Stereoconvergent 'One-Pot' Tandem [2,3]-Wittig-Anionic Oxy-Cope Rearrangement of Acyclic Bis-Allylic Ethers in the Diastereoselective Synthesis of Substituted Tetrahydropyrans

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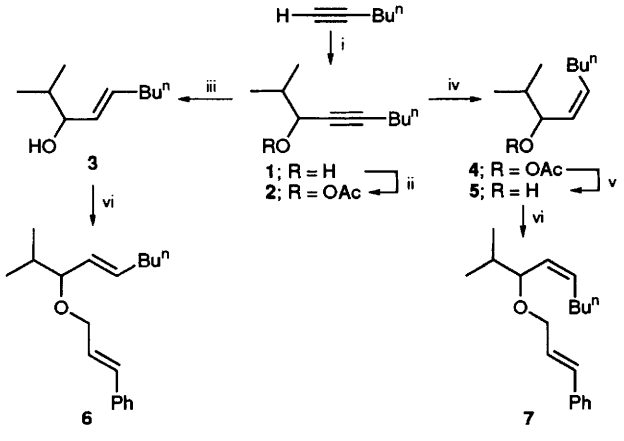
The unsaturated alcohols derived from a 'one-pot' tandem [2,3]-Wittig-anionic oxy-Cope (AOC) rearrangement undergo a halocyclisation reaction with iodine in acetonitrile to give substituted tetrahydropyrans with a high degree of stereocontrol.

Tandem reactions provide an opportunity for linking the synthetic power of two or more transformations in a single synthetic operation.[1] Sigmatropic rearrangements such as the [2,3]-Wittig,[2] and the AOC[3,4] have been widely used to set up stereocentres by rearrangement through predictable five- and six-membered transition states. Nakai and coworkers have noted the synthetic potential of sequential [2,3]-Wittig-AOC rearrangements for acyclic stereocontrol and asymmetric transmission but, as with their earlier work, there are no true tandem reactions.[5] We report here the first example of a 'one-pot' tandem [2,3]-Wittig-AOC rearrangement, which can be considered a homologated version of the Ireland ester enolate Claisen rearrangement without allylic transposition.[6] We have shown it to be a stereoconvergent reaction and to proceed with a high degree of acyclic stereocontrol. The methodology was applied to the diastereoselective synthesis of substituted tetrahydropyrans which are important structural sub-units in many natural products.[7]

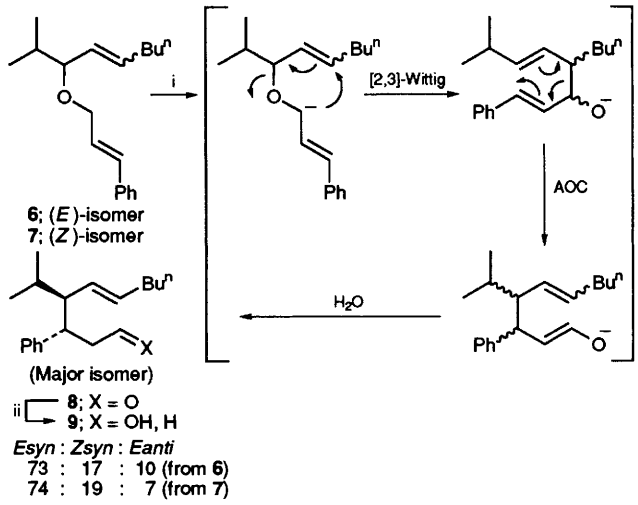
The acyclic bis-allylic ether substrates **6** and **7** for the tandem reaction were synthesised from hex-1-yne as shown in Scheme 1. Deprotonation of hex-1-yne with Bu^nLi followed by reaction with isobutyraldehyde gave the propynyl alcohol **1** in excellent yield. Stereoselective semi-hydrogenation of the propynyl alcohol **1** by aluminium hydride reduction or catalytic hydrogenation delivered the (*E*)- and (*Z*)-allylic alcohols respectively. Red-Al reduction[8] gave the (*E*)-allylic alcohol **3** with 100% geometric purity whilst the (*Z*)-allylic alcohol **5** could be obtained with 98% geometric purity by hydrogenation of the acetate **2** over palladium on barium sulfate.[9] [Catalytic hydrogenation of the propynyl alcohol **1** with the same catalyst resulted in a lower (*Z*)-geometric purity of 93%; this could be increased slightly to 96% by use of Lindlar's catalyst in hexane–hexene.[10]] Tetrabutylammonium iodide catalysed alkylation of the sodium alkoxide of the alcohols **3** and **5** with cinnamyl bromide in THF delivered the bis-allylic ethers **6** and **7** in high yield.

