Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6449-6452, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01474-3

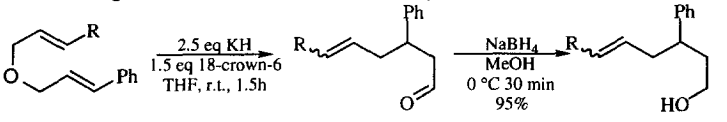
Synthetic Applications (I) of the Tandem [2,3]-Wittig-Anionic Oxy-Cope Rearrangement: Stereoselective Disubstituted Tetrahydropyran Synthesis by Electrophile Initiated Cyclisation

Nicholas Greeves* and Wai-Man Lee

Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Crown St Liverpool L69 7ZD U.K.

Abstract: Reduction of the δ,ε-unsaturated aldehydes produced by tandem [2,3]-Wittig-anionic oxy-Cope rearrangement followed by stereoselective electrophilic cyclisation and reductive removal of the electrophile leads to single diastereoisomers of tetrahydropyrans. © 1997 Elsevier Science Ltd.

Treatment of cinnamyl allylic ethers with potassium hydride and 18-crown-6 in THF produces δ,ε-unsaturated aldehydes in good yield *via* tandem [2,3]-Wittig-anionic oxy-Cope rearrangement. If the alkyl substituent R is branched (e.g. *t*-Bu, *i*-Pr), exclusive *E* olefin geometry is obtained (Scheme 1).[1]



Scheme 1. Stereoselective δ,ε-unsaturated alcohol preparation

In our initial work we reduced the aldehydes to the corresponding alcohols to allow iodine initiated electrophilic cyclisation to tetrahydropyrans to determine the stereochemistry of the tandem rearrangement.[2] We proposed six-membered chair transition states for the stereoselective cyclisation in which the phenyl group and the iodonium ion prefer to adopt an equatorial orientation, Figure 1. The newly formed ring stereocentre is the same regardless of starting alkene geometry so reductive removal of the electrophile produces a single stereoisomer. Herein we report the effect of varying the steric bulk of the alkyl group and the nature of the electrophile in the synthesis of single diastereoisomers of disubstituted tetrahydropyrans.

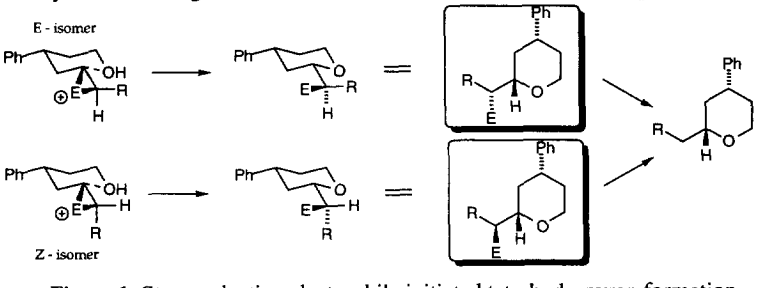
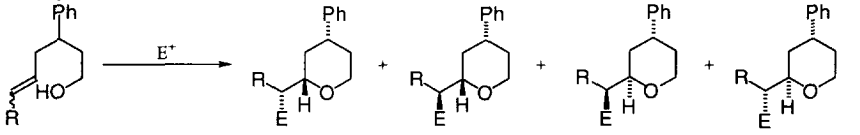


Figure 1. Stereoselective electrophile initiated tetrahydropyran formation

Reduction of the δ,ε-unsaturated aldehydes proceeded smoothly with sodium borohydride in methanol at 0 °C to produce the required unsaturated alcohols with no change in the geometric ratio of the alkene. Initially we examined halogen electrophiles; iodine (I_2),[2,3] N-iodosuccinimide (NIS),[4] and iodine monochloride (ICl)[5] were selected as sources of I^+ and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO)[6] was chosen as a convenient source of Br^+ for electrophilic cyclisation. Better yields were found when I_2 (Method A) was used as electrophile, compared with NIS, ICl and TBCO (Scheme 2 and Table 1). A single

