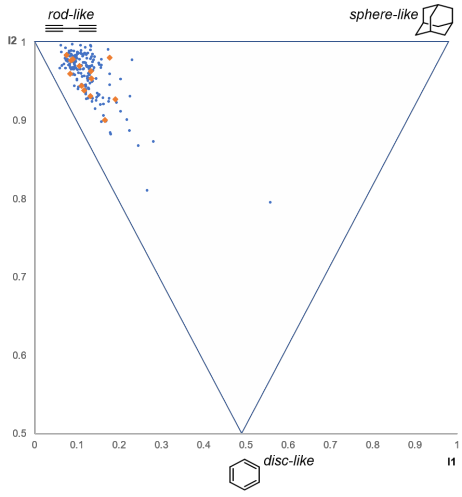


Figure 7 Principal moment of inertia plot of virtual library of oxetanes generated through LLAMA. Orange points represent compounds **17a**-**h** and **18a**-**e**.

We utilised the library modelling tool LLAMA to generate a principle moment of inertia plot of shape distribution for a virtual library of compounds (see ESI for full details), and the synthesised compounds **17a**-**h** and **18a**-**e** (Figure 7).[25] The virtual library of molecules, along with the synthesised examples, occupy the rod-like area of molecular space; reflecting the overriding contribution of the core scaffold for molecular shape – allowing for lead optimisation with a variety of decorating groups without significantly changing the overall molecule shape.

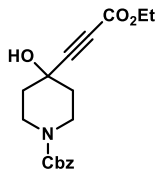
3. Conclusions

In conclusion, we have applied the gold catalysed rearrangement of propargylic alcohols to the synthesis of functionalized spirocyclic oxetane-piperidines for drug discovery. The key gold rearrangement can be undertaken on a decagram scale to generate the oxetan-3-one intermediate with three points of functionalisation. The scaffold can be further elaborated to prepare compound libraries that are of importance to medicinal chemistry due to their rod-like structure. This methodology has enabled the synthesis of 419 novel chemical entities with attractive physicochemical properties, that are available through the open access JECL for lead generation to academic and industrial groups.

4. Experimental Section

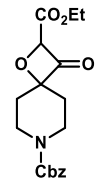
For general experimental details, and protocols for library synthesis, see Electronic Supplementary Information.

Benzyl 4-(3-ethoxycarbonylprop-1-yn-1-yl)-4-hydroxypiperidine-1-carboxylate, 7



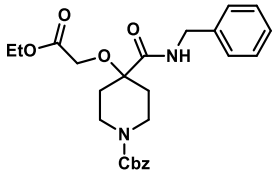
A solution of ethyl propiolate (14.8 mL, 145.9 mmol) in THF (120 mL) was cooled to -70 °C in an acetone/dry ice bath. To this was added *n*-butyllithium (2.25 M in hexanes, 57 mL, 128.2 mmol), dropwise over 1 h and the solution was stirred at -70 °C for 15 min. After this time, a solution of 1-Cbz-4-piperidone **6** (10.0 g, 42.9 mmol) in THF (120 mL) was added dropwise over an hour, ensuring that the temperature did not rise above -70 °C. The resultant solution was stirred at -70 °C for 2 h until the disappearance of the starting material was observed by TLC (50% ethyl acetate in light petroleum). The reaction was quenched at -70 °C by the dropwise addition of a aqueous ammonium chloride solution (saturated, 100 mL) over 20 min. The reaction mixture was warmed to room temperature extracted with ethyl acetate (4 × 100 mL). The combined organic phases were washed with brine (2 × 100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil (21.2 g). Purification by column chromatography (40% ethyl acetate in light petroleum) gave the *title compound* **7** as a yellow crystalline solid (10.42 g, 73%): $\boldsymbol{R_f}$ 0.47 (40% ethyl acetate in light petroleum, weakly UV active, $KMnO_4$ active); **mp** 92-94 °C; **HRMS** *m/z* (ESI^+) calcd. for $C_{18}H_{22}NO_5$ $[M+H]^+$ requires 332.1492, found 332.1498, calcd. for $C_{18}H_{21}NNaO_5$ $[M+Na]^+$ requires 354.1312, found 354.1319; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 3388, 2227, 1707, 1673, 1496, 1472, 1447, 1308, 1161, 1076, 1032, 812, 751; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.39 – 7.32 (5H, m, Ar*H*), 5.13 (2H, s, CH_2Ph), 4.24 (2H, q, *J* 7.2, OCH_2), 3.80 – 3.77 (2H, m, CH_aH$_b$-2, CH_aH$_b$-6), 3.48 – 3.42 (2H, m, CH$_a$$H_b$-2, CH$_a$$H_b$-6), 2.33 (1H, br s, O*H*), 2.02 – 1.91 (2H, m, CH_aH$_b$-3, CH_aH$_b$-5), 1.85 – 1.73 (2H, m, CH$_a$$H_b$-3, CH$_a$$H_b$-5), 1.31 (3H, t, *J* 7.2, CH$_2$CH_3); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 155.2, 153.4, 136.7, 128.7, 128.2, 128.0, 88.4, 76.8, 67.5, 66.4, 62.5, 40.5, 38.1, 14.1.

