Seven-membered ring scaffolds for drug discovery: Access to functionalised azepanes and oxepanes through diazocarbonyl chemistry.

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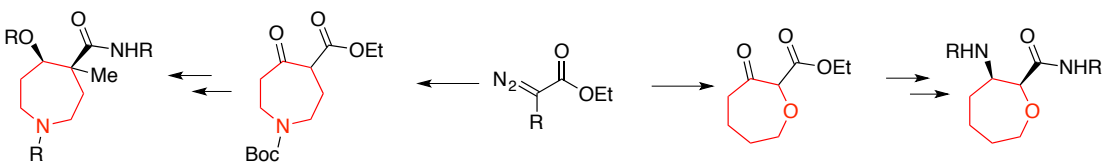
Graphical Abstract



Abstract:

Functionalised azepane and oxepane scaffolds were prepared using diazocarbonyl chemistry and elaborated to show their potential use in library synthesis. Key dicarbonyl containing seven-membered rings were functionalised *via* diastereoselective Luche reduction of the ketone followed by manipulation of the

ester and amine groups. Further scaffolds could be accessed by *C*-alkylation of the dicarbonyl compounds. In addition, an oxepane containing amino acid could be prepared *via* a diastereoselective enamine reduction.

1. Introduction

Seven-membered ring heterocycles are widely found in both natural products and medicinally active molecules. These include the azepanes claviciptic acid, imipramine and balanol, and the oxepanes (+)-isolaurepan, doxepin and hemibrevetoxin B (Figure 1).[1]

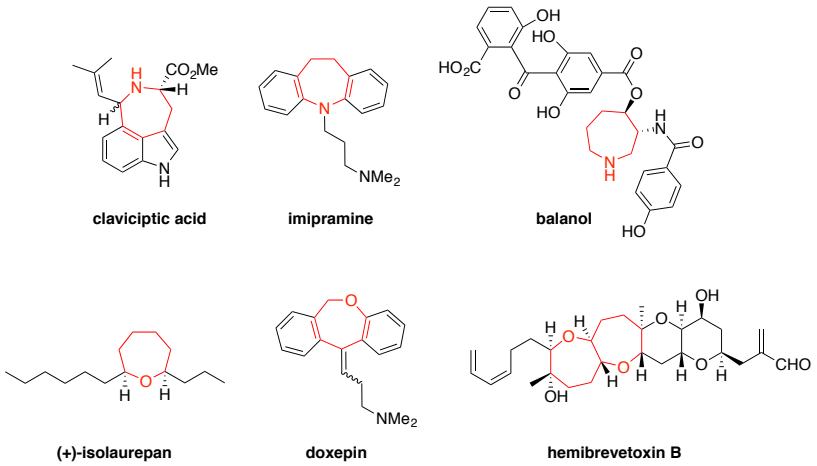


Figure 1: Azepane and oxepane containing natural products and pharmaceuticals.

Azepanes feature in the top 100 frequently used ring systems in small molecules,[2] with the dibenzazepine scaffold featuring in a wide number of analgesic and antipsychotic agents.[3,4] Synthetic methods towards the synthesis of azepane containing scaffolds have garnered significant attention,[5,6] with a wide range of reported methodologies for their preparation, including ring-closing metathesis,[7] ring-expansion,[7,8] halo-cyclisation[9] and intramolecular reductive amination.[10] Oxepane scaffolds are widely found in polyether containing natural products such as the brevetoxin[11,12] and ciguatoxin families.[13,14] Relative to five- and six-membered oxygen containing heterocycles, oxepanes are synthetically more challenging due to enthalpic and entropic constraints.[15–17] Methods towards oxepanes are diverse,[5,6,18]

with recent notable examples including organocatalytic intramolecular oxa-conjugate addition,[19] iron(III) catalysed Prins cyclisation,[20] and ring-closing ene-yne metathesis.[21]

Seven-membered rings are often flanked by aromatic ring systems and these bi- and tricyclic systems have interesting activity on the central nervous system.[1] However, this type of scaffold adds significant sp^2 character to the overall compound. In an effort to synthesise scaffolds rich in sp^3 character we report the preparation of azepane and oxepane cores through diazocarbonyl chemistry.

