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# The importance of *peri*-interactions in determining the half-chair conformation of the dihydropyran ring in 2-benzopyrans. Stereochemical consequences

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**Abstract**—*peri*-Interactions are important in determining both the conformation of the dihydropyran ring of 2-benzopyrans as well as the stereochemistry of its substituents. 

The dihydropyranoid ring found in naturally occurring naphthopyranquinones[1–4] and, for example, in the related 2-benzopyrans,[5–7] assumes a half-chair conformation as a consequence of the intra-annular double bond. The substituent (normally methyl or a fused lactone ring methylene) at C-3 is known to adopt an equatorial orientation,[8,9] irrespective of the stereochemistry at each of the three potential asymmetric centres, C-1, C-3 and C-4. For a 1,3-disubstituted system, an early example of this was established for the pair of C-3 epimeric natural products eleutherin **1** and isoeleutherin **2**,[10,11] in which the C-3 methyl is equatorial in each case while the C-1 methyl is pseudoequatorial in the first and pseudoaxial in the second as shown in Figure 1.[1–3] The half-chair conformation of the latter is inverted relative to that of the former in order to maintain the C-3 methyl equatorial.[10,11] We report here on, to our knowledge, the first three instances in which the C-3 methyl is axial in a series of 1,3,4-trisubstituted 2-benzopyrans.

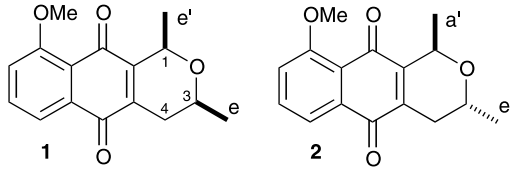
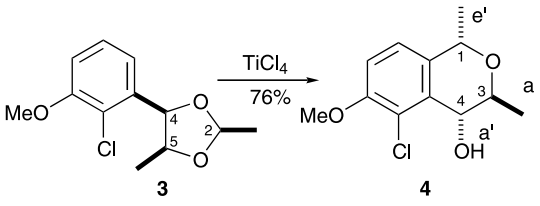



**Figure 1.**

The first example was observed when the racemic all *cis* 4-aryl-2,5-dimethyl-1,3-dioxolane **3**[12] was allowed to react with titanium(IV) chloride,[13–15] whereupon the product 2-benzopyran **4**[12] was formed in 76% yield. The $^1$H NMR spectrum showed a small coupling constant of 2.2 Hz between the *vicinal* heterocyclic ring protons 3-H and 4-H.

It is known[13–15] that the stereochemistry at C-4 and C-5 in such dioxolanes is transferred unaltered to C-4 and C-3, respectively, in the product 2-benzopyrans, and, therefore, that the substituents at these centres in the pyran **4** were *trans* as shown in Scheme 1. This small coupling constant therefore indicated that the C-3 methyl and C-4 hydroxy groups were axial and pseudo-axial, as indicated.

On the other hand, the rearrangement of the isomeric all *cis* dioxolane **5**, which differs from the dioxolane **3** only in the aromatic substitution pattern, afforded the 2-benzopyran **6** in 77% yield.[13–15] In this compound, the $^1$H NMR spectrum showed the much larger coupling




**Scheme 1.**

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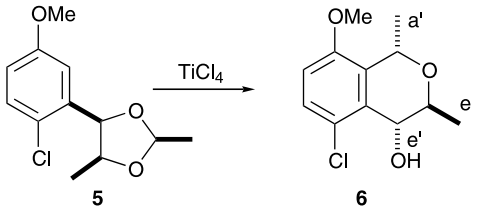



**Scheme 2.**

constant of 6.0 Hz between the *vicinal* protons 3-H and 4-H, which showed that these protons were approximately *trans* diaxial, and, therefore, that the methyl and hydroxy groups at these centres were equatorial and pseudoequatorial, as shown in Scheme 2. These experiments indicate that the dihydropyran rings of benzopyrans **4** and **6** adopt the two alternative half-chair conformations **7** and **8**, respectively (Fig. 2). This conclusion was supported by $^1$H NMR nuclear Overhauser enhancement experiments. In an NOE difference spectrum obtained for compound **4**, irradiation of the C-3 methyl group led to a 9% enhancement of the proton 1-H, but no observable enhancement occurred for the proton 3-H upon irradiation of the C-1 methyl protons. For compound **6** a similar experiment showed the proximity between the C-1 methyl and 3-H,[14] but not between the C-3 methyl and 1-H.

This conformational difference between benzopyrans **4** and **6** can be accounted for in terms of differences in *peri*-interactions within these structural isomers. For compound **6** there are significant 4,5-*peri*-interactions between the hydroxy group and the chlorine substituent, as well as 1,8-*peri*-interactions between the methyl and methoxy groups. The pseudoaxial orientation of the C-1 methyl minimises the latter interaction. The equatorial orientation of the C-3 methyl is typical of such molecules.[8–11] In isomer **4**, effective removal of the 1,8-*peri*-interactions in compound **6** through relocation of the C-8 methoxy while retaining the 4,5-*peri*-interactions induces the C-4 hydroxy group to minimise this remaining interaction by assuming the pseudoaxial orientation at the expense of the C-3 methyl becoming axial, and the C-1 methyl becomes pseudoequatorial through lack of a significant steric interaction with the proton 8-H.

