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Synthetic Applications (II) of the Tandem [2,3]-Wittig-Anionic Oxy-Cope Rearrangement: Stereoselective Trisubstituted δ-Lactone and Tetrahydropyran Synthesis

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Abstract: Di- and trisubstituted δ-lactones have been prepared by stereoselective iodolactonisation and phenylselenolactonisation of δ,ε-unsaturated carboxylic acids. The acyclic stereochemistry of the acids arises from highly stereoselective tandem [2,3]-Wittig-anionic oxy-Cope rearrangement of cinnamyl ethers with potassium hydride and 18-crown-6 in THF to give δ,ε-unsaturated aldehydes.
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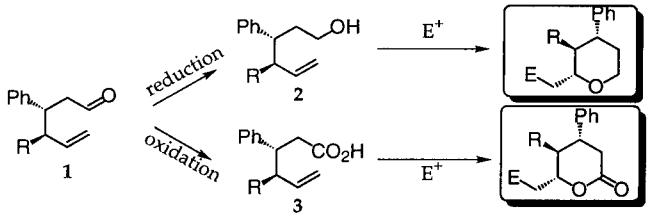
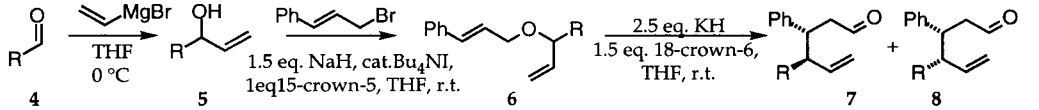
Tetrahydropyrans and six-membered lactones, which can be reduced to the corresponding lactols, are important components of a wide range of interesting biologically active natural products including polyether antibiotics and carbohydrate derivatives.[1] We have reported the application of our tandem [2,3]-Wittig-anionic oxy-Cope rearrangement[2] to the synthesis of single isomers of tetrahydropyrans by electrophilic cyclisation with various electrophiles (I^+, Br^+, PhS^+ and $PhSe^+$)[2,3,4] and acid-catalysed intramolecular epoxide opening.[3,5] Herein we report the highly diastereoselective preparation of trisubstituted δ-lactones as well as related tetrahydropyrans exploiting the acyclic stereocontrol of our tandem rearrangement. The aldehyde of major diastereoisomer **1** can either be reduced to primary alcohol **2** or oxidised to the corresponding carboxylic acid **3** followed by electrophilic cyclisation (Scheme 1).



Scheme 1. Tetrahydropyran and δ-lactone synthesis by electrophilic cyclisation

The starting substrate, bis-allylic ethers **6a-c**, could be prepared by treating the secondary alcohol **5** with 1.1 eq. of cinnamyl bromide and 1.5 eq. of sodium hydride with catalytic amount of tetrabutylammonium iodide as nucleophilic catalyst. In more hindered cases 15-crown-5 was found to be helpful for the alkylation of the secondary allylic alcohols. The subsequent tandem rearrangement was accomplished by reacting the cinnamyl ether with 2.0-2.5 eq. of potassium hydride together with 1.5 eq. of 18-crown-6 to give the useful unsaturated aldehydes **7** and **8** with high diastereoselectivity (Scheme 2) The stereochemistry was subsequently confirmed by X-ray crystallography of a cyclic derivative (*vide infra*).



4	5	6	7 : 8	
(a) R = i-Pr	99%	76%	96 : 4	79%
(b) = cyclohexyl	84%	98%	94 : 6	67%
(c) = n-Pr	99%	85%	90 : 10	74%

Scheme 2. Stereoselective tandem [2,3]-Wittig-anionic oxy-Cope rearrangement of cinnamyl ethers

The observed stereoselectivity may be understood by considering the transition states for the second phase of the tandem process which is the anionic oxy-Cope rearrangement. The well precedented *E*-selectivity of the [2,3]-Wittig rearrangement[6] makes it likely that the intermediate alkoxide will have *E,E*-geometry. Anionic oxy-Cope rearrangement *via* a chair transition state **9** leads to the major diastereoisomer **7** while the minor diastereoisomer **8** could arise from a boat transition state **10** as shown in Figure 1. The diastereoselectivities were found to be very good, from 90 : 10 to 96 : 4 in favour of the *syn* diastereoisomer, analysed by the inspection of the methine proton next to the phenyl group by ^{1}H NMR.