7-Benzyl 2-ethyl 3-oxo-1-oxa-7-azaspiro[3.5]nonane-2,7-dicarboxylate, 8



A solution of alkyne **7** (5.63 g, 17.0 mmol) in dry dichloroethane (68 mL) was prepared under nitrogen. To this was added sequentially, 4-acetylpyridine *N*-oxide (4.66 g, 34.0 mmol), a solution of trifluoromethanesulfonimide (5.74 g, 20.4 mmol) in dry dichloroethane (100 mL) and *i*PrAuNTf$_2$ (0.368 g, 0.43 mmol). The solution was then heated to 60 °C and stirred at this temperature for 24 h. After this time, the solvent was removed *in vacuo*. Purification by column chromatography (40% ethyl acetate in light petroleum) to give the *title compound* **8** as a yellow oil (3.83 g, 65%): $\boldsymbol{R_f}$ 0.65 (50% ethyl acetate in light petroleum, UV inactive, weakly $KMnO_4$ active); **HRMS** *m/z* (ESI$^+$) calcd. for $C_{18}H_{21}NNaO_6$ $[M+Na]^+$ requires 370.1261, found 370.1259; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 1823, 1747, 1695, 1429, 1237, 1198, 1003, 907, 727; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (5H, m, Ar*H*), 5.72 (1H, s, C*H*), 5.13 (2H, s, CH_2Ph), 4.37 – 4.20 (2H, m, CH_2), 3.76 – 3.56 (4H, m, CH_2), 2.15 – 1.88 (4H, m, CH_2), 1.31 (3H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 196.4, 165.0, 155.2, 136.6, 128.7, 128.3, 128.1, 108.0, 93.7, 67.6, 62.6, 40.1 (2C), 31.9, 31.5, 14.3.

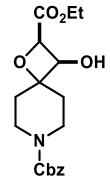
Benzyl 4-(benzylcarbamoyl)-4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate, 10



A solution of the ketone **8** (52 mg, 0.15 mmol) in dry dichloroethane (3.3 mL) was prepared under nitrogen. To this was added benzylamine (24 mg, 25 µL, 0.22 mmol) followed by glacial acetic acid (20 µL, 0.35 mmol) and the reaction mixture was stirred at room temperature for 2 h. After this time sodium triacetoxyborohydride (64 mg, 0.30 mmol) was added. The suspension was then stirred at room