2. Results and discussion

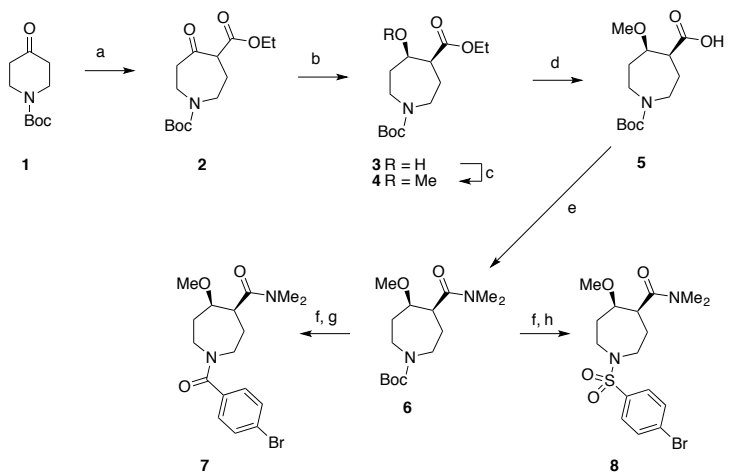
Diazo compounds have attracted great interest in organic synthesis due to their versatility as synthetic intermediates.[22] The diazo group can easily be introduced into activated methylene groups *via* Regitz diazo-transfer using sulfonyl azides as the transfer reagent.[23] Diazocarbonyl compounds generated by this method are bench stable with predictable reactivity that can be attuned to the synthetic task at hand. The main synthetic feature is the generation of a carbene or metal carbenoid to generate a reactive intermediate that undergoes a wide range of C-H and X-H insertions (X = O, N, S, Si, P). These insertion reactions provide a valuable disconnection in organic synthesis. Diazoalkanes are also used in the Lewis acid-catalysed ring expansion of cyclic ketones[24,25] that proceed via a Tiffenau-Demjanov-type intermediate, wherein the loss of molecular nitrogen drives the one-carbon ring expanded cyclic ketone.

Herein, we report the synthesis of an azepane and oxepane scaffold using these two aspects of diazocarbonyl chemistry as the key steps for the generation of the seven-membered ring. In addition, we describe the synthetic manipulation of these structures to allow for further structural elaboration suitable for the preparation of compound libraries.

2.1 Azepane scaffold

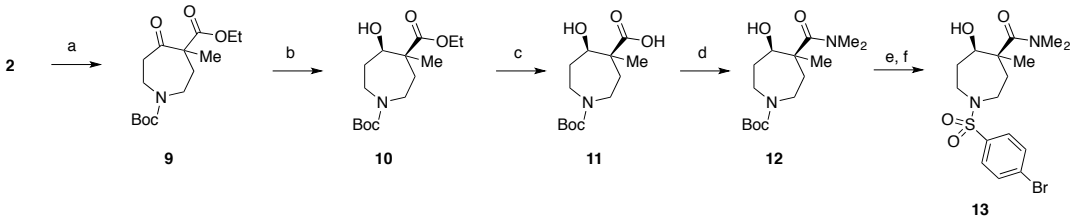
The Tiffeneau-Demjanov-type ring expansion of *N*-Boc-piperidone **1** to the corresponding dicarbonyl azepane **2** is widely documented in the literature.[8] However, the use of **2** has generally been restricted to its reactions as a 1,3-dicarbonyl building block for the preparation of spirocyclic hydantion,[26] fused pyrimidine[27] or pyrazolone scaffolds.[28] We sought to use azepane **2** as core scaffold with no further ring fusion.

In our hands, the ring expansion of **1** provided the desired azepane **2** in 85% without the need for chromatographic purification (Scheme 1). Diastereoselective reduction of the ketone under Luche conditions at -78 °C furnished the *syn*-β-ketoalcohol **3** in 62% in a 19:1 ratio of separable diastereomers (Scheme 1).[29] Alcohol **3** exists in two ring conformers which readily invert on the NMR timescale. This ring inversion results in complication of the NMR spectra for this compound and later compounds in this series. Attempts to *O*-alkylate the alcohol **3** using NaH or Ag_2O as a base with MeI or BnBr were unsuccessful, as was benzylation using benzyl trichloroacetimidate/TfOH. Methylation was accomplished using trimethyloxonium tetrafluoroborate and proton sponge to afford the methyl ether **4** in 81% yield (Scheme 1). Ester hydrolysis and subsequent amide formation with dimethylamine as a model amine furnished the amide **6** in 90% yield (Scheme 1). Deprotection of the *tert*-butoxycarbonyl group with hydrochloric acid with subsequent amide formation or sulfonylation provided the elaborated scaffolds **7** and **8** (Scheme 1).



