



A novel rearrangement reaction of β -diazo- α -ketoacetals

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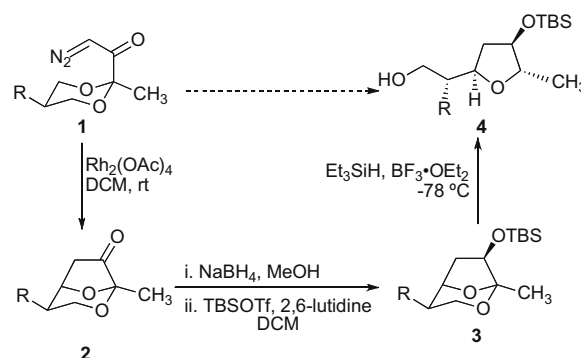
ABSTRACT

Treatment of pyruvate ketal-derived diazoacetoacetates or vinyl diazoketones with rhodium(II) complexes at elevated temperatures results in an unusual skeletal rearrangement to afford eight-membered ring lactones.

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α -Diazocarbonyl compounds are exceptionally valuable reagents for organic synthesis undergoing a wide range of transformations including insertion reactions, cyclopropanation, ylide formation and Wolff rearrangements.¹ Within the first of these reaction classes there have been many developments that enable selective insertion reactions to be undertaken in both an inter- and intramolecular fashion. In this respect we have exploited such advances in a study aimed at developing methodology for the synthesis of highly substituted cyclic ethers through a tandem C–H insertion-acetal bond cleavage sequence, [Scheme 1](#).² Whilst this proved to be effective we sought to enhance this process by incorporation of an additional carbenoid stabilising group that would also provide direct entry to a tetrasubstituted THF on acetal fragmentation. In this Letter, we describe our initial attempts to achieve this which have led to the discovery of an unusual rearrangement pathway which provides access to a novel medium ring lactone system.

We commenced this study by preparing suitable substrates focusing on diazoacetoacetate **7** and the donor–acceptor stabilised system represented by vinyl diazoketone **8**, [Scheme 2](#). The former could be prepared from the pyruvate-derived acetal **5** in a short sequence of steps involving conversion to the aldehyde **6** and then a one-pot tandem aldol condensation–oxidation using an ethyl diazoacetate, DBU and IBX combination.³ The vinyl diazoketone **8** was prepared in a longer sequence involving addition of allyl magnesium bromide to the aldehyde **6**, oxidation and diazo transfer using *p*-acetamidobenzenesulfonyl azide (ABSA). During the oxida-



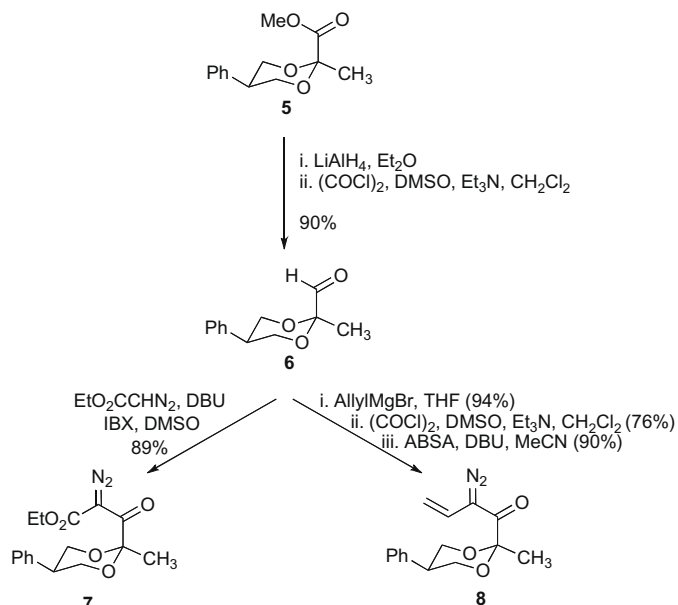
Scheme 1.

tion step partial isomerisation of the double bond occurred to form the corresponding α,β -unsaturated ketone. This, however, was of little consequence as, in the presence of a mild base, diazo transfer occurred exclusively at the kinetically favoured α -position.