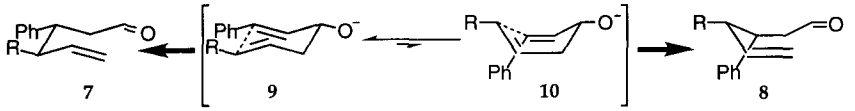
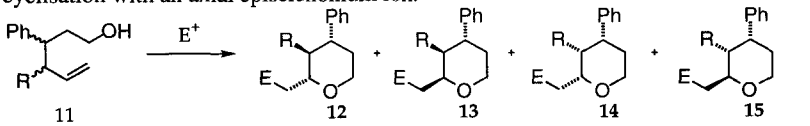


Figure 1. Possible transition states for AOC rearrangement

The aldehydes **7, 8** were reduced to the corresponding alcohols with sodium borohydride or oxidised by sodium chlorite,[7] in the presence of potassium orthophosphate buffer and 2-methyl-2-butene as an acid scavenger, to the carboxylic acids in quantitative yield.

We selected iodonium ion (I^+) and phenylselenononium ion ($PhSe^+$) as electrophiles to initiate cyclisation and the results (Table 1 and 2) leading to tetrahydropyrans and δ-lactones are shown in schemes 3, 4 and 6. Both tetrahydropyran and δ-lactone synthesis could be achieved by the use of iodine with sodium bicarbonate in acetonitrile. However, phenylselenyl functionalised tetrahydropyrans could only be synthesised by N-phenylselenophthalimide with catalytic amount of pyridinium-p-toluenesulfonate as a proton source. No reaction was found if the reagent was replaced by phenylselenyl chloride but in the presence of pyridine as weak base, δ-lactones were readily obtained.[8] The ratio of diastereoisomers produced by the tandem rearrangement was maintained in the product tetrahydropyrans and δ-lactones. The stereochemistry of all cyclic products was determined by ^{1}H NMR and COSY[9] correlating with key compounds whose structures were determined by X-ray crystallography (Figures 2, 3). The iodonium ion exhibits a clear preference for an equatorial orientation during cyclisation favouring the formation of tetrahydropyrans **12** and **14** from the *major* and *minor* isomers respectively. We observed that the episelenonium ions were more likely to adopt an axial orientation during cyclisation to form a tetrahydropyran (Scheme 3),[3] giving another diastereoisomer **13** which was oxidised to selenone[10] **20** (Scheme 5) to provide a solid derivative suitable for X-ray crystallography. We did not detect any of the diastereoisomer **15** arising from the minor diastereoisomer undergoing cyclisation with an axial episelenonium ion.



a R = *i*-Pr
b R = cyclohexyl
c R = *n*-Pr

Method A : I_2 (3 eq), $NaHCO_3$ (3 eq), MeCN, -23 °C-r.t., 72h
Method B : N-PSP (1.7 eq), PPTS (0.3 eq), DCM, -78-0 °C-r.t., 24h

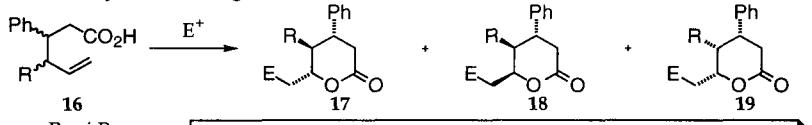
Scheme 3

Table 1. Electrophile initiated cyclisation of unsaturated alcohols **11a-c**

Entry	Substrate	R	E+	Method	Yield / %	Product ratio[a] 12	13	14	15
1	11a	i-Pr	I+	A	78	96	-	4	-
2	11a	i-Pr	PhSe+	B	84	52[b]	44[b]	4[b]	-
3	11b	cyclohexyl	I+	A	73	94	-	6	-
4	11b	cyclohexyl	PhSe+	B	63	48[b]	48[b]	4[b]	-
5	11c	n-Pr	I+	A	80	70	30	trace	-
6	11c	n-Pr	PhSe+	B	77	43[b]	48[b]	9[b]	-

[a] ratio measured by 200 MHz ^{1}H NMR; [b] ratio measured by isolation of isomers.

