Synthesis of medium-ring lactones *via* tandem methylenation/Claisen rearrangement of cyclic carbonates

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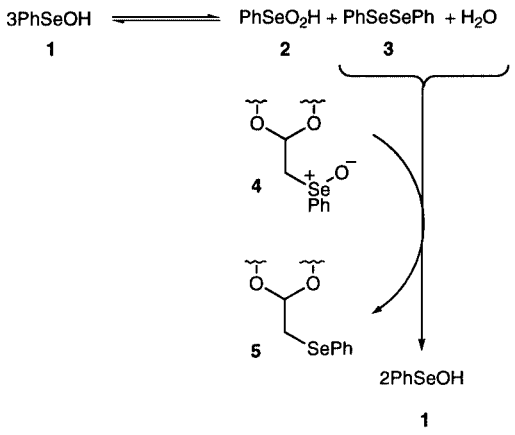
Tandem methylenation/Claisen rearrangement of cyclic carbonates derived from vinyl-substituted 1,3- and 1,4-diols afforded eight and nine-membered unsaturated lactones respectively.

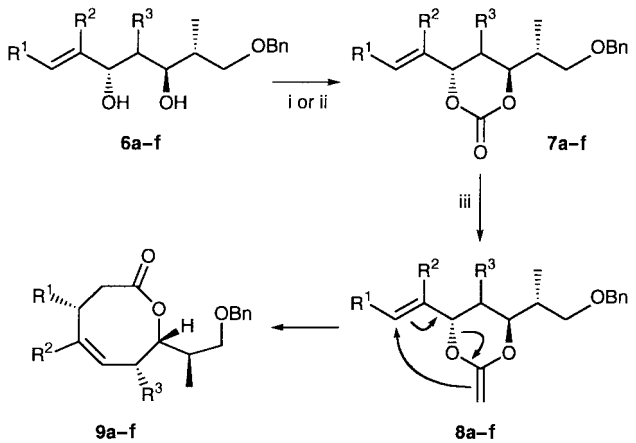
Medium-ring oxacycles form the core of many natural products such as obtusenyne[1,2] and (+)-laurencin.[3] Our approach to systems of this type has used the ring-expansion Claisen rearrangement of a vinyl-substituted ketene acetal, generated *in situ* from the thermal elimination of a selenoxide precursor (in turn derived from the oxidation of a selenoacetal) to form a medium-ring lactone.[4] Whilst this methodology provides efficient access to many medium ring lactones, several limitations became evident when the vinyl group carried electron rich substituents. In addition to the toxicity associated with selenium reagents, the formation of the selenoacetal from a 1,3- or a 1,4-diol requires somewhat harsh conditions (refluxing toluene, PPTS). This can be a problem in cases where the allylic hydroxy group of the diol is prone to β-elimination. The selenoxide elimination product, benzeneselenenic acid **1**, has been shown to disproportionate under the reaction conditions to benzeneseleninic acid **2** and diphenyl diselenide **3**.[5] The latter is postulated to act as a reducing agent, converting the selenoxide (ketene acetal precursor **4**) back into the selenoacetal **5** (Scheme 1).



Scheme 1

The disproportionation of benzeneselenenic acid can be suppressed by the use of non-nucleophilic bases and a nucleophilic silyl ketene acetal as a selenium scavenger.[6] Even under these optimal conditions, oxygen transfer from **4** to produce **5** can be a significant side reaction. Finally, selenoxide elimination and rearrangement require high temperatures (sealed tube, up to 185 °C). These conditions and the need for high dilution could make large scale preparations more troublesome. Here we report the methylenation of cyclic carbonates derived from vinyl-substituted diols using the Petasis reagent (dimethyltitanocene)[7–9] and the subsequent *in situ* Claisen rearrangement of the presumed ketene acetal intermediate.