Our first attempts to promote the desired insertion reaction focused on diazoacetoacetate **7**. Whilst using rhodium(II) acetate, $\text{Rh}_2(\text{OAc})_4$, as the catalyst at room temperature led only to recovered starting material, slow addition of **7** to a solution of rhodium(II) heptafluorobutyrate $[\text{Rh}_2(\text{pfb})_4]$ led to the isolation of bicycle **9**, arising from enolate capture of an oxonium generated by initial hydride transfer to the rhodium carbenoid, [Scheme 3](#).⁴

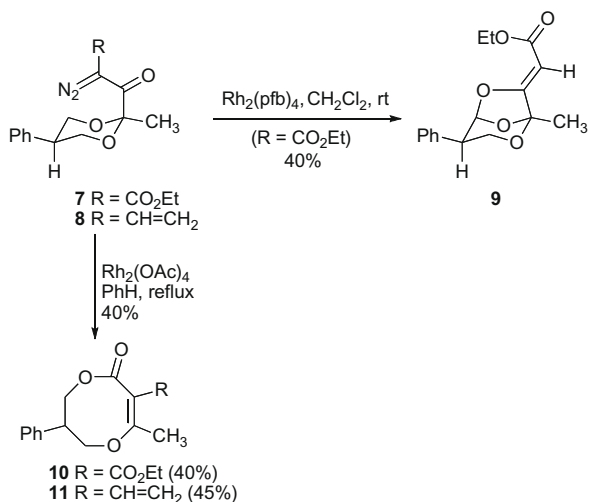
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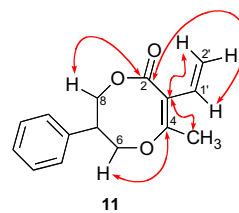


Scheme 2.

Given the enhanced electrophilicity of $\text{Rh}_2(\text{pfb})_4$, such an outcome is not surprising but did confirm that generation of the intermediate carbenoid was accessible. Consequently we explored the use of other ligands and reaction conditions. One such variation was to attempt the reaction at elevated temperatures. Whilst prolonged heating in dichloromethane led to extensive decomposition, reaction with $\text{Rh}_2(\text{OAc})_4$ in refluxing benzene for a 2 h period resulted in clean conversion to a new compound isolated as a colourless oil in 40% yield.⁵ This however was clearly not the desired bicyclic acetal as analysis of the ^{13}C NMR spectrum indicated two ester carbonyl signals (δ 168.1 and δ 166.2) that were clearly conjugated to an alkene (δ 168.5). Moreover, the ^1H chemical shift for the methyl group (δ 2.29) suggested that this too was coupled to the conjugated system. Combined with mass spectral data (ES^+) which suggested a molecular ion of $m/z = 291$ (MNa^+) led to the suggestion that the unusual lactone system **10** had been produced. Stronger evidence for such a proposal came from the similar reaction of vinyl diazoketone **8** which afforded the analogous lactone **11**. This compound, having only a single carbonyl sig-



Scheme 3.

Figure 1. Selected HMBC correlations for **11**.

nal, provided much clearer correlations in the various 2D NMR experiments undertaken. Notably, a significant NOESY correlation was observed between H-1' and the 4-CH₃ signal, consistent with a *cis* alkene and thereby confirming the cyclic nature of the lactone. Further evidence was obtained from HSQC and HMBC experiments, with the HMBC correlations of C-2 to 8-H, C-4 to 6-H, C-2 to 1'-H and C-3 to both 2'-H and 4-CH₃ providing strong support for the proposed structure, Figure 1. As for lactone **10**, the 4-CH₃ signal in the ^1H NMR spectra exhibited a marked shift to higher frequency appearing at δ 2.11 whilst the IR spectrum showed bands consistent with an ester (lactone) and C=C unsaturation at 1714 and 1617 cm^{-1} , respectively. Final evidence in support of the lactone structure was provided by the high resolution mass spectral analysis of **11** (ESI) m/z (MNa^+) = 267.0993 which was consistent with the proposed molecular formula of $\text{C}_{15}\text{H}_{16}\text{O}_3\text{Na}$. A search of various databases revealed that this structure was novel with the closest analogy being found in the fungal natural products barceloneic lactone **12**, isolated from a fungus of the genus *Phoma* in a screen for protein-farnesyl transferase (PFT-ase) inhibitors,⁶ and penicillide **13** and dehydropenicillide **14**, found in the ascomycetous fungus *Talaromyces dextrii*,⁷ Figure 2. Since synthetic approaches to these compounds have not been reported we felt that a brief examination of the scope and mechanism of this rearrangement was merited. Replacing benzene by higher boiling toluene as the solvent had no effect on the reaction outcome. By-passing the slow addition process and simply heating **7** with $\text{Rh}_2(\text{pfb})_4$ in refluxing toluene afforded a mixture of **9** (45%) and **10** (22%). That the formation of the former simply represented a background reaction occurring prior to reaching the critical reaction temperature for the rearrangement was confirmed by repeating this process in a microwave reactor. Under these conditions a cleaner reaction, with no evidence for the formation of **9**, could be achieved at much lower reaction temperatures (70 $^\circ\text{C}$) and shorter reactions times (10 min). Whilst heating is essential, it is not a sole requirement, as all attempts to achieve this transformation in the absence of a