temperature for an additional 18 h until the disappearance of the starting material was confirmed by TLC (50% ethyl acetate in light petroleum). The reaction was quenched by the addition of water (5 mL) and stirred for 1 h. The reaction was extracted with dichloromethane (3 × 5 mL) and the organic phases were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (50% ethyl acetate in light petroleum to 100% ethyl acetate) gave the *title compound* **10** as a colourless oil (24 mg, 35%): R_f 0.70 (50% ethyl acetate in light petroleum, weakly UV active, $KMnO_4$ active); **HRMS** *m/z* (ESI^+) calcd. for $C_{24}H_{31}N_2O_5$ $[M+H]^+$ requires 427.2227, found 427.2230; ν_{max} (ATR)/cm^{-1} 1722, 1672, 1640, 1537, 1450, 1242, 1220, 1000; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* 5.9, N*H*), 7.30 – 7.15 (10H, m, Ar*H*), 5.05 (2H, s, OCH_2Ph), 4.22 (2H, d, *J* 6.0, NCH_2Ph), 4.03 – 3.87 (6H, m, OC$H_2$$CO_2Et, OCH_2$$CH_3$, C$H_2$), 3.15 – 2.97 (2H, m, C$H_2$), 2.11 – 1.96 (2H, m, C$H_2$), 1.78 – 1.62 (2H, m, C$H_2$), 1.12 (3H, t, *J* 7.6, CH_2CH_3); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 173.0, 170.2, 155.2, 138.3, 136.7, 128.7, 128.5, 128.0, 127.9, 127.8, 127.5, 80.2, 67.2, 62.7, 61.6, 43.3, 39.7, 31.7, 14.0.

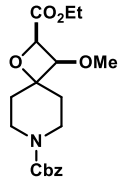
7-Benzyl 2-ethyl (2*R,3*R**)-3-hydroxy-1-oxa-7-azaspiro[3.5]nonane-2,7-dicarboxylate, 11**



A solution of the ketone **8** (3.51 g, 10.1 mmol) in dry dichloroethane (222 mL) was prepared under nitrogen. To this was added sodium triacetoxyborohydride (4.29 g, 20.2 mmol) immediately followed by glacial acetic acid (0.98 mL, 17.2 mmol) and the suspension was stirred at room temperature for 17 h. After this time, additional sodium triacetoxyborohydride (2.14 g, 10.1 mmol) and glacial acetic acid (0.5 mL, 8.1 mmol) were added. The suspension was then stirred at room temperature for an additional 18 h until the disappearance of the starting material was confirmed by TLC (50% ethyl acetate in light petroleum). The reaction was quenched by the addition of water (100 mL) and stirred for 15 min. The

reaction was extracted with dichloromethane (3 × 100 mL) and the organic phases were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a pale yellow oil (3.67 g). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed a 20:1 ratio of diastereomers (*syn*:*anti).* Purification by column chromatography (50% ethyl acetate in light petroleum) gave the major diastereomer **11** as a white oily solid (2.70 g, 77%): $\boldsymbol{R_f}$ 0.21 (50% ethyl acetate in light petroleum, UV inactive, $KMnO_4$ active); **HRMS** *m/z* (ESI^+) calcd. for $C_{18}H_{24}NO_6$ $[M+H]^+$ requires 350.1598, found 350.1599, calcd. for $C_{18}H_{23}NNaO_6$ $[M+Na]^+$ requires 372.1418, found 372.1415; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 3384, 1721, 1702, 1422, 1222, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 - 7.29 (5H, m, Ar*H*), 5.12 (2H, s, CH_2Ph), 5.08 (1H, d, *J* 7.1, C*H*), 4.58 (1H, d, *J* 7.1, CH), 4.35 - 4.23 (2H, m, CH_2), 3.73 – 3.62 (2H, m, CH_2), 3.47 (2H, tdd, *J* 13.2, 9.2, 3.7, CH_2), 3.02 (1H, br s, O*H*), 2.10 – 1.72 (4H, m, CH_2), 1.31 (3H, t, *J* 7.1, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.5, 155.4, 136.8, 128.6, 128.2, 128.0, 89.0, 78.8, 72.2, 67.3, 61.7, 40.1, 40.0, 36.6, 30.8, 14.4.

