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# A Method for Effectively Favouring 5-*Endo*- over 5-*Exo*-Cyclisations

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**Abstract**:- *Iodocyclisation of sulfonamido-alcohol* ***6*** *proceeds by a 5-exo pathway to give amino-THFs* ***9*** *whereas the furyl derivative* ***10*** *gives the pyrrolidines* ***11*** *and* ***12****, most likely by an alternative 5-exo mechanism, instigated by the furan ring.*

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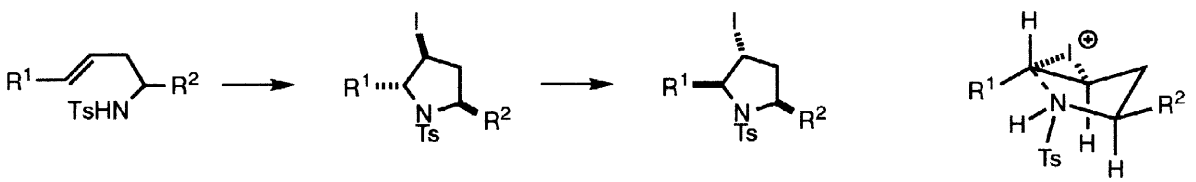
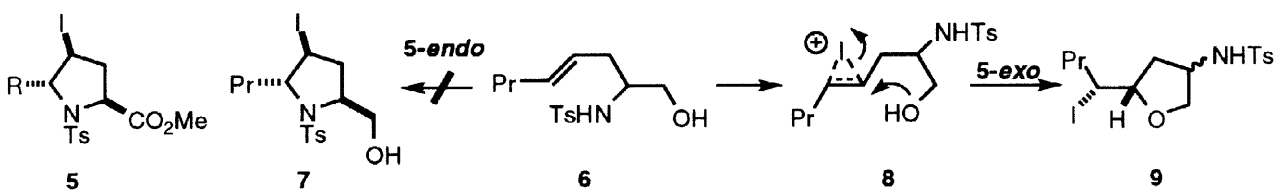
Our recent finding that homoallylic sulfonamides **1** undergo smooth iodocyclisation upon treatment with three equivalents each of iodine and potassium carbonate in acetonitrile to give the 2,5-*trans*-pyrrolidines **2** has opened up a new approach to these important heterocycles. An additional feature of this methodology is that, in the absence of base, the initial products **2** undergo smooth isomerization to the corresponding 2,5-*cis* isomers **3**.[1] Although apparently 5-*endo*-trig cyclisations, it seems that such cyclisations are not exceptions to Baldwin's rules,[2] as they are electrophile- rather than nucleophile-driven,[3] and proceed initially *via* a chair-like transition state **4** wherein the stereochemistry is controlled by an equatorial positioning of substituent $R^2$.




**1** **2** **3** **4**

A significant concern regarding this methodology was the lack of functionality present in the substituents [*ie* **1**; $R^1$, $R^2$ = alkyl or Ph) during our initial studies.[1] However, we have recently found that ester groups can be accommodated (*ie* **1**; $R^2 = CO_2Me$), resulting in a new approach to substituted prolines **5**.[4] In contrast, exposure of the corresponding alcohols **6** to the cyclisation conditions did not give the pyrrolidines **7** *via* a 5-




**5** **7** **6** **8** **9**

*endo* process, but rather the sulfonamidoTHFs **9**, by a 5-*exo* cyclisation of intermediate **8**. Hence, despite being an electrophile-driven reaction, the rules still apply: 5-*exo*-trig is strongly favoured over 5-*endo*-trig

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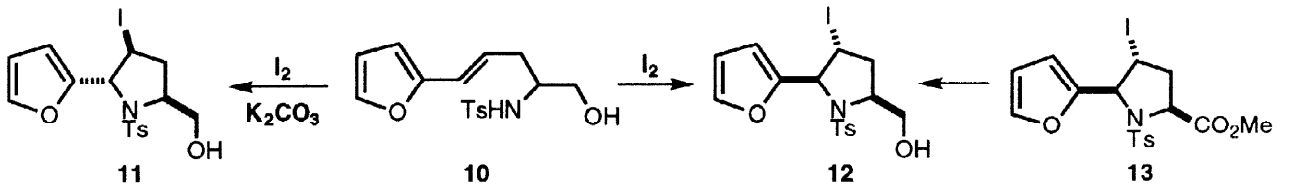
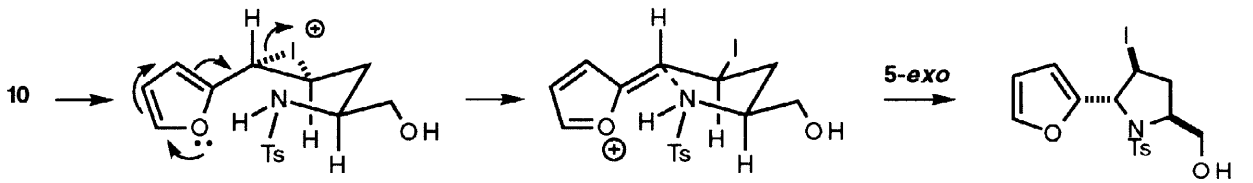
confirming our suspicions that additional functionality could create problems of competing cyclisation modes.

Herein, we report a method for reversing this preference. When the 2-furyl derivative **10** was cyclized under basic conditions,[1] we were delighted to isolate an excellent 85% yield of the pyrrolidine **11**, whereas under acidic conditions,[1] the corresponding 2,5-*cis* isomer **12** was formed, in 69% yield. Structural proof, beyond the usual characterization data, was obtained by Dibal-H reduction [toluene, 0°C, 3 h] of the esters [**5**; R = 2-furyl] and **13**,[4] which gave samples identical to those obtained from these direct cyclisations.




**11** **10** **12** **13**

Our explanation for these contrasting findings is that the cyclisations are controlled additionally by the furan ring oxygen. Thus, the expected intermediate **14** could undergo C-I bond cleavage, induced by the furan oxygen as shown, to give intermediate **15** which is set up to undergo a 5-*exo* cyclisation to give the observed product **11**. Hence, the apparent dichotomy of a 5-*endo*-trig cyclization process competing successfully with an alternative 5-*exo* pathway involving the hydroxyl group could actually be an excellent example of the veracity of Baldwin's rules as, effectively, a 5-*exo* pathway is competing with a less favoured 6-*exo* process.




**14** **15** **11**

The synthetic utility of a furan residue (cleavage to acid or aldehyde; oxidations to other *O*-heterocyclic systems), together with this additional synthetic flexibility provided by the influence of the furan residue at the cyclisation stage, allowing the incorporation of additional useful functionality, suggests that the pyrrolidines **11** and **12** and related structures will be valuable synthetic intermediates;[5] efforts to exploit this are underway.

**Acknowledgements**

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