diastereoisomer of iodotetrahydropyran **2c**, **4c** and **2d** was isolated if the precursor alcohol was geometrically pure (entries 6 and 7, R = *i*-Pr, *t*-Bu) otherwise two diastereoisomers of halogenated tetrahydropyrans **2, 3** were isolated in ratios that were consistent with stereospecific conversion of the starting geometry of the alkene (entries 1-5, R = Me, *n*-Bu).[7]



a R = Me
b R = *n*-Bu
c R = *i*-Pr
d R = *t*-Bu
e R = *n*-Pr

Method A : I_2 (3 eq), $NaHCO_3$ (3 eq), MeCN, -23 °C - r.t., 24 h
Method B : NIS (1.2 eq), CH_2Cl_2, -78 °C - r.t.
Method C : ICl (2 eq), NEt_3 (2 eq), CH_2Cl_2, -78 °C - r.t.
Method D : TBCO (1.2 eq), CH_2Cl_2, dark, r.t., 1 week
Method E : 1.1eq Phenylthiomorpholine (1.1 eq), TfOH (1.1 eq), CH_2Cl_2, 0°C , 2 h
Method F : NPSP (1.7 eq), PPTS (0.3 eq), CH_2Cl_2, -78 °C - r.t., 9 h

Scheme 2.

Table 1. Electrophile initiated cyclisation of unsaturated alcohols (**1a-e**)

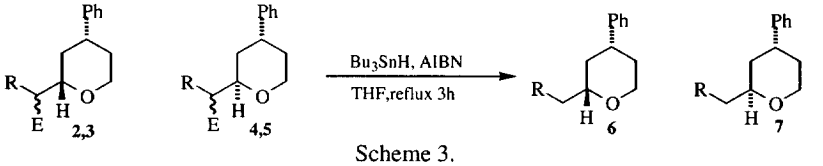
Entry	Substrate	R	Substrate geometry[a] *E* : *Z*	E^+	Method	Yield /%	Product ratio[b] 2 : 3 : 4 : 5
1	**1a**	Me	75 : 25	I^+	A	65	77 : 23 : - : -
2	**1a**	Me	75 : 25	I^+	B	39	77 : 23 : - : -
3	**1a**	Me	75 : 25	I^+	C	26	77 : 23 : - : -
4	**1b**	*n*-Bu	79 : 21	I^+	A	78	87 : 13 : - : -
5	**1b**	*n*-Bu	79 : 21	Br^+	D	56	79 : 21 : - : -
6	**1c**	*i*-Pr	100 : 0	I^+	A	80	74[c] : - : 26[c] : -
7	**1d**	*t*-Bu	100 : 0	I^+	A	62	100 : - : - : -
8	**1e**	*n*-Pr	84 : 16	PhS^+	E	57	28[d] : 6[d] : 59[d] : 7[d]
9	**1e**	*n*-Pr	84 : 16	$PhSe^+$	F	86	28[d] : 9[d] : 57[d] : 6[d]
10	**1d**	*t*-Bu	100 : 0	$PhSe^+$	F	97	57[c] : - : 43[c] : -

[a] *E*:*Z* ratio measured by GC; [b] Ratio measured by GC; [c] ratio measured by mass from flash column chromatography isolation; [d] ratio measured by mass between diastereoisomer pair 2,3 and 4,5 and then GC analysis of each pair.

The stereochemical relationship between tetrahydropyran diastereoisomers listed in Table 1 was proved by treatment with Bu_3SnH and catalytic amount of AIBN which produced a single diasterisomer of disubstituted tetrahydropyran **6** or **7** stereoconvergently (Scheme 3) as demonstrated by 400 MHz ^1H NMR, and GC analysis.[8] This demonstrated unequivocally that the only difference between **2a** and **3a** was at the stereogenic centre bearing iodine, arising directly from the double bond geometry, and not from the orientation of the iodonium ion during cyclisation. The stereoconvergency of diastereoisomeric pairs of **2, 3** and **4, 5** after the reductive removal of electrophile is shown in Table 2.

