

Stereodivergent radical cyclisation reactions of cyclohexa-1,4-dienes

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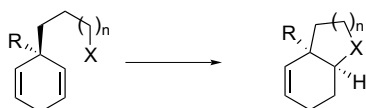
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Abstract—Derivatives of cyclohexa-1,4-diene diol **5** undergo highly diastereoselective free-radical cyclisation reactions. Selective reaction of either double bond is possible depending on the protecting groups used.

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Desymmetrisation reactions have been used to great effect in organic synthesis,¹ offering an elegant entry into a range of natural and non-natural compounds, including acyclic,² carbocyclic³ and heterocyclic.⁴ Cyclohexadiene systems have a great deal of potential in this area, some of which has been realised in a number of studies. The Birch-reduction/alkylation sequence allows the easy formation of cyclohexadienes with a quaternary centre,⁵ desymmetrisation of which will lead to the stereoselective formation of a quaternary stereogenic centre⁶ in addition to at least one other stereogenic centre (Scheme 1).

Within this general strategy, there are many cyclisation reactions which could be used. Similarly, there is a broad range of potential substrates with a variety of stereochemical directing groups. We initially set out to investigate free-radical cyclisation reactions onto cyclohexadiene rings, with the aim of elucidating the conformational bias in such systems.⁷ We now report a versatile cyclisation reaction, which provides both diastereoisomers of the cyclised product stereoselectively by control of the substrate conformation.



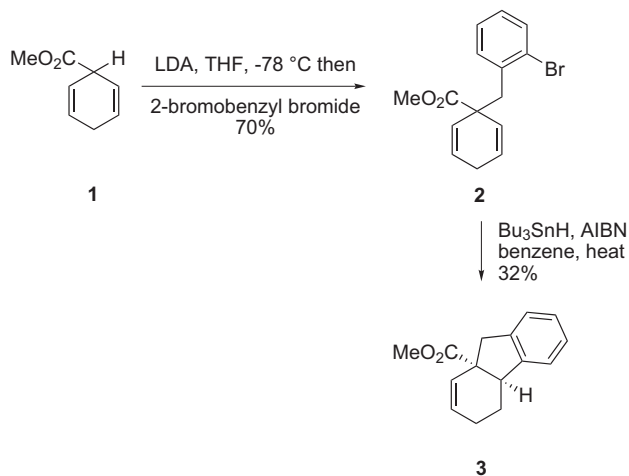
Scheme 1.

Keywords: Desymmetrisations; Free-radical reactions; Cyclisations.

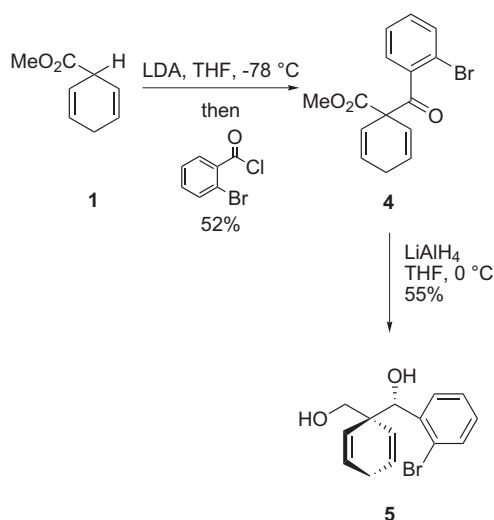
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In order to test the general approach, achiral substrate **2** was prepared by alkylation of Birch-reduction product **1**. Although compound **2** could conceivably be prepared in a one-pot Birch reduction/alkylation, this would require an excess of 2-bromobenzyl bromide, so the method shown in Scheme 2 is more convenient. Cyclisation of compound **2** under standard conditions gave tricycle **3**,⁸ albeit in somewhat disappointing yield.⁹

With this result in hand, we next set about preparing chiral cyclohexadiene derivatives in order to examine the diastereoselective process. Deprotonation of **1** and reaction with 2-bromobenzaldehyde failed, but we were able to react the same anion with 2-bromobenzoyl chloride to give ketone **4**. While reduction of the ketone gave



