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A flexible synthesis of privileged structural motifs using the Ollis–Sweeney ammonium ylid rearrangement

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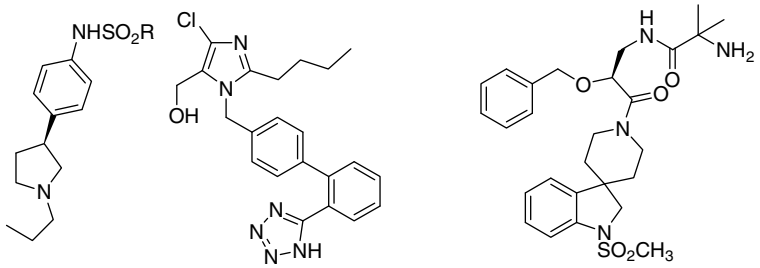
ABSTRACT

The Ollis–Sweeney ammonium ylid rearrangement has been effectively utilized to provide access to hitherto unknown hybrid privileged structural motifs. The rearrangement of didehydropiperidinium salts containing tethered olefins at the 4-position afforded, after subsequent ring closing metathesis, novel spirocyclic scaffolds suitable for further elaboration and incorporation of final structures into HTS sets.

The judicious identification and synthesis of compounds for inclusion in the corporate screening collections of pharmaceutical companies remains a formidable undertaking. Several approaches to the selection of compounds have been adopted. One such approach consists of the targeting of compound libraries to specific protein families, such as kinases, G-protein coupled receptors and ion channels. In this context, it has become apparent that certain classes of chemical structures, namely privileged structures, have a higher chance of eliciting pharmacological activity than other 'random' chemotypes. The term 'privileged structure' was first introduced in 1988.[1] A privileged structure was defined as 'a single molecular framework able to provide ligands for diverse receptors'. It was envisaged that the privileged structures could be a valuable alternative in the search for new receptor ligands by suitably decorating these substructures. Since then, an increasing number of substructural frameworks have been described as privileged structures,[2] including indoles, aryl piperazines, spiro piperidines, biphenyls, and 3-phenyl pyrrolidines (Fig. 1).

These structures have since then been used extensively in medicinal chemistry programs to identify new ligands, especially for G-protein coupled receptors (GPCRs). As part of our efforts to elaborate novel variants of privileged motifs as quality lead structures, we took advantage of the underutilized Sweeney[3] protocol for the [2,3]-sigmatropic rearrangement of didehydropiperidinium ylids to provide 3-vinyl-substituted pyrrolidines. Our initial targets are shown in Figure 2, and all incorporate privileged structural motifs.

From a design perspective, it was envisioned that by incorporating a suitable olefinic handle at the 4-position of the starting pyridines, a final ring-closing metathesis step would access the



WO2007118899
D3 receptor antagonist

Losartan
A2 receptor antagonist

MK-0677
Growth Hormone secretagogue

Figure 1.

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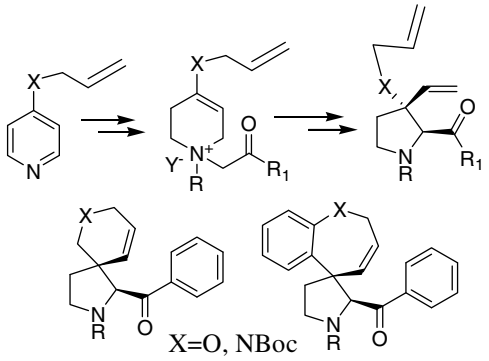
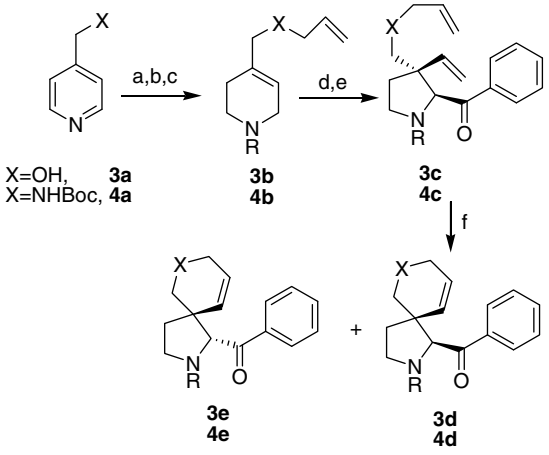


Figure 2.