A second case involved the completely diastereoselective cyclisation[16] of the tethered phenolic lactaldehyde **9**[12] with titanium(IV) isopropoxide to afford, in 73% yield, the enantiopure 2-benzopyran-4,5-diol **11**,[12] for which the $^1$H NMR spectrum showed the expected[16] large coupling constant of 7.0 Hz between the vicinal protons 3-H and 4-H. This confirmed that these two protons were approximately *trans*-diaxial and, therefore, that the C-3 methyl was equatorial and the C-4 hydroxy group pseudoequatorial.[16] Conversion of diol **11** into the corresponding 4,5-diacetate **13**[12] was accompanied in the $^1$H NMR spectrum by an unexpectedly small 3-H/4-H coupling constant[16] of only 2.0 Hz. For the methoxy analogue **10**[16] of lactaldehyde **9**, similar entirely diastereoselective cyclisation afforded the 2-benzopyran-4,5-diol **12**, for which the 3-H/4-H coupling constant was 8.6 Hz, and 4.8 Hz for the corresponding diacetate **14**, in contrast to the case of **13** (2.0 Hz) (Scheme 3). This suggested that the dihydropyran ring of compound **11** had undergone conformational inversion upon acetylation. The reason for this inversion is ascribed to the fact that in **11** and **13** the 1,8-*peri*-interactions are small, unlike other related molecules for which it is general to have a substituent at C-8 that is larger than hydrogen. In the case of diol **11** the 4,5-*peri*-interactions between the two hydroxy groups, possibly aided by mutual hydrogen bonding, are sufficiently small to tolerate a pseudoequatorial orientation for the alcohol at C-4. In the diacetate **13**, however, the 4,5-*peri*-interactions between the adjacent acetoxy substituents are sufficiently large to achieve a conformational inversion at the expense of the C-3 methyl and C-4 acetoxy being axial and pseudoaxial, respectively, while the lack of significant 1,8-*peri*-interactions allows the C-1 methyl to become pseudoequatorial.

This conformational inversion was supported again for the diacetate **13** by $^1$H NMR nuclear Overhauser difference and NOESY spectroscopy. In particular, close proximity between the C-3 methyl and C-1 proton as expected for conformation **7** was indicated, whereas little or no correlation was observed between the C-1 methyl and the proton 3-H. The reverse observations would be anticipated for the alternative conformation **8**.

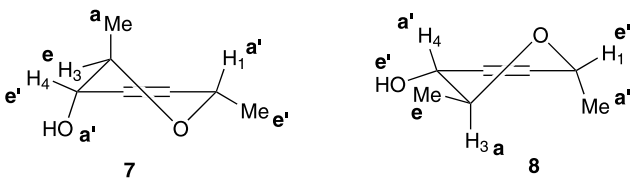
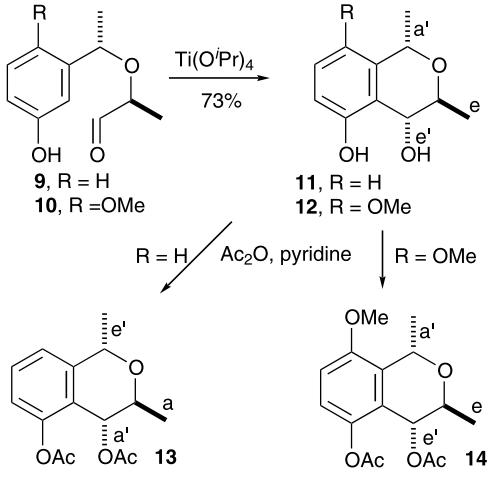
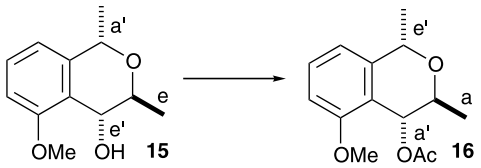