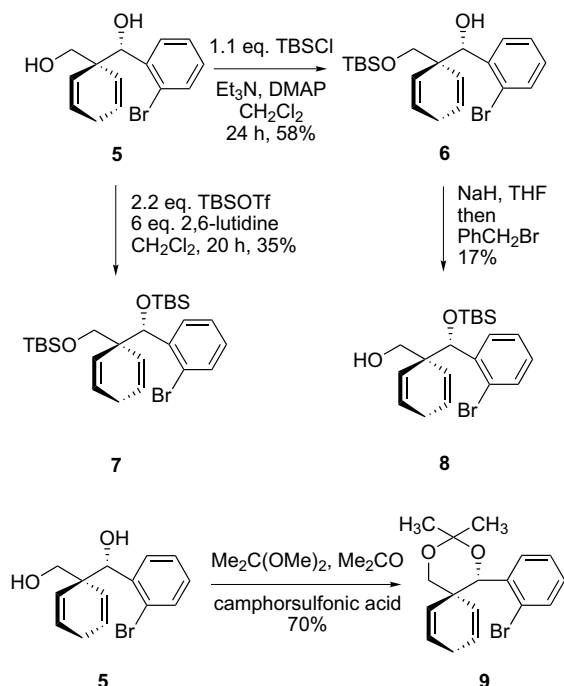
Scheme 2.



Scheme 3.

significant quantities of 2-bromobenzyl alcohol, presumably formed by retro-aldol reaction and further reduction, exhaustive reduction with lithium aluminium hydride gave diol **5** cleanly (Scheme 3).

Based on recent work by Grainger et al.,¹⁰ we expected the level of stereocontrol to be affected by the presence of protecting groups on the secondary alcohol. Regioselective protection of the primary alcohol in **5** as the TBS ether **6** was straightforward, as was simultaneous protection of both hydroxy groups. Attempted acetylation of **6** gave a small amount of the bis-acetate, while attempted benzylation gave a low yield of compound **8** in which the silyl group had migrated from the primary to the secondary alcohol. Tethering the two alcohols in the acetonide **9** is of particular interest, as it reduces the

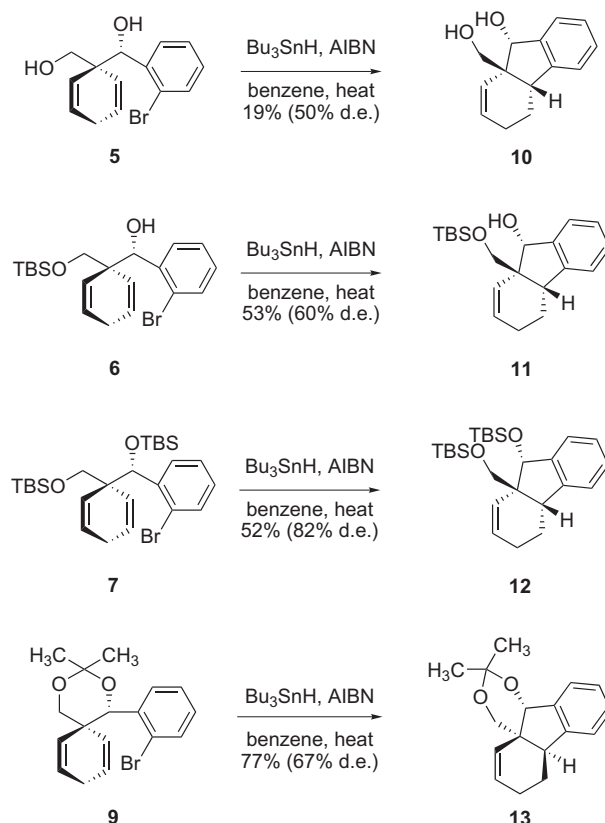


Scheme 4.