A single diastereoisomer of iodolactone **17a** was isolated and the structural and stereochemical information were confirmed by X-ray crystallography (Figure 3). The minor diastereoisomer of carboxylic acid **16a** did not cyclise and was recovered unchanged. While the preference for an equatorial iodonium ion during cyclisation was maintained, the conformation of this lactone was observed to be a boat both by X-ray and ^{1}H NMR analysis of the methine proton next to phenyl group.[9] This represents a possible source of error in stereochemical determination based on coupling constant analysis of an assumed chair conformation in δ-lactones. We have been careful to determine the conformation of all the lactones to avoid such errors. This is the first example of the stereochemistry of tandem rearrangement that can be proved by X-ray crystallography in Figures 2 and 3. It is possible that the lower energy of the boat conformation is also reflected in the transition state of the cyclisation (Figure 4).[11]



a R = *i*-Pr
b R = cyclohexyl
c R = *n*-Pr

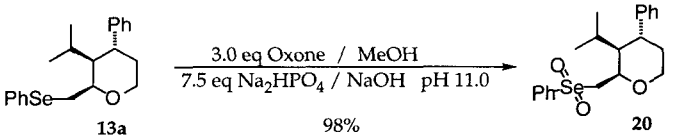
Method A : I_2 (3 eq), $NaHCO_3$ (3 eq), MeCN, 0 °C-r.t., 48h
Method B : PhSeCl (1.1 eq), pyridine (1.1 eq), DCM, -78 °C-r.t., 24h

Scheme 4

Table 2. Electrophilic lactonisation of unsaturated carboxylic acids **16a-c**

Entry	Substrate	R	E+	Method	Yield / %	Product ratio[a] 17	18	19	conformation of **17**
1	16a	i-Pr	I+	A	65	100	-	-	boat
2	16a	i-Pr	PhSe+	B	71	96		4	boat
3	16b	cyclohexyl	I+	A	59	94	-	6	boat
4	16b	cyclohexyl	PhSe+	B	66	94	-	6	boat
5	16c	n-Pr	I+	A	80	30[b]	61[b]	9[b]	chair
6	16c	n-Pr	PhSe+	B	79	71	29	trace	chair

[a] ratio measured by 200 MHz ^{1}H NMR; [b] ratio measured by isolation of isomers.



Scheme 5. Oxidation of selenide **13a** to solid selenone **20**

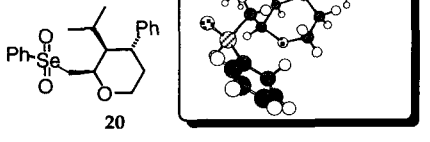


Figure 2. X-ray structure of selenone **20**

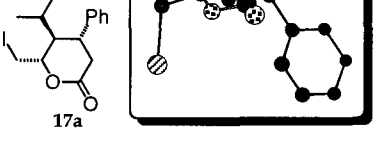
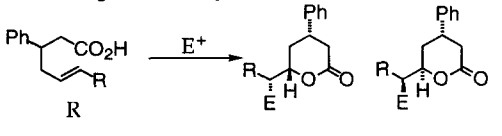
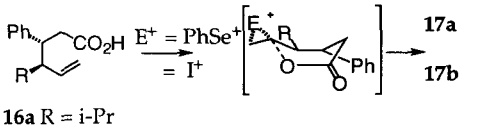


Figure 3. X-ray structure of iodolactone **17a**



i-Pr, 71%	Method A	71	:	29
t-Bu, 78%	Method A	51	:	49
t-Bu, 75%	Method B	41	:	59

Scheme 6. Formation of disubstituted lactones



16a R = i-Pr
16b R = cyclohexyl

Fig. 4. Boat transition state for iodolactonisation

With a branched R group, both iodine and selenium induced cyclisations produced excellent diastereoselectivity in the resulting lactones all of which adopted a boat conformation. However, the chair conformation was observed as R was changed to the less bulky *n* -Pr group (Scheme 4) or simply a proton (Scheme 6) and the cyclisation selectivity changed dramatically. The results suggest the size of alkyl group R and presence of the sp^2 carbonyl group (planar structure and missing methylene proton) are responsible for governing the preference of boat-chair conformation and in turn the cyclisation stereoselectivity. In contrast, during the iodine mediated tetrahydropyran synthesis, only a chair conformation was observed demonstrating the importance of methylene protons in favouring the chair conformation (Figure 5). With both the major *syn* and minor *anti* diastereoisomers the stereochemistry of the products **12a,b** and **14a,b** respectively can be explained by cyclisation *via* a transition state with an equatorial iodonium ion.