When the alkyl group R was *i*-Pr (Table 1, entry 6) two separable compounds were formed, one was the expected iodotetrahydropyran **2c** and the other an unexpected diastereoisomer **4c** which was the result of the iodonium ion adopting an axial orientation during cyclisation. Phenylsulfonium[9] PhS^+ and phenylselenononium[10] $PhSe^+$ ions, generated by phenylthiomorpholine[11]/triflic acid and N-phenylselenophthalimide (NPSP)/PPTS[10] respectively also promoted efficient cyclisation producing a mixture of four diastereomeric tetrahydropyrans **2, 3, 4, 5** (entries 8-10). Fortunately diastereoisomers **2** and **3** were separable by flash column chromatography from the other pair of diastereoisomers **4** and **5** corresponding to equatorial and axial orientation respectively of the ions during cyclisation. The

diastereoisoselectivity between the isomeric pairs **2, 3** and **4, 5** was not high as observed for iodine, where **4, 5** was observed only once, and favoured the *axial* product. When the alkyl group R was *t*-Bu and there was therefore a single geometry of alkene in the substrate, cyclisation occurred with $PhSe^+$ to produce two separable diastereoisomers (entry 10, **2d** and **4d**) of tetrahydropyran in excellent yield. This demonstrates unequivocally that use of PhS^+ and $PhSe^+$ as electrophiles leads to the phenylsulfonium and phenylselenononium ions adopting an axial orientation in preference to the equatorial orientation selected by the corresponding iodonium ion during cyclisation (Scheme 4). $PhSe^+$ as the electrophile gave better yields than PhS^+ but showed very little difference in diastereoselectivity. The stereochemistry of all separable diastereoisomers was proven by detailed structural analysis (400 MHz ^1H NMR and COSY experiments[12] and GC) and identity of samples produced by reductive removal of the electrophile. In particular, the reduction of mixtures of diastereoisomers to produce a single diastereoisomer confirmed the stereoconvergency of the overall process.(Table 2)

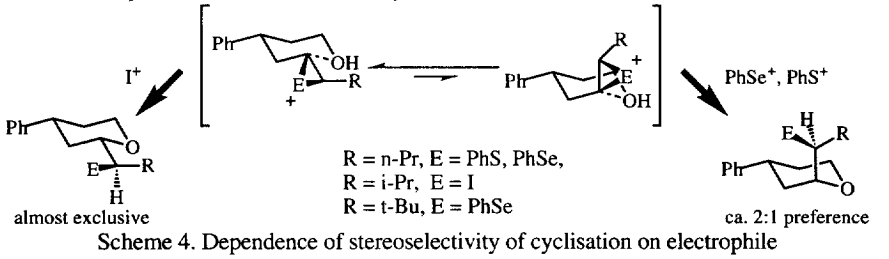


Scheme 3.

Table 2. Reductive removal of the electrophile - proof of tetrahydropyran stereochemistry

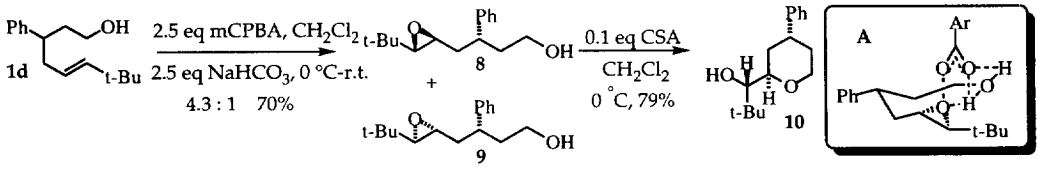
Substrate	R	E	Yield/%	Product[a]
2a + 3a	Me	I	71	6a
2e + 3e	*n*-Pr	PhSe	96	6e
4e + 5e	*n*-Pr	PhSe	90	7e
2c	*i*-Pr	I	80	6c
4c	*i*-Pr	I	80	7c
2d	*t*-Bu	PhSe	89	6d
4d	*t*-Bu	PhSe	89	7d

[a] single diastereoisomeric product isolated and confirmed by 400 MHz ^1H NMR, COSY and GC.