The tandem [2,3]-Wittig-AOC reaction was accomplished by treatment of the bis-allylic ethers **6** and **7** with potassium hydride and 18-crown-6 in Me_2SO (Scheme 2).[11] Reaction was typically complete after 1 h at room temp. even in the absence of 18-crown-6 (although the selectivity was slightly lower without the sequestering agent).† Analysis of the δ,ε-unsaturated aldehyde products **8** by ^1H NMR showed the tandem reaction to be stereoconvergent, with both geometric isomers **6** and **7** giving the same major (*E*)-product. The reactions also gave a minor (*E*)-product and a minor (*Z*)-product. All products resulted from initial regioselective deprotonation at the unsubstituted carbon atom, as reported previously by Nakai *et al.*[12] The stereochemistry of the [2,3]-Wittig-AOC aldehyde products **8** was analysed using Nakai's transition states for rearrangement of acyclic AOC substrate.[11] Both the major (*E*)-aldehyde and the (*Z*)-aldehyde were expected to have *syn* relative configuration from rearrangement *via* chair transition states. The minor (*E*)-product, with opposite (*anti*) relative configuration, is likely to be formed by rearrangement through a boat transition state. Hydrogenation of the double bond confirmed that the major (*E*)-isomer and the (*Z*)-isomer had the same relative configuration.‡ About 15% yield from the reaction was made up of isomers formed by another pathway, possibly a [1,2]-Wittig-AOC tandem reaction. The isomeric mixture of aldehydes from the tandem reaction was converted to the corresponding alcohols **9** by treatment with sodium borohydride in methanol.

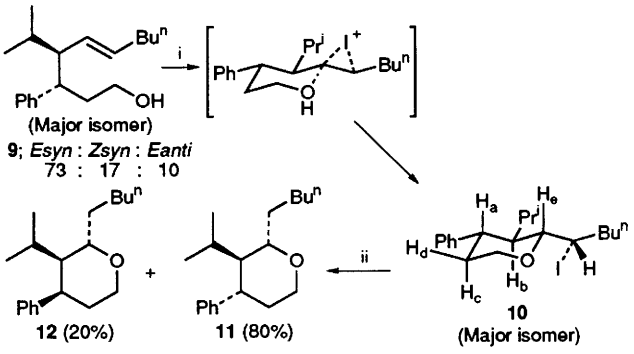
The *syn* relative configuration of the major isomer from the tandem reaction was proved by conversion of a 75 : 17 : 10 mixture of isomeric unsaturated alcohols *Esyn*-**9**, *Zsyn*-**9** and *Eanti*-**9**, obtained from a tandem reaction of the (*E*,*E*)-bis-allylic ether **6**, to iodotetrahydropyrans **10** (Scheme 3). The base-catalysed iodocyclisation reaction was accomplished



Scheme 1 *Reagents and conditions*: i, Bu^nLi, isobutyraldehyde, THF, −78 °C, 3 h, 95%; ii, Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temp., 22 h, 93%; iii, Red-Al, Et_2O, reflux, 19 h; potassium sodium tartrate, 86%, [100% (*E*)-isomer]; iv, H_2, 1 atm, Pd-$BaSO_4$, MeOH, quinoline, 90%; v, K_2CO_3, H_2O–MeOH, room temp., 16 h, 64%, [98% (*Z*)-isomer]; vi, NaH, cinnamyl bromide, Bu_4NI (cat), 40 °C, 20 h, 76% **6** and 83% **7**



Scheme 2 *Reagents and conditions*: i, KH, 18-crown-6, Me_2SO, room temp., 1 h, 44% (yield of **8** from **7**); ii, $NaBH_4$, MeOH, 0 °C, 30 min, 57% (yield of **9** from **6**)