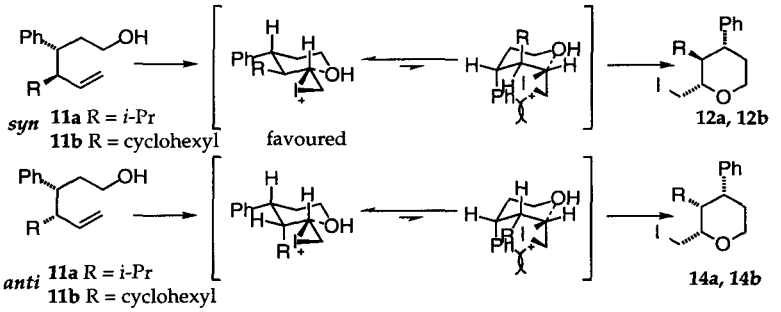


Figure 5. Possible transition states for tetrahydropyran formation

In conclusion, we have demonstrated the diastereoselective synthesis of tetrahydropyrans and δ-lactones exploiting the acyclic stereocontrol of the tandem [2,3]-Wittig-anionic oxy-Cope rearrangement and stereoselective cyclisation. Their synthesis in enantiomerically enriched form through chirality transfer in the tandem rearrangement are in progress and will be reported later.

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§Author to whom enquires about the X-ray crystallography analysis of compounds **17a** and **20** should be directed.

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9. (**17a** E=I) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.3-7.1 (5H, m, Ph), 4.1-4.0 (1H, ddd, *J* 9.4, 5.0 and 3.3 Hz, ICH_2CHOCO), 3.7-3.6 (1H, dd, *J* 11.0 and 3.3 Hz, ICH_2), 3.4 (1H, dd, *J* 11.5 and 4.9 Hz, ICH_2), 3.2-3.1 (1H, q, *J* 6.6 Hz, CHPh), 2.8-2.7 (1H, dd, *J* 15.9 and 6.6 Hz, $COCOCH_2$), 2.6-2.5 (1H, dd, *J* 16.5 and 7.1 Hz, $COCOCH_2$), 2.2-2.1 (1H, ddd, *J* 11.0, 9.3 and 3.3 Hz, CHi-Pr), 1.8-1.7 (1H, hept of d, *J* 7.1 and 3.3 Hz, $CHMe_2$), 0.9 (3H, d, *J* 7.1 Hz, $CHMe_2$), 0.8-0.7 (3H, d, *J* 7.1 Hz, $CHMe_2$).
   (**12a** E=SePh) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.6-7.1 (10H, m, Ph), 4.1-4.0 (1H, ddd, *J* 11.5, 4.9 and 1.6 Hz, CHOCHeqHax), 3.6-3.5 (1H, ddd, *J* 11.5, 8.2 and 3.3 Hz, CHaxOCH$_2$), 3.5-3.4 (1H, td, *J* 12.0 and 2.7 Hz, CHOCHeqHax), 3.3-3.2 (1H, dd, *J* 11.5 and 3.3 Hz, $PhSeCH_2$), 3.2-3.1 (1H, dd, *J* 11.5, 8.2 Hz, $PhSeCH_2$), 2.7-2.6 (1H, td, *J* 11.5 and 4.4 Hz, CHaxPh), 1.9-1.5 (4H, m, CHi-Pr, $CHMe_2$ and $PhCHCH_2CH_2O$), 0.8 (3H, d, *J* 7.1 Hz, $CHMe_2$), 0.5 (3H, d, *J* 7.1 Hz, $CHMe_2$).
   (**13a** E=SePh) ^{1}H (200 MHz, $CDCl_3$, TMS) δ : 7.5-7.1 (10H, m, Ph), 4.3-4.2 (1H, dt, *J* 11.5 and 4.4 Hz, $PhSeCH_2CHeqOCH_2$), 3.8-3.7 (2H, m, $PhSeCHOCH_2$), 3.7-3.6 (1H, t, *J* 11.5 Hz, $PhSeCH_2$), 3.0 (1H, dd, *J* 11.5 and 3.8 Hz, $PhSeCH_2$), 2.9-2.8 (1H, td, *J* 10.4 and 4.9 Hz, CHaxPh), 2.3-2.2 (1H, dt, *J* 11.0 and 4.9 Hz, CHaxi-Pr), 1.9-1.6 (3H, m, $PhCHCH_2$ and $CHMe_2$), 0.8 (3H, d, *J* 7.1 Hz, $CHMe_2$), 0.7 (3H, d, *J* 7.1 Hz, $CHMe_2$).
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