Scheme 4. Dependence of stereoselectivity of cyclisation on electrophile

Acid-catalysed epoxide opening[13] was used to produce the substitution pattern opposite to that favoured by iodine mediated cyclisation (Scheme 5). The single geometric isomer of unsaturated alcohol **1d** was epoxidised with mCPBA with slight excess of $NaHCO_3$ in CH_2Cl_2 at 0 °C to form two diastereoisomers in the ratio of 4.3:1. This is consistent with the hydrogen-bonded interaction between oxygen and hydrogen atoms of peracid and the unsaturated alcohol.[14] A possible chelated transition state **A** is proposed based on the observed diastereoselectivity of the epoxidation. The major *anti* diastereoisomer of epoxide **8** was subjected to cyclisation catalysed by camphorsulfonic acid *via* epoxide opening from intramolcular nucleophilic attack of hydroxyl group giving hydroxyl-functionalised tetrahydropyran **10** as a single diastereoisomer.[15]



Scheme 5. Stereoselective epoxidation and acid-catalysed stereospecific cyclisation

In conclusion, we have demonstrated the use of I^+, Br^+, $PhSe^+$ and PhS^+ ions as useful electrophiles for cyclisation after the reduction of the aldehydes from tandem [2,3]-Wittig-anionic oxy-Cope rearrangement of bis-allylic ethers. Halogen based reagents were generally more diastereoselective, favouring the *cis* substitution pattern, than phenylselenyl and phenylsulfenyl analogues which were found to be more likely to allow axial orientation of the intermediate PhS^+ or $PhSe^+$ ions leading to the *trans* substitution pattern. A hydroxyl-functionalised tetrahydropyran was also synthesised as a single diastereoisomer by employing stereospecific acid catalysed epoxide opening.

Acknowledgement: We would like to thank ORS for the partial financial support.

References and notes

1. Preceeding paper in this issue, Greeves, N.; Lee, W. M. *Tetrahedron Lett.*, **1997**, 38, 6445.
2. Greeves, N.; Vines, K. J. *J. Chem. Soc., Chem. Commun.*, **1994**, 1469-1470.
3. a) Bedford, S. B.; Bell, K. E.; Fenton, G.; Hayes, C. J.; Knight. D. W.; Shaw, D. *Tetrahedron Lett.*, **1992**, 33, 6511-6514. b) Grote, J.; Harigaye, Y.; Williams, D. R. *Tetrahedron Lett.*, **1984**, 25, 5231-5234.
4. Kawamura, S-I.; Tamaru, Y.; Yoshida, Z-I. *Tetrahedron Lett.*, **1985**, 26, 2885-2888.
5. Duan, J. J-W.; Smith, A. B. *J. Org. Chem.*, **1993**, 58, 3703-3711.
6. Bartlett, P. A.; Ting, P. C. *J. Am. Chem. Soc.*, **1984**, 106, 2668-2671.
7. **(2d E=I)** ^{1}H (400 MHz, $CDCl_3$, TMS) δ : 7.3-7.2 (5H, m, Ph), 4.3 (1H, d, *J* 3.4 Hz, C<u>H</u>I), 4.1 (1H, ddd, *J* 11.6, 4.4, and 1.7 Hz, OC<u>H</u>$_{eq}$H$_{ax}$), 3.6 (1H, td, *J* 11.6 and 2.4 Hz, OCH$_{eq}$<u>H</u>$_{ax}$), 3.0 (1H, ddd, *J* 10.4, 3.4, and 2.2 Hz, R$_2$C<u>H</u>$_{ax}$OR), 2.8 (1H, tt, *J* 12.2 and 4.0 Hz, C<u>H</u>$_{ax}$Ph), 1.8-1.6 (4H, m, CH_2), 1.1 (9H, s, *t*-Bu).
8. **(6a)** ^{1}H (400 MHz, $CDCl_3$, TMS) δ : 7.3-7.1 (5H, m, Ph), 4.1 (1H, ddd, *J* 11.4, 3.8, and 2.3 Hz, OC<u>H</u>$_{eq}$H$_{ax}$), 3.5 (1H, tdd, *J* 11.5, 5.5, and 2.7 Hz, OCH$_{eq}$<u>H</u>$_{ax}$), 3.3-3.2 (1H, tdd, *J* 10.4, 6.0, and 2.2 Hz, R$_2$C<u>H</u>$_{ax}$OCH$_2$R), 2.7 (1H, tt, *J* 12.1 and 3.8 Hz, C<u>H</u>$_{ax}$Ph), 1.8-1.3 (6H, m, CH_2), 0.9 (3H, t, *J* 7.4 Hz, Me).
9. Brownbridge, P.; Jones, K.; Lopez-Tudanca, P. L. *Tetrahedron Lett.*, **1991**, 32, 2261-2264.
10. Grab, L. A.; Salvino, J. M.; Willard, P. G.; Wrensford, G. *Tetrahedron Lett.*, **1990**, 31, 4257-4260.
11. Krogh, J. A.; Sosnovsky, G. J. *Synthesis*, **1979**, 228-230.
12. **(2e, 3e** E = SePh) ^{1}H (400 MHz, $CDCl_3$, TMS) δ : 7.5-7.1 (10H, m, Ph), 4.2-4.1 (1H, ddd, *J* 11.6, 4.0, and 2.0 Hz, R$_2$OC<u>H</u>$_{eq}$H$_{ax}$), 3.6 (1H, tdd, *J* 11.6, 5.2, and 2.0 Hz R$_2$OCH$_{eq}$<u>H</u>$_{ax}$) 3.5 (1H, ddd, *J* 11.0, 8.0 and 4.4 Hz R$_2$C<u>H</u>$_{ax}$OCH$_2$), 3.1 (1H, dt, *J* 8.8 and 4.8 Hz, C<u>H</u>SePh), 2.8-2.6 (1H, tt, *J* 12.0 and 3.8 Hz, C<u>H</u>$_{ax}$Ph), 2.0-1.2 (8H, m, CH_2), 0.9 (3H, t, *J* 7.2 Hz, Me).

