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Short synthesis of a tetrasubstituted tetrahydropyran with five stereogenic centres—stereoselective double tandem rearrangements and cyclisation

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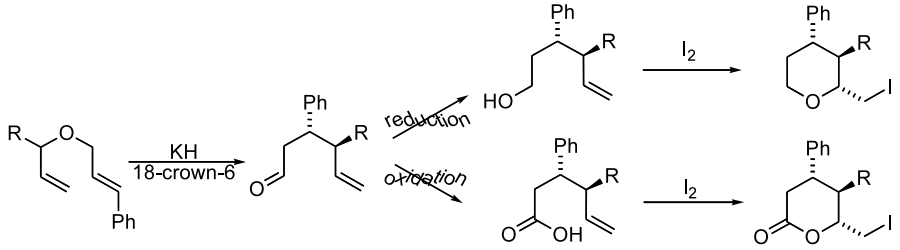
Abstract—A stereoselective potassium hydride/18-crown-6 mediated double tandem etherification-[2,3]-Wittig-anionic oxy-Cope rearrangement was used to prepare a δ,ε-unsaturated aldehyde with *syn* stereochemistry. Wittig olefination, dihydroxylation and stereoselective iodine induced cyclisation completed the tetrahydropyran skeleton.

Tandem reactions are proving an increasingly popular basis for synthetic strategy in organic synthesis because they offer the opportunity for multiple bond-forming/bond-breaking processes under a single set of reaction conditions.[1–3] This inevitably leads to a reduction in the number of steps required with associated savings in time and purification costs.

Polysubstituted tetrahydropyrans are found in a wide range of marine natural products,[4] many of which exhibit interesting biological activity. The wide variety of substitution patterns and stereochemistry that is possible has made them popular targets for synthesis and methodological study.[5] The variety of recent solutions to the problem of controlling the relative stereochemistry of the substituents demonstrates the importance of this area and includes hetero Diels–Alder reactions,[6,7] acid promoted Prins cyclisations,[8,9] cyclisations of alcohols via conjugate addition,[7] onto alkenes activated by electrophiles,[10] and dicobalt hexacarbonyl-stabilised propargylic cations,[11] or alternatively silyl nucleophiles participate in formal [4+2] cycloaddition with crotyl silanes,[12] and ene-intramolecular Sakurai processes.[13]

The creation of new stereogenic centres controlled by pre-existing stereochemical features of the substrate is a constant challenge in modern organic synthesis.[14] Such stereocontrol in acyclic molecules, which are conformationally flexible, is especially difficult as there is no easy way to reduce the number of rotational degrees of freedom of the molecule. Most examples in this area utilise the proximity of the reacting centre to the inducing centre (Cram and Felkin models),[15] or the interme-



Scheme 1. Tetrahydropyran and δ-lactone synthesis by tandem [2,3]-Wittig-AOC rearrangement iodocyclisation.

Keywords: ether; sigmatropic; anionic oxy-Cope; [2,3]-Wittig; iodoetherification.

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diacy of a chelated species (chelate-Cram) to achieve stereoselectivity. Sigmatropic rearrangements with their well-defined cyclic transitions states offer attractive prospects for stereochemical control in acyclic systems. We have previously used our tandem [2,3]-Wittig-anionic oxy-Cope rearrangement to establish the acyclic stereochemistry in the stereoselective synthesis of trisubstituted δ-lactones and tetrahydropyrans followed by iodocyclisation (Scheme 1).[16]

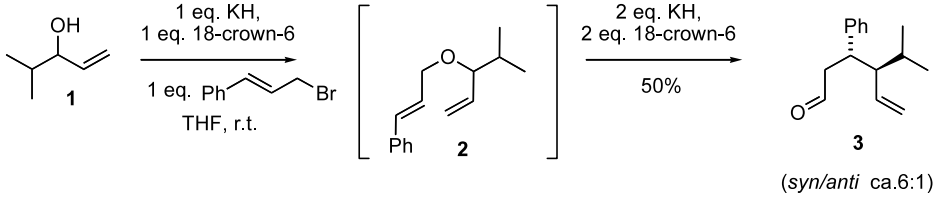
In addition, our crown ether mediated ether synthesis[17] which used sodium hydride and 15-crown-5 suggested the possibility of combining the etherification with the tandem sigmatropic rearrangement which required potassium hydride and 18-crown-6. This double tandem reaction proceeded smoothly under the strongly basic conditions with increased synthetic efficiency as there was no need to isolate and purify the intermediate ether. Scheme 2 shows the one step synthesis of aldehyde **3** from commercially available starting materials. The overall yield was 50%, which is acceptable for such a short synthesis, and the diastereoselectivity was ca. 6:1 in favour of the *syn* diastereoisomer, as observed for the stepwise sequence.