Scheme 1: Synthesis of compounds **2**-**8**. *Reagents and conditions*: (a) ethyl diazoacetate, $BF_3.OEt_2$, Et_2O, -20 ° C to 0 ° C, rt, 3 h, 85%; (b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ° C, 1 h, 62%; (c) trimethyloxonium tetrafluoroborate, proton sponge, CH_2Cl_2, 0 ° C to rt, 16 h, 81%; (d) LiOH, THF:MeOH:H_2O, 0 ° C to rt, 16 h, 82%; (e) dimethylamine hydrochloride, HATU, *i*PrNEt$_2$, DMF/CH_2Cl_2 (1:1), 0 ° C to r.t, 16 h, 90%; (f) 4M HCl/dioxane solution, CH_2Cl_2, rt, 16 h, quant.; (g) 4-bromobenzoic acid, HATU, *i*PrNEt$_2$, DMF/CH_2C_{l2} (1:1), 0 ° C to r.t ,16 h, 50%; (h) 4-bromobenzenesulfonyl chloride, pyridine, NEt_3, CH_2Cl_2, 0 ° C to r.t, 16 h, 96%.

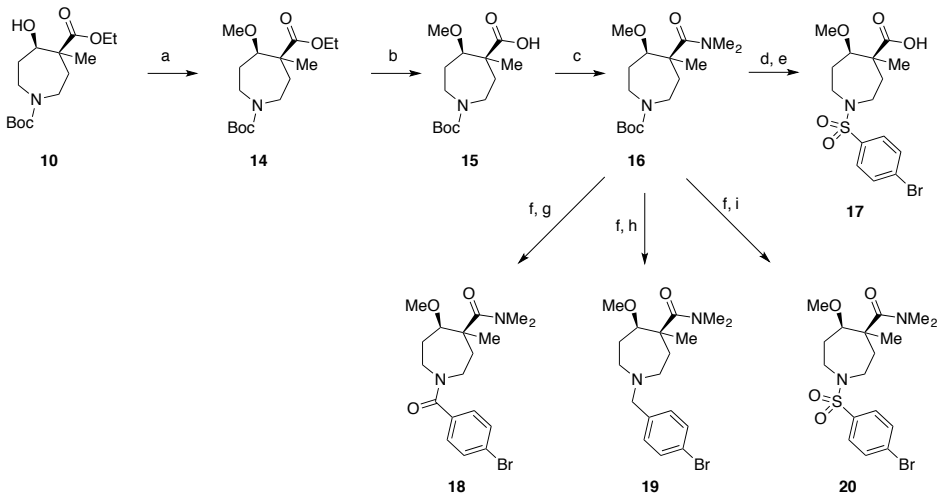
Azepane **2** also underwent *C*-alkylation using caesium carbonate and iodomethane to provide the quaternary carbon centre in ester **9** (Scheme 2). Following similar steps as previously described, Luche reduction provided *syn*-alcohol **10** in a 9:1 ratio of separable diastereomers (Scheme 2).[29] Ester hydrolysis of alcohol **10** provided carboxylic acid **11**, which was effectively transformed into the dimethylamide **12** in 50% yield (Scheme 1). Deprotection of the Boc-group of dimethylamide **12** with HCl provided the desired amine which underwent sulfonylation to give brosylate **13** in 55% yield (Scheme 2).