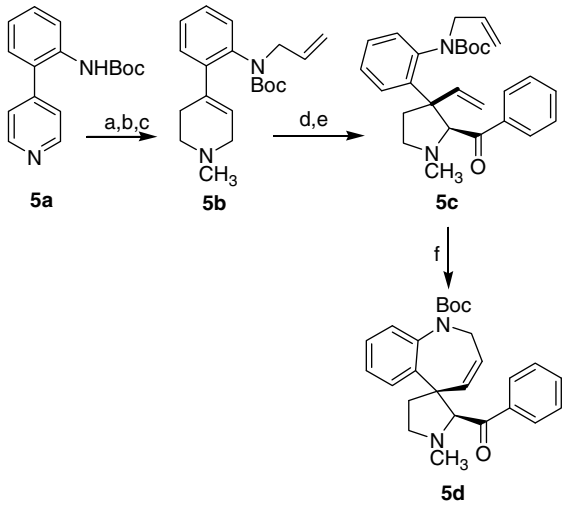
desired spirocycles. As minimal prior work had been done on the investigation of the [2,3]-sigmatropic rearrangement of didehydropiperidinium ylids derived from 4-substituted pyridines, we were anxious to determine the relative stereochemistry of substituents in the final products. Construction of the requisite intermediates for the simple oxa- and aza-spirocycles proceeded uneventfully and in good yield as outlined in Scheme 1. Based on literature precedent for the rearrangement reactions of ylides derived from 4-unsubstituted didehydropiperidinium salts, we anticipated that the rearrangement would occur via an endo transition state to provide products, where the 3-vinyl and 2-benzoyl groups resided in the cis configuration. This presupposition proved to be correct as, in both cases, the cis product was obtained upon exposure of the salts to sodium hydride in warm DME. After purification on silica gel, **3c** and **4c** were both subjected to ring-closing metathesis using the Grubbs 2 catalyst to provide the anticipated spirocycles. Interestingly, the reaction to produce the azaspirocycle **4d** also produced a small amount of the isomer **4e,** presumably formed by scrambling of the C2 stereogenic center due to the high acidity of the C-2 proton (3:1 ratio of products). This scrambling was not a problem in our environment, where a major goal is to produce and evaluate, in a biological setting, as many different structural types as possible. It should be noted that we were not able to isolate any of the corresponding regioisomers in the oxacyclic case.



Scheme 1. Reagents and conditions: X = OH, R = $(CH_2)_2Ph$, (a) $Ph(CH_2)_2Br$, CH_3CN, reflux, 12 h, 81%; (b) $NaBH_4$,CH_3OH, 0 °C, 41%; (c) NaH, THF, allyl iodide, 16 h, 22%; (d) bromoacetophenone, CH_3CN, 40 °C, 12 h, 90%; (e) NaH,1 equiv, DME, 85 °C, 3 h, 40%; (f) Grubbs II, *p*-TsOH·H_2O, CH_2Cl_2, reflux, 30 min, 70%. X = NHBoc, R = CH_3, (a) $NaNTMS_2$, allyl bromide, 55 °C, 16 h, 53%; (b) CH_3I, CH_3CN, 40 °C, 20 h, 90%; (c) $NaBH_4$, CH_3OH, 0 °C, 77%; (d) bromoacetophenone, CH_3CN, 70 °C, 4 h, 95%; (e) NaH, 1 equiv, DME, 85 °C, 8 h, 76%; (f) Grubbs II, pTsOH·H_2O, CH_2Cl_2, reflux, 1 h, 91%, 3:1 ratio of **3d**–**e**.