We intended to convert the aldehyde into an α,β-unsaturated ester and then dihydroxylate the terminal alkene to produce an alcohol nucleophile for tetrahydropyran formation. We expected that the *syn* stereochemistry of the substrate would facilitate cyclisation as both bulky substituents would be equatorial. The diene **4** was prepared with the *syn* relationship between the substituents at the two stereocentres from aldehyde **3**. Wittig olefination with methyl (triphenylphosphoranylidene)acetate, gave diene **4**. The newly formed alkene was exclusively *E* as judged by proton NMR, which was important for subsequent analysis.When diene **4** was dihydroxylated using a solution of catalytic potassium osmate dihydrate with *N*-methyl morpholine *N*-oxide (Scheme 3) reaction occurred only at the more electron deficient double bond, no product resulting from osmylation of the terminal double bond was isolated. This may be because attack of the bulky osmium tetroxide is blocked by the very bulky adjacent centre. In contrast, the α,β-unsaturated bond is much more accessible.

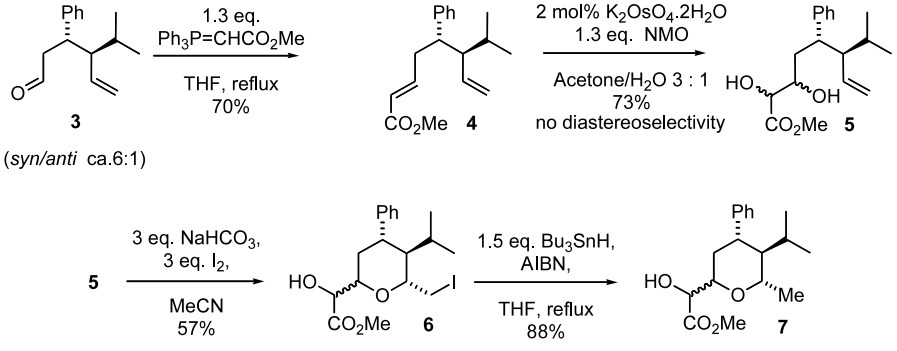
Analysis in acyclic systems is very difficult, so to probe the facial selectivity of the osmylation we converted the crude mixture of diols into tetrasubstituted tetrahydropyrans. The terminal alkene provided the required opportunity for cyclisation. Iodine induced ring formation and subsequent reductive dehalogenation led sequentially to tetrahydropyrans **6** and **7**. The iodocyclisation was highly stereoselective, in accordance with our earlier results with simpler systems; the iodomethyl group was formed exclusively equatorial as a result of the intermediate iodonium ion adopting an equatorial position preferentially (Scheme 3).[18]

Tetrahydropyran **7** was obtained as a mixture of isomers, subsequent GCMS analysis of the mixture revealed two main products in a ratio of 3.25:1. This was unexpected as the osmylation was shown to be nonstereoselective by conversion into the corresponding acetonides which were analysed by GC. Separation of the two isomers **7a** and **7b** by column chromatography facilitated GC peak identification and characterisation of **7a** and **7b** (Fig. 1).

The subsequent ^{1}H NMR and, in the case of **7a**, crystal structure analysis (Fig. 2), gave us conformation of the orientation of the α-hydroxy ester side chain at the C1 position in both isomers. In the major diastereoisomer



Scheme 2. Double tandem 'one pot' etherification-[2,3]-Wittig-anionic oxy-Cope sequence.



Scheme 3. Regioselective osmylation of diene **4** and stereoselective iodocyclisation-reduction.

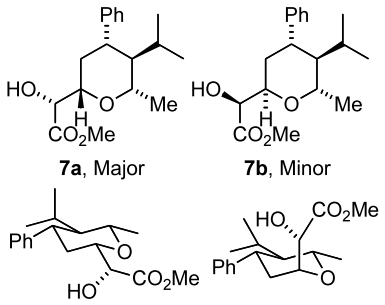


Figure 1. Stereochemistry of tetrasubstituted tetrahydropyrans.