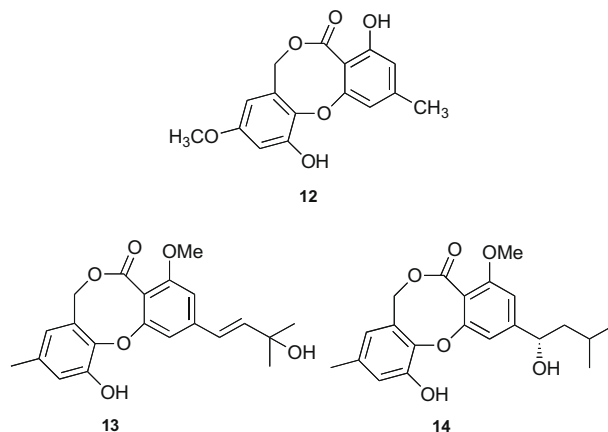
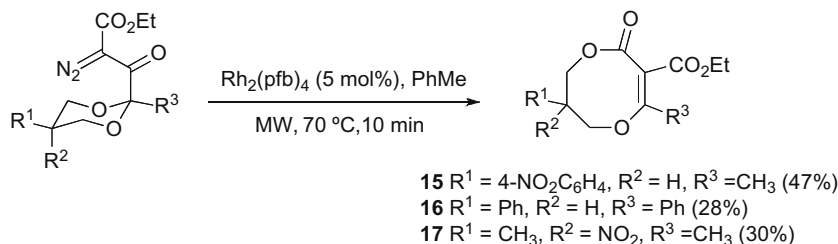


Figure 2. Structurally related natural products.



Scheme 4.

Rh(II) complex failed leading to a complex product mixture with no evidence for any lactone formation. Similarly, all attempts to reproduce this transformation using diazoketone **1** which lacks the additional stabilising element failed leading only to extensive decomposition. However, variation in both components of the acetal is tolerated leading to similar yields of products in all cases, Scheme 4.⁸

To account for these observations we propose a pathway in which initial carbene generation is achieved under promotion by the Rh(II) complex, Scheme 5. At room temperature this reacts to afford the 'O insertion' product **21**. However, at higher temperatures, potentially through dissociation of the metal carbenoid **19** to afford the free carbene, a Wolff rearrangement can occur leading to the ketene **22**.⁹ In the absence of a stabilising group (alkene or ester unit) this is unstable and undergoes decomposition at these elevated temperatures, cf. compound **1**. However, when substituted this is sufficiently long-lived to allow a formal 1,3 shift of one of the acetal oxygen atoms to occur to give the observed lactones.¹⁰ In support of such a hypothesis, heating of acetal **7** with Rh₂(pfb)₄ in a mixture of toluene and methanol (1:1) afforded the diester **25** along with trace amounts of lactone **10**.