We next turned our attention to the synthesis of the completely novel 'hybrid' privileged structure. Our main concern in this campaign centered on whether we could coax the requisite [2,3] sigmatropic rearrangement to occur with a functionalized 4-phenyl substituent present on the didehydropiperidinium ring, given the anticipated steric congestion present in the transition state.[4] Gratifyingly, the rearrangement proceeded smoothly and rapidly at 50 °C to provide the desired product. Interestingly, the cis and trans products (vinyl and benzoyl group relative stereochemistry) were isolated after silica gel chromatography, and each pure isomer was found to equilibrate on standing to reprovide the mixture. However, when the mixture of isomers was exposed to ring closing-metathesis conditions, once again using Grubbs 2 catalyst, a single product **5d** was observed (Scheme 2).[5]

The structure of this compound was confirmed by X-ray structural analysis (Fig. 3), and was found to be, not unexpectedly, the isomer where the phenyl and benzoyl group exhibited a trans relationship. Summarily, we have used the Sweeney–Ollis [2,3]-rearrangement of didehydropiperidinium ylids to provide the hitherto unknown privileged spirocyclic motifs and the structurally intriguing hybrid structure **5d**. The protocol has been shown



Scheme 2. Reagents and conditions: (a) $NaN(TMS)_2$, allyl bromide, 55 °C, 2 h, 56%; (b) CH_3I, CH_3CN, 38 °C, 12 h, 90%; (c) $NaBH_4$, CH_3OH, 0 °C, 69%; (d) bromoacetophenone, CH_3CN, 65 °C, 4 h, 95%; (e) NaH, 1 equiv, DME, 85 °C, 2.5 h, 55%; (f) Grubbs II, pTsOH·H_2O, CH_2Cl_2, reflux, 30 min, 28%.

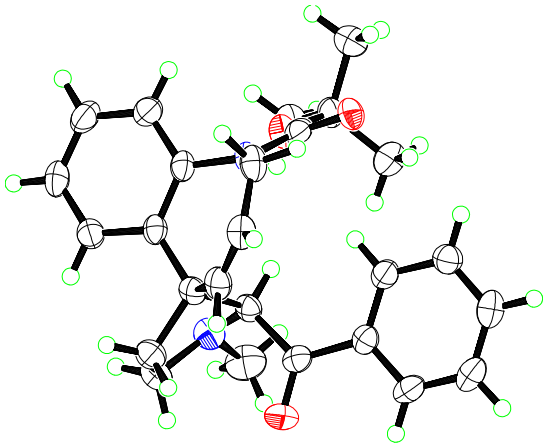


Figure 3.

to work, for the first time, with a selection of 4-substituted didehydropiperidines (other than 4-methyl and phenyl) and with a variety of N-1 substituents for example, methyl and phenethyl. The ultimate ring-closed products were also effectively designed for further modification and for library production using differential chemofunctionalization of the molecules at their two reactive sites (or three if the double bond is utilized). Further extensions of this methodology, incorporating other functionalities and substituents on the starting 4-substituted pyridines, should provide access to other novel structures for pharmacological interrogation.