Scheme 2: Synthesis of compounds **9**-**13**. *Reagents and conditions*: (a) MeI, Cs_2CO_3, DMF, 0 ° C to r.t, 16 h, 92%; (b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ° C, 1 h, 62%; (c) LiOH, dioxane:H_2O, reflux, 16 h, quant.; (d) dimethylamine hydrochloride, HATU, *i*PrNEt$_2$, DMF/CH_2Cl_2 (1:1), 0 ° C to r.t, 16 h, 50%; (e) 4M HCl/dioxane solution, CH_2Cl_2, rt, 16 h, quant.; (f) 4-bromobenzenesulfonyl chloride, pyridine, NEt_3, CH_2Cl_2, 0 ° C to r.t, 16 h, 55%.

Similarly, methylation of alcohol **10** with trimethyloxonium tetrafluoroborate/proton sponge furnished the desired methyl ether **14** in 77% yield (Scheme 3). Methyl ether **14** underwent the same transformation to provide acid **15** and dimethylamide **16**

(Scheme 3). Treatment of **16** with HCl resulted in deprotection of the dimethylamide along with the *tert*-butoxycarbonyl group, this was confirmed by brosylation to give the acid **17** (Scheme 3). Selective Boc deprotection was accomplished by reaction with trifluoroacetic acid (Scheme 3) followed by amide formation, reductive amination or sulfonylation to provide compounds **18**, **19** and **20** respectively (Scheme 3).

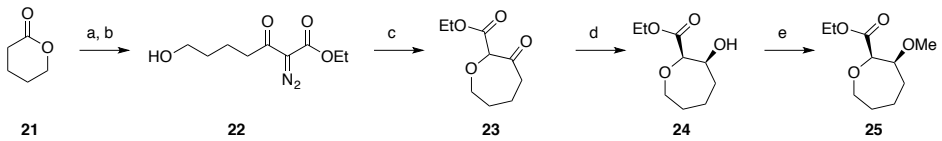


Scheme 3: Synthesis of compounds **14**-**20**. *Reagents and conditions*: (a) trimethyloxonium tetrafluoroborate, proton sponge, CH_2Cl_2, 0 ° C to rt, 16 h, 81%; (b) LiOH, dioxane:H_2O, reflux, 16 h, quant.; (c) dimethylamine hydrochloride, HATU, *i*$PrNEt_2$, DMF/CH_2Cl_2 (1:1), 0 ° C to r.t, 16 h, 72%; (d) 4M HCl/dioxane solution, CH_2Cl_2, rt, 16 h, quant.; (e) 4-bromobenzenesulfonyl chloride, pyridine, NEt_3, CH_2Cl_2, 0 ° C to r.t, 16 h, 45%; (f) TFA, CH_2Cl_2, rt, 3 h, quant.; (g) 4-bromobenzoic acid, HATU, *i*$PrNEt_2$, DMF/CH_2Cl_2 (1:1), 0 ° C to r.t ,16 h, 50%; (h) 4-bromobenzaldehyde, $Na(OAc)_3BH$, 1,2-dichloroethane, 0 ° C to r.t, 16 h, 62%; (i) 4-bromobenzenesulfonyl chloride, pyridine, NEt_3, CH_2Cl_2, 0 ° C to r.t, 16 h, 40%.

2.2 Oxepane scaffold

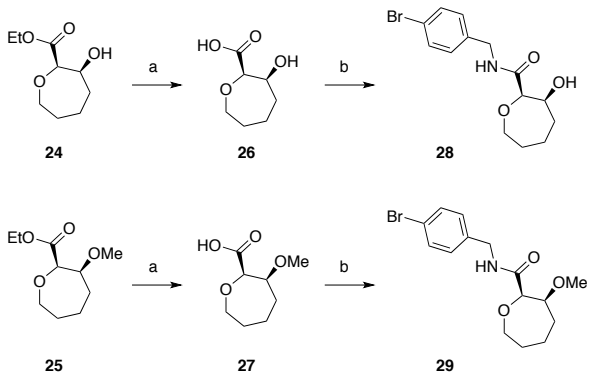
The key oxepane scaffold **23** was prepared *via* an intramolecular carbene O-H insertion. The precursor diazocarbonyl compound **22** has previously been reported through the addition of lithiated ethyl diazoacetate to δ-valerolactone **21**.[30] In our hands this proved difficult to replicate on decagram scale, and therefore we chose to follow the “one-pot” addition-diazotransfer reported by Chen *et al*.[31] This proceeded in 78% over 2 steps on a 10 g scale (Scheme 4). Intramolecular O-H insertion was

