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

**Nicholas Greeves* and Katya Jane Vines**

*Robert Robinson Laboratories, Department of Chemistry, Liverpool University, PO Box 147, Liverpool, UK L69 3BX*

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.

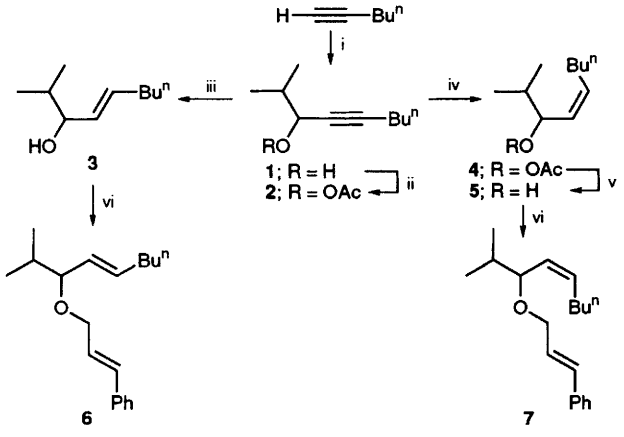


Tandem reactions provide an opportunity for linking the synthetic power of two or more transformations in a single synthetic operation.[1] Sigmatropic rearrangements such as the [2,3]-Wittig,[2] and the AOC[3,4] have been widely used to set up stereocentres by rearrangement through predictable five- 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]

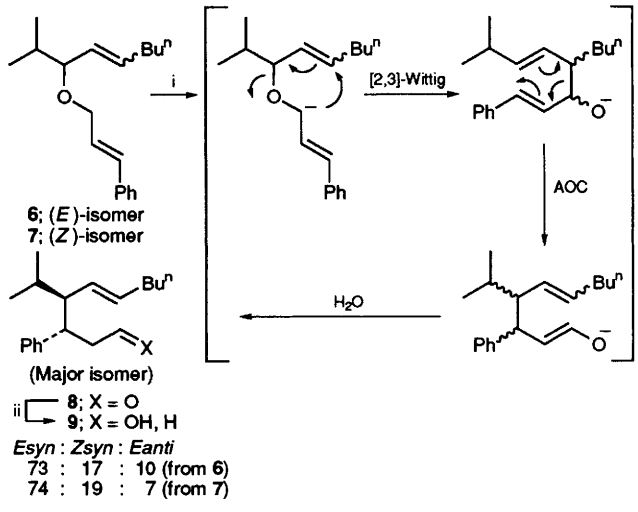
The acyclic bis-allylic ether substrates **6** and **7** for the tandem reaction were synthesised from hex-1-yne as shown in Scheme 1. Deprotonation of hex-1-yne with Bu$^n$Li followed by reaction with isobutyraldehyde gave the propynyl alcohol **1** in excellent yield. Stereoselective semi-hydrogenation 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.

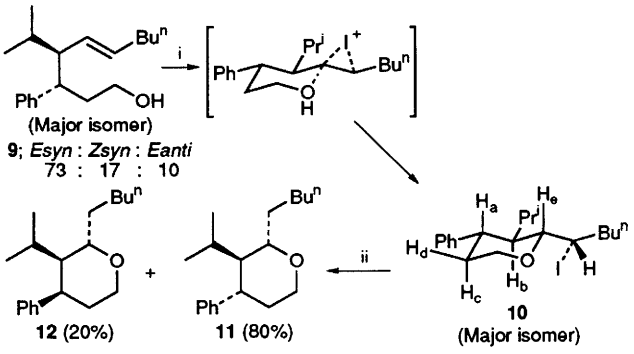
The *syn* relative configuration of the major isomer from the tandem reaction was proved by conversion of a 75 : 17 : 10 mixture of isomeric unsaturated alcohols *Esyn*-**9**, *Zsyn*-**9** and *Eanti*-**9**, obtained from a tandem reaction of the (*E*,*E*)-bis-allylic ether **6**, to iodotetrahydropyrans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




**Scheme 1** *Reagents and conditions*: i, Bu$^n$Li, 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%

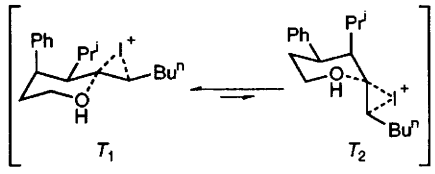



**Fig. 1** Transition states for formation of minor tetrahydropyran isomer **12**

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.

We are grateful to SERC and Zeneca Pharmaceuticals for financial support (CASE award to K. J. V.) and to Drs R. Andrew and S. Pegg for many helpful discussions.

*Received, 25th March 1994; Com. 4/01795A*

## 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.

## References

1 T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992.
2 K. Mikami and T. Nakai, *Synthesis*, 1991, 594.
3 S. R. Wilson, *Org. React.*, 1993, **43**, 93.
4 L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 609.
5 S. Y. Wei, K. Tomooka and T. Nakai, *J. Org. Chem.*, 1991, **56**, 5973.
6 R. E. Ireland and M. D. Varney, *J. Am. Chem. Soc.*, 1984, **106**, 3668.
7 T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309.
8 S. E. Denmark and T. K. Jones, *J. Org. Chem.*, 1982, **47**, 4595.
9 J. S. Panek and T. D. Clark, *J. Org. Chem.*, 1992, **57**, 4323.
10 L. Deng and E. N. Jacobsen, *J. Org. Chem.*, 1992, **57**, 4320.
11 S. Y. Wei, K. Tomooka and T. Nakai, *Tetrahedron*, 1993, **49**, 1025.
12 T. Nakai, K. Mikami, S. Taya and Y. Fujita, *J. Am. Chem. Soc.*, 1981, **103**, 6492.
13 W. E. Barnett and W. H. Sohn, *J. Chem. Soc., Chem. Commun.*, 1972, 472.