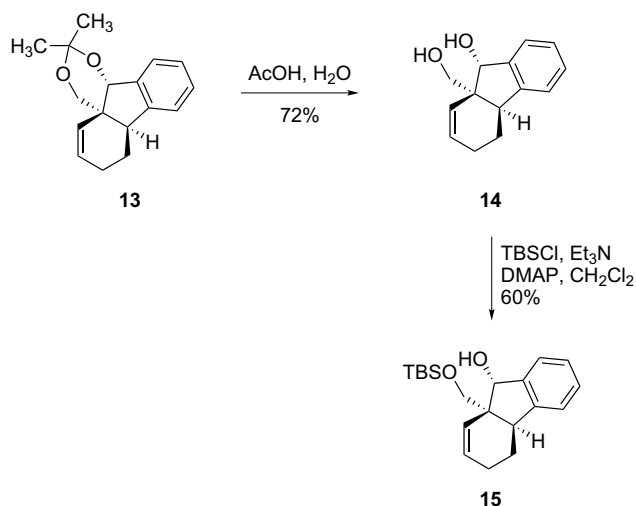
flexibility of the compound considerably. Formation of this compound was accomplished without difficulty (Scheme 4).

With substrates **5**, **6**, **7** and **9** in hand, we investigated the free-radical cyclisation reactions as shown in Scheme 5. In all cases, a moderate to high level of diastereoselectivity was obtained, with only the formation of compound **10** proceeding in an unacceptably low yield. The preferential formation of stereoisomer **13** from **9** was confirmed by NOE studies. The stereochemistry of compounds **10** and **11** was indirectly proved by conversion of **13** into compounds **14** and **15** (Scheme 6). Both of these compounds could be clearly seen as the minor component in the formation of compounds **10** and **11**. The stereochemistry of compound **12**, for which an impressive 10:1 isomer ratio was observed, was assigned by comparison of the ¹H NMR data with those of **10** and **11**.

The stereochemical outcome of these reactions warrants discussion. In the structure **9**, it might be expected that attack of the radical would only be possible on the double bond shown. In fact, with the 1,3-dioxane ring in the expected chair form as shown in Figure 1, the conformational bias towards the right-hand double bond is only slight. However, this is clearly sufficient to provide good stereocontrol. In the case of compounds **5**, **6** and **7**, there is a significant bias towards a staggered conformation in which the hydroxy group is over the cyclohexadiene ring (Fig. 2). From this point, the radical is closer to the left-



Scheme 5.



Scheme 6.

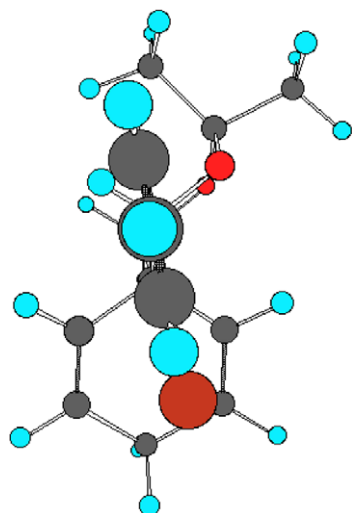


Figure 1. MM2 minimised 3D structure of compound 9.

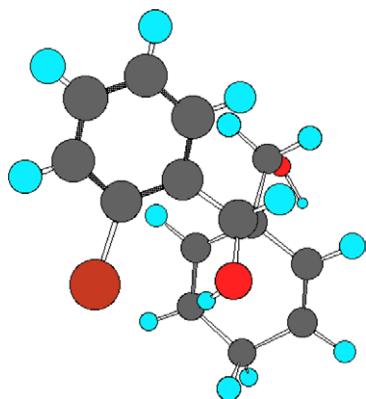


Figure 2. MM2 minimised 3D structure of compound 5.

hand double bond giving rise to the observed major stereoisomer.

This conformational preference is presumably due in large part to electronic repulsion between the two hydroxy groups giving the fully staggered conformation shown. In the case of compounds **5** and **6** it is possible that some hydrogen bonding may over-ride this preference, giving significant amounts of the diastereomeric product. However, the higher stereoselectivity in the cyclisation of **7** may be solely attributable to steric effects.

In summary, the sense of diastereoselection in free-radical cyclisation reactions of cyclohexa-1,4-dienes can be controlled by judicious choice of protecting groups, giving products **10–15**, all with good levels of stereocontrol.

Acknowledgements

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