Preparation of the 1,3-diols **6a–f** (Scheme 2, Table 1) was carried out according to the methods described previously.[4] The carbonates **7a**,**c–f** were synthesised from the diols using carbonyldiimidazole.† Alternatively, the carbonates **7a–c** were prepared using a modification of a procedure with triphosgene.[10] Dimethyltitanocene was synthesised by the reported procedure,[11] and could be stored in the freezer as a solution in toluene for several months without degradation. Treatment of the carbonates **7a–f** with dimethyltitanocene in refluxing toluene provided the Claisen rearrangement eight-membered lactone products **9a–f** as single diastereomers (^{1}H NMR), in reasonable to good yields (Scheme 2, Table 1), presumably *via* the ketene acetal intermediates **8a–f**. Comparison of the yields over two steps with the combined yields for the analogous selenium route shows this method to be superior to the selenoxide route in many cases.[4]



Scheme 2 *Reagents and conditions*: i, carbonyldiimidazole, toluene, reflux; ii, triphosgene, pyridine, Et_3N, −78 °C, 4 Å molecular sieves, CH_2Cl_2; iii, Cp_2TiMe_2, toluene, reflux in absence of light.

Nine-membered lactones may also be prepared. The 1,4-diols **10a–c** could be prepared from 2-deoxy-D-ribose in three steps. Treatment of the lactols derived from 2-deoxy-D-ribose by our previously reported route[12] with a variety of vinyl Grignard reagents provided mixtures of separable diastereomers of each of the diols **10a–c**. Exposure of the diols to triphosgene in dichloromethane and triethylamine–pyridine gave the carbonates **11a–c** which were converted into the lactones **13a–c**, as

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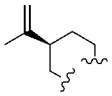
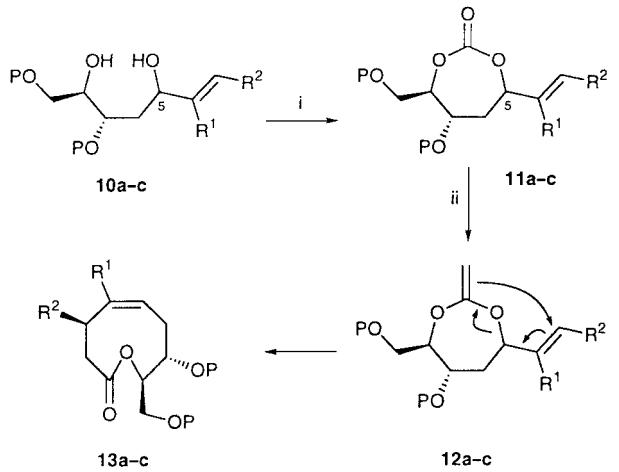
Table 1 Preparation of the carbonates **7a–f** and lactones **9a–f** from the diols **6a–f**

Substrate	R^1	R^2	R^3	Yield **7a–f** (%) (*t*/h)	Yield **9a–f** (%) (*t*/h)
6a	H	H	H	66[a] (48)	52 (3.5)
6a	H	H	H	45[b,c] (0.25)	52 (3.5)
6b	Me	H	H	77[b] (0.5)	52 (2.5)
6c	Me	Me	H	46[b] (1.0)	34 (4.5)
6c	Me	Me	H	32[a] (25)	34 (4.5)
6d	H	Me	(*R*)-Me	100[a] (23)	48 (3)
6e	H	Me	(*S*)-Me	91[a] (20)	67 (0.5)
6f			H	28[a] (24)	25 (24)

[a] *Conditions*: Scheme 1, i. [b] *Conditions*: Scheme 2, ii. [c] 33% Recovered **6a**.



Scheme 3 *Reagents and conditions*: i, triphosgene, pyridine, Et_3N, −78 °C, 4 Å molecular sieves, CH_2Cl_2; ii, Cp_2TiMe_2, toluene, reflux in absence of light. P = TBDPS.

single diastereomers (^{1}H NMR), upon rearrangement of the *in situ* generated ketene acetals **12a–c** (Scheme 3, Table 2).

In summary, an alternative route to medium-sized lactones by a tandem methylenation/Claisen rearrangement has been developed. This milder route avoids the use of toxic selenium compounds and the problematic side reactions associated with certain selenoxides under elimination conditions. The application of this methodology to the synthesis of fused lactone derivatives is described in the following Communication.

Table 2 Preparation of carbonates **11a–c** and lactones **13a–c** from diols **10a–c**

Substrate	R^1	R^2	C-5 Configuration	Yield **11a–c** (%) (*t*/h)	Yield **13a–c** (%) (*t*/h)
10a	H	H	*R*	65 (1.75)	70 (1.2)
10b	H	H	*S*	69 (0.25)	49 (2)
10c	TMS	Me	*S*	91 (0.25)	51 (0.5)

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Notes and references

† All new compounds exhibited spectroscopic and analytical (C, H, N) or exact mass data in accordance with the assigned structure.

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