Scheme 3 *Reagents and conditions*: i, I_2, $NaHCO_3$, MeCN, −23 °C–room temp., 24 h, 45%; ii, Bu_3SnH, AIBN (cat), THF, room temp., 16 h, 97%

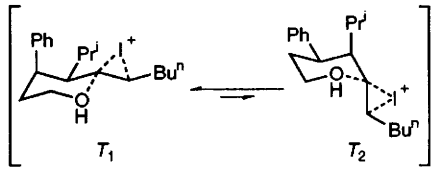


Fig. 1 Transition states for formation of minor tetrahydropyran isomer **12**

using iodine and sodium hydrogen carbonate in acetonitrile, conditions for kinetic control.[13] Recovery of the starting material from the cyclisation reaction showed preferential reaction of the (*E*)-isomers. The ^1H NMR of the iodotetrahydropyran product showed one major product (>80% of the mixture) and two stereoisomers; the major isomer was isolated by flash chromatography. Assignment of the ^1H NMR spectrum by decoupling and COSY experiments showed this isomer to be the all-equatorial iodotetrahydropyran from cyclisation through a transition state in which the iodonium cation is equatorial. The methine proton on the phenyl-bearing carbon, H_a, exhibited two large couplings (*J* 11.5 Hz) to the *trans*-diaxial protons H_b and H_c, and a smaller coupling to the equatorial proton H_d (*J* 4 Hz). Thus, the isopropyl and phenyl groups must be *syn* in the acyclic molecule.

De-iodination of the original mixture of iodotetrahydropyran stereoisomers with tributyltin hydride gave just two tetrahydropyrans **11** and **12** in a 4 : 1 ratio. The major isomer **11** was shown to be derived from the major iodotetrahydropyran isomer by comparison of the ^1H NMR spectra. Examination of the ^1H NMR spectrum of the minor isomer **12** showed it to have arisen from the tandem reaction product with *anti* relative configuration; the signal for the axial methine proton H_a (see assignment for **10**) showed one large coupling to the diaxial proton H_c (*J* 12 Hz) and two small couplings to equatorial protons H_b and H_d (*J* 5 Hz). The axial orientation of the *n*-pentyl group was confirmed by an NOE experiment; irradiation of the axial proton H_a resulted in no enhancement of the signal due to the methine proton on the *n*-pentyl-bearing carbon, H_e, (this contrasted with irradiation of the same proton in the major iodotetrahydropyran isomer which showed a strong enhancement of the axial methine proton resonance). We suggest that the minor isomer is formed *via* a cyclisation transition state, T_1, in which the iodonium ion is actually equatorial (Fig. 1) as the alternate transition state, T_2, would be destabilised by the presence of two axial substituents. The observed minor tetrahydropyran conformation must therefore be the thermodynamic product.

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Footnotes

† *Typical experimental procedure*: KH (2–3 equiv.) was washed with THF to remove mineral oils, dried, and transferred under argon to a Schlenk flask holding an argon atmosphere before being treated with dry Me_2SO (80 equiv.). After effervescence had subsided, 18-crown-6 (1.5 equiv.) was added to the clear, homogeneous solution. After 5 min a solution of the bis-allylic ether in a small volume of Me_2SO was added and the deep-purple solution was stirred for *ca.* 1 h at room temp. before being poured onto an ice–brine mixture. After acidification to pH 7 with 1 mol dm^{-3} HCl, the aqueous layer was extracted several times with ethyl acetate and the combined organic extracts were washed with H_2O to remove Me_2SO. Drying (Na_2SO_4) and concentration *in vacuo* gave the crude tandem reaction product. Analysis of the stereoselectivity of the reaction by GC was carried out on the crude reaction mixture. The aldehyde products **8** could be obtained pure by flash chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) containing triethylamine, or reduced directly to the alcohols **9**.

‡ Hydrogenation of a 58 : 13 : 13 : 16 mixture of *Esyn*-**9**, *Zsyn*-**9**, *Eanti*-**9** and other isomers with Adam's catalyst gave a 72 : 18 : 10 ratio of saturated alcohols; calculated ratio, 71 : 16 : 13.

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