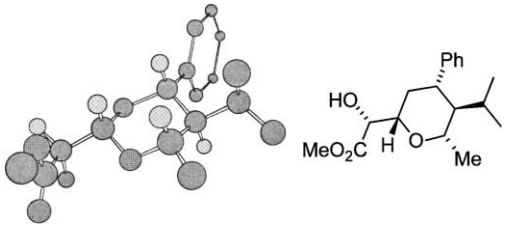


Figure 2. X-Ray structure of major tetrahydropyran **7a** showing important hydrogen atoms only.

7a the side chain was equatorial while the minor **7b** diastereoisomer had an axial orientation.

Scheme 4 shows the probable cyclisation transition states that lead to the two iodomethyl pyran diastereoisomers, and the diol precursors that gave rise to each isomer. Hence diol **5a** reacts faster than diastereoisomer **5b** giving kinetic stereoselectivity in the cyclisation so that a 1:1 mixture of **5** was converted into a 3.25:1 mixture of tetrahydropyrans **7**. The recovered starting material was enriched in the uncyclised diol **5b**. No cyclised products were observed from the *anti* diastereoisomer of aldehyde **3** which was also present in small quantities. All of these observations can be explained by the reduced rate of cyclisation if a branched axial substituent is required (Scheme 4).

Overall the highly substituted tetrahydropyran **7a** with five stereogenic centres was constructed in five steps using a novel stereoselective double tandem reaction and a kinetically selective cyclisation. These and related tetrahydropyrans could in turn be useful building blocks for more complex targets that may be inaccessible by other methods.

Crystallographic data for the tetrahydropyran **7a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 147869.

Procedure for the double tandem alkylation-[2,3]-Wittig-AOC rearrangement: 4-Methyl-1-penten-3-ol (1.0 g, 9.98 mmol) in THF (2 ml) was added dropwise to potassium hydride (0.44 g, 10.9 mmol hexanes washed and vacuum dried) in dry THF (10 ml) at 0°C under nitrogen. This mixture was allowed to warm and stir at room temperature for 15 min then cinnamyl bromide (1.96 g, 9.98 mmol) in THF (5 ml) was added dropwise. The reaction mixture was allowed to stir for 2 h before being cooled again in a ice/water bath. Potassium hydride (0.80 g, 19.9 mmol), followed by 18-crown-6 (5.26 g, 19.9 mmol) in THF (10 ml) was then added upon which the solution turned instantly from yellow/brown to blue/black. This was left to stir overnight and workup was effected by pouring the solution into a 250 ml separating funnel containing 50 ml of ice cooled pH 7 phosphate buffer solution. Ether was then added (30 ml) and the layers separated. The aqueous layer was then extracted with ether (3×40 ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude orange oil. Column chromatography eluting with petroleum ether (40/60)/diethyl ether 9:1 gave the aldehyde as a yellow oil (1.08 g, 4.99 mmol) 50%. $R_f = 0.42$ in petroleum ether/diethyl ether 8:2.

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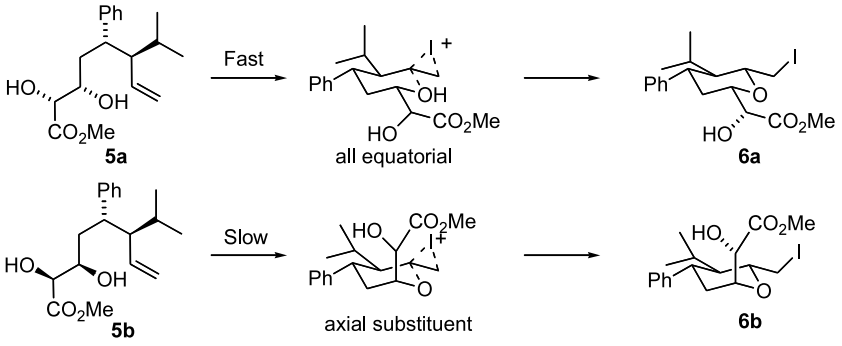

Scheme 4. Transition states for iodocyclisation and corresponding diol stereostructures.

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