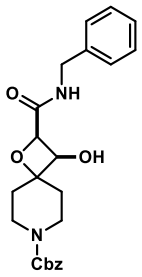
7-Benzyl 2-ethyl (2*R,3*R**)-3-methoxy-1-oxa-7-azaspiro[3.5]nonane-2,7-dicarboxylate, 12**



Silver(II) oxide (660 mg) was added to a solution of alcohol 11 in iodomethane (12.2 g, 5.3 mL, 86.0 mmol). The reaction mixture was stirred at 45 °C for 48 h. Following this time, the reaction mixture was cooled to room temperature and filtered under vaccum, the filtrate was washed with dichloromethane (3 × 10 mL). The solvent was removed *in vacuo*. Purification by column chromatography (50% ethyl acetate in light petroleum) to give the title compound **12** as a colourless oil (150 mg, 72%). $\boldsymbol{R_f}$ 0.60 (50% ethyl acetate in light petroleum, UV inactive, $KMnO_4$ active); **HRMS** *m/z* (ESI^+) calcd. for $C_{19}H_{25}NNaO_6$ $[M+Na]^+$ requires 386.1574, found 386.1575; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 2933, 1750, 1693, 1428, 1226, 1192, 1131, 1038, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (5H, m, Ar*H*), 5.13 (1H, d, *J* 7.3, C*H*OMe), 4.28 (2H, q, *J*

7.3, CH_2), 4.13 (1H, d, J 7.3, C*H*), 3.81 – 3.68 (2H, m, CH_2), 3.47 – 3.36 (2H, m, CH_2), 3.36 (3H, s, OCH_3), 2.14 – 1.77 (4H, m, CH_2), 1.31 (3H, t, *J* 7.3, CH_2CH_3); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 170.0, 155.4, 136.9, 128.6, 128.1, 128.0, 89.0, 81.0, 79.2, 67.3, 61.3, 59.4, 40.1, 40.0, 37.2, 30.9, 14.4.

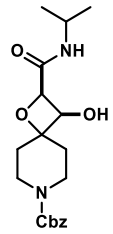
Benzyl (2*R,3*R**)-2-(benzylcarbamoyl)-3-hydroxy-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate, 13**



Benzylamine (87 µL, 0.80 mmol) was added to a suspension of DABAL-Me_3 (0.21 g, 0.80 mmol) in dry THF (4.3 mL) under nitrogen in a Schlenk flask. The flask was sealed and the reaction mixture was stirred at 40 °C for 1 h. After this time, a solution of the ester **11** (187 mg, 0.54 mmol) in dry THF (2 mL) was added and the reaction mixture was stirred at 65 °C for 20 h. The disappearance of the starting material was observed by TLC (100% ethyl acetate) and the reaction mixture was cooled to room temperature. Aqueous ammonium chloride solution (saturated, 10 mL) was added and the product was extracted with ether (3 × 10 mL). The solvent was removed *in vacuo*. Purification by column chromatography (100% ethyl acetate) to give the *title compound* **13** as a colourless oil (160 mg, 71%). $\boldsymbol{R_f}$ 0.41 (100% ethyl acetate, weakly UV active, $KMnO_4$ active); **HRMS** *m/z* (ESI^+) calcd. for $C_{23}H_{27}N_2O_5$ $[M+H]^+$ requires 411.1914, found 411.1913, calcd. for $C_{23}H_{26}N_2NaO_5$ $[M+Na]^+$ requires 433.1734, found 433.1731; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 3172, 1682, 1646, 1537, 1451, 1431, 1234, 1223, 1002, 729, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (10H, m, Ar*H*), 7.17 (1H, t, *J* 6.0, N*H*), 5.11 (2H, s, CH_2Ph), 4.98 (1H, d, *J* 6.6, C*H*), 4.64 (1H, dd, *J* 15.0, 6.0, NC$H_a$$H_b$Ph), 4.56 (1H, d, *J* 6.6, C*H*), 4.44 (1H, dd, *J* 15.0, 6.0, NCH_aH_bPh), 4.05 (1H, br s, O*H*), 3.60 – 3.43 (4H, m, CH_2), 1.98 (1H, dt, *J* 12.8, 5.7, C$H_a$$H_b$), 1.83 (2H, br s, C$H_2$), 1.76 – 1.69 (1H, m, CH_aH_b);