    (6e) ^{1}H (400 MHz, $CDCl_3$, TMS) δ : 7.3-7.1 (5H, m, Ph), 4.1 (1H, ddd, *J* 11.6, 4.0, and 2.0 Hz, R$_2$OC<u>H</u>$_{eq}$H$_{ax}$), 3.5 (1H, tdd, *J* 11.6, 5.5, and 2.7 Hz R$_2$OCH$_{eq}$<u>H</u>$_{ax}$), 3.4-3.3 (1H, tdd, *J* 10.4, 5.2, and 2.4 Hz, R$_2$C<u>H</u>$_{ax}$OCH$_2$), 2.7 (1H, tt, *J* 12.0 and 4.0 Hz, C<u>H</u>$_{ax}$Ph), 1.8-1.3 (10H, m, CH_2), 0.9 (3H, t, *J* 7.2 Hz, Me).

    (4e,5e E = SePh) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.5-7.0 (10H, m, Ph), 3.8 (1H, td, *J* 9.3 and 4.4 Hz, R$_2$C<u>H</u>$_{eq}$OR), 3.7 (2H, m, R$_2$OCH$_2$) 3.5-3.4 (1H, td, *J* 9.5 and 3.3 Hz, R$_2$C<u>H</u>SePh), 2.8-2.7 (1H, tt, *J* 12.6 and 3.8 Hz C<u>H</u>$_{ax}$Ph), 2.2 (1H, dt, *J* 13.6 and 4.4 Hz, C<u>H</u>$_{eq}$H$_{ax}$RCOCH$_2$R), 2.0 (1H, ddd, *J* 13.6, 9.2, and 4.4 Hz, CH$_{eq}$<u>H</u>$_{ax}$RCOCH$_2$R), 1.4-1.4 (6H, m, CH_2), 0.9 (3H, t, *J* 7.1 Hz, Me).