effected using rhodium(II) acetate in dichloromethane to provide oxepane dicarbonyl ether **23** in 75% on a multigram scale (Scheme 4).[30] Ether **23** was of sufficient purity to be carried onto next step without the need for further purification. Luche reduction ($CeCl_3/NaBH_4$) provided the alcohol as a 2:1 mixture of diastereomers (Scheme 4),[29] with the *syn*-alcohol **24** being isolated in 53% yield after chromatography. Interestingly, alcohol **24** exists as a single conformer on the NMR timescale. Methylation with trimethyloxonium tetrafluoroborate/proton sponge gave methyl ether **25** in 87% yield (Scheme 4).



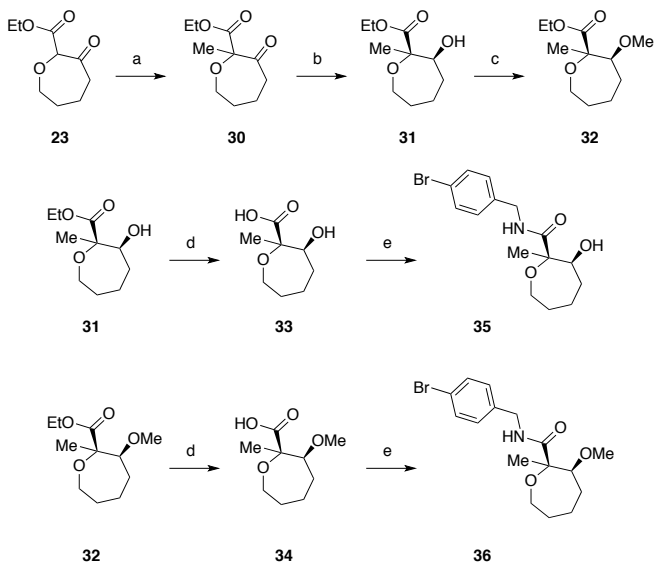
Scheme 4: Synthesis of compounds **22**-**25**. *Reagents and conditions*: (a) i. LDA, THF, -78 ° C, 0.5 h, ii. EtOAc, -78 ° C, 0.5 h, iii. lactone **21**, -78 ° C, 2 h; (b) *p*-acetamidobenzenesulfonyl azide, Et_3N, CH_3CN, -0 ° C, 16 h, 78%; (c) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 1.5 h, 75%; (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ° C, 1 h, 53%; (e) trimethyloxonium tetrafluoroborate, proton sponge, CH_2Cl_2, 0 ° C to rt, 16 h, 87%.

Subsequent hydrolysis of esters **24** and **25** provided the corresponding carboxylic acids **26** and **27** respectively (Scheme 5). Functionalisation of these scaffolds *via* an amide provides a point of further molecular diversity. This was exemplified by formation of the 4-bromobenzylamides **28** and **29** in 88 and 77% yield (Scheme 5).



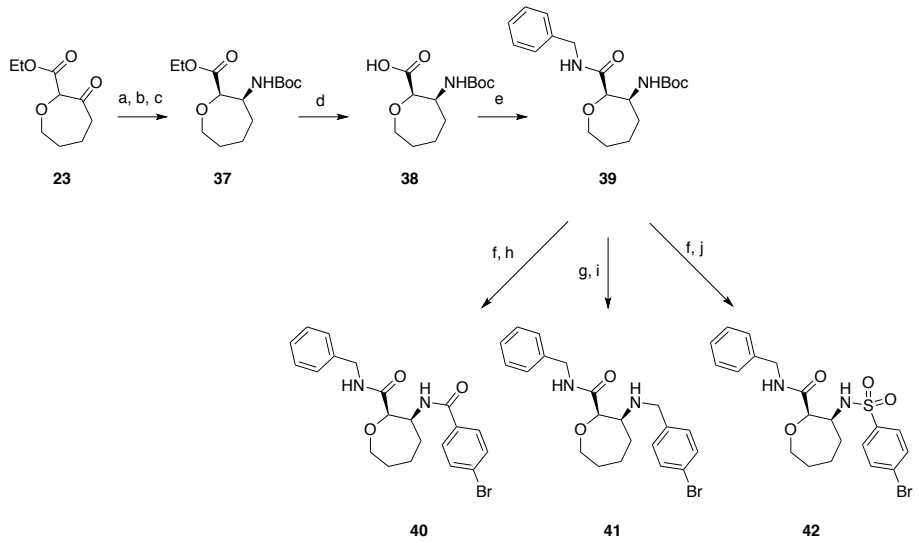
Scheme 5: Synthesis of compounds **26**-**29**. *Reagents and conditions*: (a) LiOH, THF:MeOH:H_2O, 0 ° C to rt, 16 h, **26** = quant, **27** = quant; (b) 4-bromobenzylamine hydrochloride, HATU, *i*PrNEt_2, DMF, 0 ° C to r.t, 16 h, **28** = 77%, **29** = 88%.