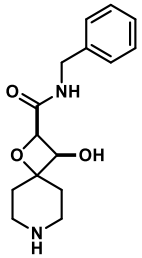
^{13}C NMR (100 MHz; $CDCl_3$) δ 170.5, 155.3, 137.5, 136.8, 129.0, 128.7, 128.2, 128.0, 127.9, 127.6, 88.5, 79.0, 71.6, 67.4, 43.0, 40.33, 40.26, 36.5, 31.5.

Benzyl (2*R,3*R**)-3-hydroxy-2-(isopropylcarbamoyl)-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate, 14**



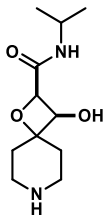
iso-Propylamine (74 µL, 0.86 mmol) was added to a suspension of DABAL-Me_3 (220 mg, 0.86 mmol) in dry THF (4.6 mL) under nitrogen in a Schlenk flask. The flask was sealed and the reaction mixture was stirred at 40 °C for 1 h. After this time, a solution of the ester **11** (200 mg, 0.57 mmol) in dry THF (2 mL) was added and the reaction mixture was stirred at 65 °C for 20 h. The disappearance of the starting material was observed by TLC (100% ethyl acetate) and the reaction mixture was cooled to room temperature. Aqueous ammonium chloride solution (saturated, 10 mL) was added and the product was extracted with ether (3 × 10 mL). The solvent was removed *in vacuo*. Purification by column chromatography (100% ethyl acetate) to give the *title compound* **14** as a colourless oil (140 mg, 69%). $\boldsymbol{R_f}$ 0.28 (100% ethyl acetate, weakly UV active, $KMnO_4$ active); **HRMS** *m/z* (ESI^+) calcd. for $C_{19}H_{27}N_2O_5$ $[M+H]^+$ requires 363.1914, found 363.1906, calcd. for $C_{19}H_{26}N_2NaO_5$ $[M+Na]^+$ requires 385.1734, found 385.1734; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 3328, 1652 (2), 1532, 1428, 1223, 998, 729; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (5H, m, Ar*H*), 6.69 (1H, d, *J* 8.4, N*H*), 5.12 (2H, s, CH_2Ph), 4.87 (1H, d, *J* 6.4, C*H*), 4.59 – 4.56 (2H, m, OH and C*H*), 4.13 (1H, dsept, *J* 8.4, 6.6, C*H*), 3.66 – 3.44 (4H, m, CH_2), 2.03 – 1.77 (4H, m, CH_2), 1.21 (3H, d, *J* 6.6, CH_3), 1.17 (3H, d, *J* 6.6, CH_3); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 169.7, 155.3, 136.8, 128.6, 128.1, 128.0, 88.6, 79.3, 71.4, 67.3, 41.2, 40.4, 40.3, 36.6, 31.5, 23.0, 22.7.