    (7e) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.3-7.1 (5H, m, Ph), 3.8 (1H, td, *J* 5.5 and 3.3 Hz, R$_2$C<u>H</u>$_{eq}$OR), 3.8-3.7 (1H, td, *J* 11.5 and 6.0 Hz, R$_2$OCH$_{eq}$<u>H</u>$_{ax}$), 3.7-3.6 (1H, dt, *J* 11.5 and 4.4 Hz, R$_2$OC<u>H</u>$_{eq}$H$_{ax}$), 3.0 (1H, tt, *J* 13.1 and 4.4 Hz, C<u>H</u>$_{ax}$Ph), 2.0 (1H, ddd, *J* 13.7, 9.4, and 4.4 Hz, CH$_{eq}$<u>H</u>$_{ax}$RHCOCH$_2$R) 1.9-1.8 (1H, dd, *J* 11.5 and 6.0 Hz, R$_2$OCH$_2$C<u>H</u>$_{eq}$H$_{ax}$), 1.7 (1H, dt, *J* 13.7 and 4.4 Hz, C<u>H</u>$_{eq}$H$_{ax}$RHCOCH$_2$R), 1.5-1.2 (5H, m, CH_2), 0.9 (3H, t, *J* 6.6 Hz, Me).

    (6d) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.3-7.1 (5H, m, Ph), 4.1-4.0 (1H, dt, *J* 11.5 and 3.3 Hz, R$_2$OC<u>H</u>$_{eq}$H$_{ax}$R), 3.6-3.5 (1H, tdd, *J* 11.5, 5.5 and 2.7 Hz, R$_2$OCH$_{eq}$<u>H</u>$_{ax}$R), 3.5-3.4 (1H, ddd, *J* 10.4, 6.0, and 2.2 Hz, R$_2$C<u>H</u>$_{ax}$OCH$_2$) 2.8-2.7 (1H, tt, *J* 11.5 and 3.8 Hz, C<u>H</u>$_{ax}$Ph), 1.8-1.2 (6H, m, CH_2), 0.9 (9H, s, *t*-Bu).

    (7d) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.3-7.1 (5H, m, Ph), 4.0-3.9 (1H, td, *J* 7.7 and 4.4 Hz, R$_2$C<u>H</u>$_{eq}$OR), 3.8(1H, td, *J* 11.5 and 5.5 Hz, ROC<u>H</u>$_{ax}$H$_{eq}$R), 3.7-3.6 (1H, dt, *J* 11.5 and 4.4 Hz, ROCH$_{ax}$<u>H</u>$_{eq}$R), 3.1-2.9 (1H tt, *J* 13.1 and 3.8 Hz, C<u>H</u>$_{ax}$Ph), 2.0-1.2 (6H, m, CH_2), 0.9 (9H, s, *t*-Bu).
13. a) Hwang, C. K.; Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K. *J. Am. Chem. Soc.*, **1989**, 111, 5335-5340. b) Ho, P. T. *Can. J. Chem.*, **1982**, 60(1), 90-94.
14. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.*, **1993**, 93, 1307-1370.
15. **(10)** ^{1}H (400 MHz, $CDCl_3$, TMS) δ : 7.3-7.2 (5H, m, Ph), 3.8 (1H, ddd, *J* 11.5, 5.8, and 4.4 H R$_2$CHOC<u>H</u>$_{eq}$H$_{ax}$R), 3.7 (1H, ddd, *J* 9.2, 5.3, and 4.4 Hz, R$_2$C<u>H</u>$_{ax}$OR), 3.6 (1H, ddd, *J* 11.7, 8.0, and 3.8 Hz, R$_2$CHOCH$_{eq}$<u>H</u>$_{ax}$R), 3.5 (1H, d, *J* 5.3 Hz, C<u>H</u>OH), 3.2-3.1 (1H, quin, *J* 5.7 Hz, C<u>H</u>$_{eq}$Ph), 2.2-1.9 (4H, m, CH_2), 1.7 (1H, br. s, OH), 0.9 (9H, s, *t*-Bu).

(*Received in UK* 5 *June* 1997; *revised* 16 *July* 1997; *accepted* 18 *July* 1997)