As with the azepane scaffold, a quaternary centre could be accessed by the *C*-alkylation of oxepane **23** with caesium carbonate and iodomethane providing oxepane **30** in 62% yield on a multigram scale (Scheme 6). Subsequent Luche reduction furnished the alcohol **31** as an inseperable mixture of diastereomers (15:1 ratio) in quantitative yield (Scheme 6).[29] Methylation with Meerweins salt gave the methyl ether **32** in 88% (15:1 *dr*) (Scheme 6). Subsequent hydrolysis of esters **31** and **32** was undertaken with lithium hydroxide providing carboxylic acids **33** and **34** (15:1 *dr*) (Scheme 6). Elaboration as the amides was carried out using 4-bromobenzylamine and HATU. The desired amides **35** and **36** were isolated in excellent yield as single diastereomers (Scheme 6).



Scheme 6: Synthesis of compounds **30**-**36**. *Reagents and conditions*: (a) MeI, Cs_2CO_3, DMF, 0 ° C to r.t, 16 h, 62%; (b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ° C, 1 h, quant., 15:1 *dr*; (c) trimethyloxonium tetrafluoroborate, proton sponge, CH_2Cl_2, 0 ° C to rt, 16 h, 88%, 15:1 *dr*; (d) LiOH, dioxane:H_2O, reflux, 16 h, **33** = quant, 15:1 *dr,* **34** = quant, 15:1 *dr*; (e) 4-bromobenzylamine hydrochloride, HATU, *i*PrNEt_2, DMF, 0 ° C to r.t, 16 h, **35** = 92% (OH), **36** = 80% (OMe).

The β-ketoester oxepane **23** could additionally be converted to Boc-protected amino acid **37** (Scheme 7). Treatment of dicarbonyl compound **23** with ammonium acetate generated the enamine that was immediately reduced with sodium cyanoborohydride to generate the amine (Scheme 7).[32,33] Boc-protection of the amine with di-*tert*-butyl dicarbonate provided the *syn*-Boc-protected amino acid **37** in a 64% yield over 3 steps in 6.5:1 diastereomeric ratio with the *trans*-isomer (Scheme 7). Ester hydrolysis with lithium hydroxide gave the carboxylic acid **38** in quantitative yield (6.5:1 dr) (Scheme 7). HATU mediated amide coupling of acid **38** with benzylamine gave the amide **39** in 70% yield as a single diastereoisomer (Scheme 7). *tert*-Butoxycarbonyl deprotection could be accomplished using HCl or trifluoroacetic acid followed by amide formation, reductive amination and sulfonylation to provide compounds **40**, **41** and **42** in excellent yield (Scheme 7).



Scheme 7: Synthesis of compounds **37**-**42**. *Reagents and conditions*: (a) ammonium acetate, MeOH, r.t, 16 h; (b) $NaBH_3CN$, AcOH, THF, 0 ° C, 1 h; (c) Boc_2O, Et_3N, CH_2Cl_2, r.t, 16 h, 64% over 3 steps; (d) LiOH, THF:MeOH:H_2O, r.t, 16 h, quant, 6.5:1 *dr*; (e) benzylamine, HATU, *i*$PrNEt_2$, DMF, 0 ° C to r.t, 16 h, 70%; (f) 4M HCl/dioxane solution, CH_2Cl_2, r.t, 3 h, quant; (g) TFA, CH_2Cl_2, r.t, 3 h, quant; (h) (g) 4-bromobenzoic acid, HATU, *i*$PrNEt_2$, DMF (1:1), 0 ° C to r.t, 16 h, 94%; (h) 4-bromobenzaldehyde, $Na(OAc)_3BH$, 1,2-dichloroethane, 0 ° C to r.t, 16 h, 82%; (i) 4-bromobenzenesulfonyl chloride, pyridine, NEt_3, CH_2Cl_2, 0 ° C to r.t, 16 h, 98%.