(2*R,3*R**)-*N*-Benzyl-3-hydroxy-1-oxa-7-azaspiro[3.5]nonane-2-carboxamide, 15**



Palladium on carbon (10%, 44 mg) was added to a solution of amide **12** (440 mg, 1.07 mmol) in trifluoroethanol (20 mL). The flask was evacuated and a balloon of hydrogen introduced. The suspension was then stirred at room temperature for 26 h. After this time, the disappearance of the starting material was observed by TLC. The reaction mixture was filtered through Celite and extracted with dichloromethane (3 × 10 mL). The solvent was removed *in vacuo* to give the *title compound* **15** as a white crystalline solid (291 mg, 99%): **mp** 69-70 °C; **HRMS** *m/z* (ESI^+) calcd. for $C_{15}H_{21}N_2O_3$ $[M+H]^+$ requires 277.1547, found 277.1544, calcd. for $C_{15}H_{20}N_2NaO_3$ $[M+Na]^+$ requires 299.1366, found 299.1362; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 3250, 2923, 1652, 1526, 1128, 992, 730, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (5H, m, Ar*H*), 7.22 (1H, t, *J* 6.0, N*H*), 4.98 (1H, d, *J* 7.0, C*H*), 4.62 (1H, dd, *J* 15.0, 6.0, NCH_aH$_b$Ph), 4.57 (1H, d, *J* 7.0, C*H*), 4.44 (1H, dd, *J* 15.0, 6.0, NCH$_a$$H_b$Ph), 3.01– 2.79 (6H, m, O*H*, N*H* and 2 × CH_2), 2.09 – 2.03 (1H, m, CH_2), 1.94 – 1.81 (2H, m, CH_2), 1.75 – 1.68 (1H, m, CH_2); **^{13}C NMR** (100 MHz; $CDCl_3$) 170.6, 137.7, 128.9, 127.7, 127.6, 88.8, 79.2, 71.9, 43.0, 42.7, 42.5, 37.5, 32.3.

2*R,3*R**)-3-Hydroxy-*N*-isopropyl-1-oxa-7-azaspiro[3.5]nonane-2-carboxamide, 16**



Palladium on carbon (10%, 58 mg) was added to a solution of amide **13** (580 mg, 1.60 mmol) in trifluoroethanol (20 mL). The flask was evacuated and a balloon of hydrogen introduced. The suspension was then stirred at room temperature for 24 h. After this time, the disappearance of the starting material was observed by TLC. The reaction mixture was filtered through Celite and extracted with dichloromethane (3 × 10 mL). The solvent was removed *in vacuo* to give the *title compound* **16** as a yellow oily solid (358 mg, 98%). **HRMS** *m/z* (ESI^+) calcd. for $C_{11}H_{21}N_2O_3$ $[M+H]^+$ requires 229.1547, found 229.1545, calcd. for $C_{11}H_{20}N_2NaO_3$ $[M+Na]^+$ requires 251.1366, found 251.1365; $\boldsymbol{\nu_{max}}$ (ATR)/cm^{-1} 3290, 2932, 1656, 1531, 1130, 999; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.71 (1H, d, *J* 8.4, N*H*), 4.86 (1H, d, *J* 6.9, C*H*), 4.55 (1H, d, *J* 6.9, C*H*), 4.14 (1H, dsept, *J* 8.4, 6.5, C*H*), 3.23 (2H, br s, O*H* and N*H*), 3.03 – 2.96 (2H, m, CH_2), 2.89 – 2.79 (2H, m, CH_2), 2.11 – 2.05 (1H, m, CH_2), 1.94 – 1.70 (3H, m, CH_2), 1.21 (3H, d, *J* 6.5, CH_3), 1.17 (3H, d, *J* 6.5, CH_3); **^{13}C NMR** (100 MHz; $CDCl_3$) 169.7, 89.0, 78.9, 71.7, 42.8, 42.6, 41.2, 37.9, 32.6, 23.0, 22.7.

Author Contributions

AN conceived the project, and with GCG, carried out all the synthesis and analysis of scaffold structures, overseen by CJM; CAP conducted the library syntheses overseen by DH and GJ. AN wrote the paper with contributions from CJM, GCG and DH.

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A. Supplementary Material

Electronic Supplementary Information (ESI) available: experimental details for library generation, copies of ^{1}H and ^{13}C NMR spectra. See DOI: xxxxxxxx

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