**Figure 2.**




**Scheme 3.**

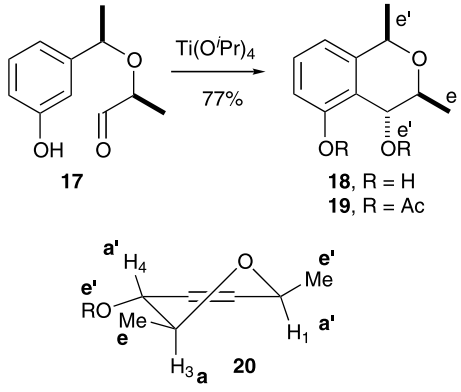



**Scheme 4.**

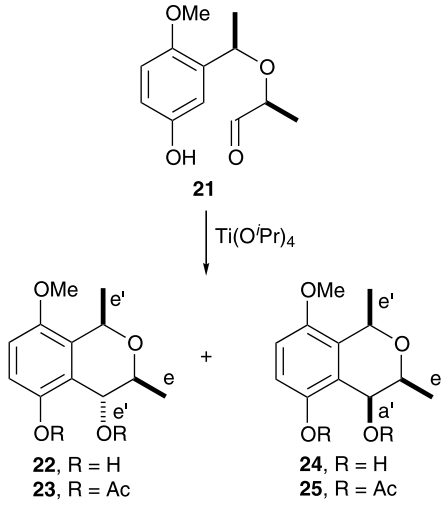
A further example of this conformational inversion was observed when the methyl ether **15**[12] of the 4,5-diol **11** was transformed into the acetate **16**[12] (Scheme 4). For the methyl ether **15**, the 3-H/4-H coupling constant was 5.4 Hz, which indicated, once again, that these protons are approximately *trans* diaxial. For the acetate **16** this coupling constant was 1.9 Hz, indicating the alternative conformation. These conformational assignments were made on the same basis as those used for compounds **11** and **13**. The coupling constant (5.4 Hz) observed in the methyl ether **15** was smaller than those (8–9 Hz) normally found in related 5,8-dimethyl ethers[13,14,17–19] and reflected a smaller dihedral angle between 3-H and 4-H. Dreiding models show that this angle reduces at the inception of the conformational inversion, once again encouraged by the absence of a C-8 substituent on the aromatic ring.

Tethered lactaldehyde **17**,[12] the benzylic epimer of compound **9**, afforded the 4,5-diol **18**[12] in 77% yield as a single diastereoisomer with the conformation **20** for the heterocyclic ring, in which all the substituents were equatorial/pseudoequatorial (Scheme 5). This was established from the 3-H/4-H coupling constant of 9.0 Hz, and a chemical shift for 3-H of $\delta$ 3.54 that confirmed the 1,3-*cis*-dimethyl arrangement, relative to $\delta$ 3.93 for the 1,3-*trans*-dimethyl compound **11**.[13,17,20–22] The 4,5-diacetate **19**[12] also possessed conformation **20** as shown by a 3-H/4-H coupling constant of 8.2 Hz, which confirmed that its formation from diol **18** was not accompanied by a conformational inversion that would have required all its heterocyclic ring substituents to become axial/pseudoaxial (cf. **13** from **11**).

These observations provide an explanation for the fact that the methoxy lactaldehyde **21** cyclises *without* complete diastereoselectivity to yield the pair of C-4




**Scheme 5.**




**Scheme 6.**

epimeric *cis*-1,3-dimethylbenzopyran-4-ols **22** and **24** (Scheme 6) in a ratio of 3:1,[16] (and thence their diacetates **23** and **25** without conformational inversion), whereas lactaldehydes **10**, the benzylic epimer of **21**, and **17**, the demethoxy derivative of **21**, both cyclise *with* complete diastereoselectivity to afford only the pseudoequatorial C-4 alcohols **12** and **18**, respectively. In the transition states for the cyclisations leading to the benzopyrans **12** and **18**, the C-4 alcohol assumes the pseudoequatorial orientation to minimise the inter-oxygen distance for titanium coordination, and the C-3 methyl is equatorial to avoid 1,3 diaxial interactions. For the transition state leading to benzopyran **12**, the C-1 methyl is pseudoaxial, which minimises the 1,8-*peri*-interactions with the neighbouring methoxy and **12** is therefore the exclusive product. For that leading to pyran **18**, the C-1 methyl is pseudoequatorial, which is preferred since there are no significant 1,8-*peri*-interactions with the neighbouring hydrogen. For that leading to pyran **22**, however, the C-1 methyl orientation is pseudoequatorial, for which there are significant 1,8-*peri*-interactions. The alternative conformation **26**[16] of the transition state is therefore adopted by ~25% of the molecules, in which the incipient C-4 alcohol retains the pseudoequatorial orientation to minimise the inter-oxygen distance through coordination. The C-1 methyl becomes pseudoaxial to reduce the 1,8-*peri*-interactions with the neighbouring methoxy at the expense of the C-3 methyl becoming axial, and intramolecular arylation in **26** (numbering for developing benzopyran ring-system in Figure 3) occurs at the *Si* face of the aldehyde.[16] Upon hydrolysis of the titanium complex

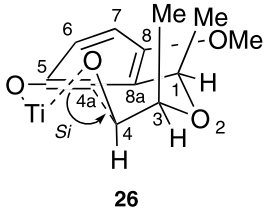



**Figure 3.**

the conformation of the derived pyran ring inverts so that the C-1 and C-3 methyls become pseudoequatorial and equatorial, respectively, and the C-4 alcohol becomes pseudoaxial. The pyran **24** obtained from this alternative transition state is therefore the C-4 epimer of pyran **22**.

These results show that the half-chair conformation selected for the dihydropyran ring arises through a balance between the preference of the C-3 methyl to be equatorial and the intensities of the 1,8- and 4,5-*peri*-interactions within the molecule concerned.

## Acknowledgements

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