In conclusion, we have discovered a novel rearrangement of acetal-containing diazocarbonyl compounds that provide access

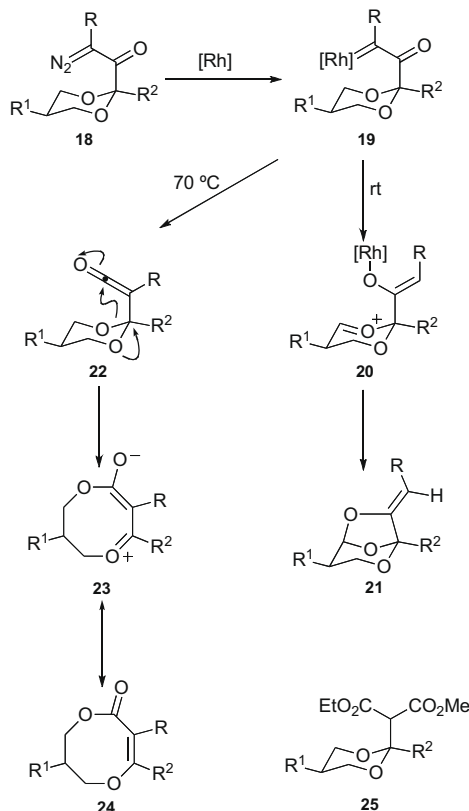
to medium ring lactones found in a range of naturally occurring compounds. We are actively exploring the potential for this transformation to be applied to the synthesis of these structures and will report on these studies in due course.

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- Typical experimental procedure:* (Z)-4-methyl-7-phenyl-3-vinyl-7,8-dihydro-1,5-dioxocin-2(6H)-one **11**: rhodium(II) perfluorobutyrate, Rh₂(CO₂C₃F₇)₄ (5 mol %) solution in toluene (10 ml) placed in a microwave vial (20 ml) was argon flushed and maintained at 70 °C. After 2 min, a solution of vinyl diazoketone **8** (0.10 g, 0.37 mmol) in toluene (5 ml) was added and it was immediately placed into the reactor. The vial was then immediately placed into the reactor and heated at 70 °C for 15 min to give complete reaction (determined by monitoring a series of trial reactions, involving variations of time and temperature). The reaction mixture was then allowed to attain room temperature, silica gel was added and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (ether/petroleum ether: 2/8) to give the title lactone **11** as a colourless oil (0.04 g, 45%). *v*_{max} (ATR): 1714 (C=O, lactone), 1617 (C=C), 1494, 1390, 1302, 1258, 1173, 1012, 896, 764, 700, 616 cm⁻¹. *δ*_H (700 MHz, CDCl₃): 7.37–7.35 (2H, m, Ar-H), 7.31–7.30 (3H, m, Ar-H), 6.43 (1H, dd, *J* 17.1, 11.1, CH=CH₂), 5.27 (1H, d, *J* 17.1, CH=CH₂), 5.13 (1H, d, *J* 11.1, CH=CH₂), 4.54–4.91 (2H, m, 8-H), 4.37 (1H, dd, *J* 13.5, 3.4, 6-H), 4.24 (1H, dd, *J* 13.5, 6.8, 6-H), 3.35–3.31 (1H, m, 7-H), 2.11 (3H, s, 4-CH₃). *δ*_C (175 MHz; CDCl₃): 169.7 (C-2), 157.4 (C-4, enol ether), 137.6 (*ipso* Ar-C), 131.0 (CH=CH₂), 128.9 (Ar-C), 128.1 (Ar-C), 127.8 (Ar-C), 114.2 (CH=CH₂), 105.3 (C-3), 68.0 (C-8), 67.4 (C-6), 47.2 (C-7), 19.0 (4-CH₃). *m/z* (ES⁺): 308 (M+Na⁺+CH₃CN, 20%), 267 (M+Na⁺, 20), 245 (M+H⁺, 60). HRMS (ES⁺) found: 267.0993 (C₁₅H₁₆O₃Na requires 267.0992).
- For a similar example of Wolff rearrangements occurring at elevated temperatures see: Boukraa, M.; Dayoub, W.; Doutheau, A. *Lett. Org. Chem.* **2006**, 3, 204–206.
- A referee has suggested an alternative pathway involving hydrolysis of the ketene to afford a dioxane-2-acetic acid derivative. Subsequent β-elimination of the dioxolane leads to a hydroxy acid intermediate which can then undergo cyclisation to give the observed lactone. Whilst we cannot definitively rule out such a pathway, we note that the lactone products can be observed directly in the reaction mixture even in the absence of any potential water source, that is, prior to the addition of the silica gel.



Scheme 5.