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4. Soldatova, S. A.; Akbulatov, S. V.; Gimranova, G. S., et al *Chem. Heterocycl. Compd.* **2005**, *41*, 681. Rearrangement of a 4-phenyl didehydropiperidium ylid afforded a mixture of the expected pyrrolidine and a tetrahydroazepine.
5. Analytical data for final compounds, **3d**, purified on silica gel, 1:3, EA/hexane, R_f 0.4 **4d**, purified on silica gel, 1:1, EA/hexane, R_f 0.5 **4e** purified on silica gel, 1:1, EA/hexane, R_f 0.2 **5d**, purified on silica gel, 1:4, EA/hexane, R_f 0.4 ^{1}H NMR spectra were recorded at 500.5 MHz in DMSO-d_6 or pyridine-d_5, and data are reported as follows; chemical shift in ppm from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, bd = broad doublet, t = triplet, dt = doublet of triplets, td = triplet of doublets, and m = multiplet), integration value. ^{13}C NMR were recorded at 125.9 MHz in DMSO-d_6 or pyridine-d_5, and data are reported as follows; chemical shift in ppm from tetramethylsilane as an internal standard. *Compound* **3d**: ^{1}H NMR (DMSO-d_6, 500.5 MHz, 30 °C) δ 7.90 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 7.4 Hz, 2H), 7.11 (d, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 2H), 5.53 (dt, J = 10.3 and 2.3 Hz, 1H), 5.28 (bd, J = 10.3, 1H), 4.47 (s, 1H), 3.96 (dt, J = 16.8 and 2.3 Hz, 1H), 3.92 (dt, J = 16.8 and 2.3 Hz, 1H), 3.78 (d, J = 10.8 Hz, 1H), 3.39 (d, J = 10.8 Hz, 1H), 3.18 (td, J = 8.8 and 3.1 Hz, 1H), 2.87 (dt, J = 8.8 Hz, 1H), 2.79–2.64 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 1.87 (dt, J = 12.4 and 8.3 Hz, 1H), 1.75 (ddd, 12.4, 7.3 and 3.2 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125.9 MHz, 30 °C) δ 202.4, 140.8, 138.5, 133.8, 129.9, 129.2 (4 C′s), 129.0 (4 C′s), 128.4, 126.6, 73.5, 73.0, 65.5, 54.7, 51.4, 46.8, 35.6, 35.1. *Compound* **4d**: ^{1}H NMR (Pyridine-d_5, 500.5 MHz, 80 °C) δ 8.10 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 5.60 (d, J = 10.2 Hz, 1H), 5.37 (dt, J = 10.2 and 3.1 Hz, 1H), 4.30 (s, 1H), 3.98 (d, J = 12.7 Hz, 1H), 3.84 (bd, J = 18.5 Hz, 1H), 3.74 (bd, J = 18.5 Hz, 1H), 3.31 (d, J = 12.7 Hz, 1H), 3.25 (td, J = 8.4 and 2.7 Hz, 1H), 2.78 (dt, J = 8.4 Hz, 1H), 2.39 (s, 3H), 2.06 (dt, J = 12.7 and 8.5 Hz, 1H), 1.85 (ddd, J = 12.7, 7.1 and 3.0 Hz, 1H), 1.56 (s, 9H). ^{13}C NMR (Pyridine-d_5, 125.9 MHz, 80 °C) δ 201.3, 155.0, 139.3, 132.9, 131.7, 128.8 (4 C′s), 125.2, 79.5, 76.2, 54.1, 51.0, 48.9, 43.8, 39.9, 37.0, 28.8 (3 C′s). *Compound* **4e**: ^{1}H NMR (Pyridine-d_5, 500.5 MHz, 80 °C) δ 8.11 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 5.90 (dt, J = 10.1 and 2.3, 1H), 5.46 (dt, J = 10.1 and 3.1, 1H), 3.95 (s, 1H), 3.73 (bd, J = 18.7 Hz, 1H), 3.64 (bd, J = 12.7 Hz, 1H), 3.41 (bd, J = 12.7 Hz, 1H), 3.33 (bd, J = 18.7 Hz, 1H), 3.16 (td, J = 8.6 and 3.4 Hz, 1H), 2.47 (dt, J = 8.6 Hz, 1H), 2.29 (s, 3H), 2.04 (dt, J = 12.7 and 8.2, 1H), 1.74 (ddd, J = 12.7, 8.6 and 3.3 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (Pyridine-d_5, 125.9 MHz, 80 °C) δ 198.6, 154.9, 139.2, 133.3, 133.0, 128.9 (2 C′s), 128.5 (2 C′s), 124.0, 79.6, 77.9, 54.2, 48.8, 48.2, 43.6, 40.5, 37.3, 28.6 (3 C′s). *Compound* **5d**: ^{1}H NMR (DMSO-d_6, 500.5 MHz, 30 °C) δ 7.77 (d, J = 7.3 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.3 Hz, 2H), 7.42 (d, J = 7.4 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 5.33 (d, J = 11.7 Hz, 1H), 5.25 (d, J = 11.7 Hz, 1H), 4.86 (s, 1H), 4.53 (d, J = 18.4 Hz, 1H), 3.37 (d, J = 18.4 Hz, 1H), 3.19–3.06 (m, 2H), 2.82 (dd, J = 13.3 and 6.4 Hz, 1H), 2.60 (dt, J = 13.3 and 10.0 Hz, 1H), 2.15 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (DMSO-d_6, 125.9 MHz, 30 °C) δ 202.5, 142.4, 141.0, 139.4, 133.5, 132.2, 130.0, 129.3 (2 C′s), 129.0, 128.4 (2 C′s), 127.9, 127.5, 126.3, 80.9, 77.2, 53.6, 52.5, 46.7, 40.1, 37.5, 29.1 (3 C′s).