3. Conclusion

We have developed a series of azepane and oxepane scaffolds through the use of diazocarbonyl chemistry to construct the seven-membered ring. The scaffolds can be further elaborated and functionalised to allow for the preparation of compound libraries containing seven-membered rings.

4. Acknowledgements

We thank Dr Daniel Hamza (Sygnature Discovery) for helpful discussions. The research leading to these results was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution.

5. Supplementary information

Full experimental details and NMR spectra for all compounds are provided in the Supplementary Information.

6. General Experimental Procedures

C-alkylation

To a solution of β-ketoester (1 equiv.) in dry DMF at 0 °C, was added caesium carbonate (1.05 equiv.) and stirred for 15 min. Methyl iodide (2.5 equiv) was added slowly. The solution was allowed to warm to room temperature and stirred for 15 h. The solution was concentrated

in vacuo and diluted with ether and water. The organic layer was separated and the aqueous layer extracted with ether). The organic layers were combined and washed with aqueous ammonium chloride (saturated) and brine. The organics were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the desired quaternary alkylated product.

Luche reduction

To a solution of β-ketoester (1 equiv.) in dry methanol was added $CeCl_3.7H_2O$ (1.05 equiv.) and cooled to -78 °C. Sodium borohydride (0.7 equiv.) was added in small portions. Upon complete addition the solution was stirred for a further hour at -78 °C. The reaction was quenched with aqueous hydrochloric acid (2M) and warmed to room temperature. The reaction mixture was extracted with ether. The organic layers were combined and washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude residue was diluted with dichloromethane and evaporated onto silica gel. Purification by silica gel chromatography, eluting with ethyl acetate and light petroleum (5:95 to 15:85), provided the desired alcohol

Methylation with Meerwein Salt

To a solution of alcohol (1 equiv.) in dry dichloromethane at 0 °C was added proton sponge (3-8 equiv.), followed by trimethyloxonium tetrafluoroborate (2.5-4 equiv.). The suspension was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with aqueous ammonium chloride (saturated) and diluted with dichloromethane. The reaction mixture was partitioned and the aqueous phase extracted with dichloromethane. The organic layers were combined and washed with aqueous hydrochloric acid (2M) and brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was uptaken in dichloromethane and evaporated onto silica gel. Purification by silica gel chromatography, eluting with ethyl acetate and light petroleum (10:90) provided the desired methyl ether.

Ester hydrolysis for non-quaternary carbon compounds

To a solution of ester (1 equiv.) in THF:methanol:water (4:1:1) was added lithium hydroxide monohydrate (10 equiv.) the suspension was stirred at room temperature for 16 h. The reaction mixture was washed with ether. The aqueous layer was acidified to pH = 1 with aqueous hydrochloric acid (2M) and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the desired carboxylic acid.

Ester hydrolysis for quaternary carbon compounds

To a solution of ester **31** (1 equiv.) in dioxane:H_2O (4:1) was added lithium hydroxide monohydrate (10 equiv.) the reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled to room temperature and washed with ether. The aqueous layer was acidified to pH = 1 with aqueous hydrochloric acid (2M) and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the desired carboxylic acid.

Amide formation

To a solution of carboxylic acid (1 equiv.) in dry DMF at 0 °C was added 4-bromobenzylamine hydrochloride (1.5 equiv.) and di*iso*propylethylamine (3 equiv.). The reaction mixture was stirred for 15 min and HATU (1.5 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 16 h. Following this time, the solvent was removed under reduced pressure and the residue diluted with ethyl acetate and water. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The organic layers were combined and washed with aqueous hydrochloric acid (2M), aqueous sodium carbonate solution (saturated) and brine. The organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was uptaken in dichloromethane and evaporated onto silica gel. Purification by silica gel chromatography provided the desired amide.

7. References

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