

A One-Pot C–H Insertion/Olefination Sequence for the Formation of α -Alkylidene- γ -butyrolactones

Matthew G. Lloyd, Richard J. K. Taylor,* and William P. Unsworth*

Department of Chemistry, University of York, Heslington, York, YO10 5DD, U.K.

Supporting Information



ABSTRACT: A one-pot C–H insertion/olefination sequence for the conversion of α -diazo- α -(dialkoxyphosphoryl)acetates into α -alkylidene- γ -butyrolactones is reported. The key C–H insertion process is achieved using a catalytic amount of a dirhodium carboxylate catalyst, using operationally simple conditions. The size and electronic properties of the attached substituents were found to influence the regio- and diastereoselectivity of the process. The utility of the process is demonstrated by the synthesis of a known *Staphylococcus aureus* (MRSA) virulence inhibitor.

 α -Alkylidene- γ -butyrolactones are found in a vast number of important bioactive natural products; remarkably, approximately 3% of all known natural products contain this structural motif (*e.g.*, **1–5**, Figure 1).¹





A number of methods for the synthesis of α -alkylidene- γ butyrolactones have been reported,^{1,2} most commonly involving initial lactone formation followed by methylenation, e.g. via aldol-type processes. However, many of the reported procedures are either impractical or low yielding due to problems handling the relatively sensitive products and/or the length of the synthetic routes. Previous work in our own laboratory³ aimed to redress this via the application of telescoped reaction processes.⁴ We first reported a telescoped intramolecular Michael/olefination (TIMO)³ sequence which enabled the construction of α -alkylidene- γ -butyrolactones, in good overall yields, from phosphonates (6) derived from γ hydroxy unsaturated carbonyl compounds.⁵ This reaction is initiated by deprotonation and intramolecular Michael addition, to generate an intermediate anion (7). An aldehyde may then be added directly to the reaction mixture, resulting in Horner– Wadsworth–Emmons-type (HWE) olefination (Scheme 1), furnishing product 8. We subsequently showed^{3c,d} that acylated phosphoranes, prepared *in situ* by the reaction of functionalized alcohols (9) with Bestmann's ylide,⁶ react similarly, thus incorporating an additional synthetic step into the telescoped sequence (Scheme 1).

Both procedures are relatively simple to perform experimentally and give good yields of the desired products. However, a notable drawback of both methods is that three functional groups (an alcohol, an alkene, and a carbonyl group) are necessary for the desired reactions to take place, which reduces the generality of the methodology in cases where the starting material synthesis is not trivial. The strategy reported herein is based on an efficient rhodium-catalyzed C–H activation process,⁷ which is used in place of the Michael addition in the TIMO sequence. Using this method, the starting material synthesis is simplified dramatically, so that simple, unfunctionalized alcohol derivatives (10) may be used as precursors to α -alkylidene- γ -butyrolactones. In addition, Michael acceptors are no longer required, thus increasing the generality of the process.

To the best of our knowledge, only three examples (contained in a single report)⁸ of the rhodium-catalyzed C– H insertion of α -diazo- α -(dialkoxyphosphoryl)acetates⁹ are known and these reactions were reported to furnish mixtures

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Scheme 1. One-Pot C-H Insertion/Olefination Compared with Previous Michael Addition Methodology



of β - and γ -lactones in moderate/low yield. Related α -diazo- α -(dialkoxyphosphoryl)acetamides are also known to react similarly, but in this case there is a stronger bias toward formation of the β -lactam C–H insertion product.^{8,10} Note that the HWE reactions of the C-H insertion products were not examined in any of these reports. A desire to avoid β -lactone formation directed our decision to use substrates 10a and 10b to test the key C-H insertion reaction; rhodium(II) carbenoids are highly electrophilic and typically insert preferentially into electron-rich C-H bonds,7 and thus it was expected that the use of benzylic substrates would expedite the desired γ -lactone formation. The requisite substrates were made in two steps from alcohols 13a and 13b via coupling with diethyl phosphonoacetic acid (DEPAA) using propyl phosphonic anhydride (T3P)¹¹ and N,N-diisopropylethylamine (DIPEA), followed by a Regitz diazo-transfer reaction (Scheme 2).¹²



Pleasingly, both substrates reacted with 5 mol % of $Rh_2(esp)_2$ in DCM at 45 °C to generate γ -lactones **11a** and **11b** as single regio- and diastereoisomers (Table 1, entries 1–2). The structural assignment of compound **11a** is supported by X-ray crystallography (see Supporting Information).^{13,14} Additional optimization experiments (entries 3–12) examined the catalyst choice and its loading, the reaction concentration, and the reaction vessel, revealing that heating the substrate **10b** in an

Table 1. Optimization of Rhodium-Catalyzed C-H Insertion of Diazophosphonates 10a and 10b

	0 N ₂ R 10a R = 10b R =	O H_OEt OEt <u>Rh(II), DCN</u> 45 °C, 20 h • Ph • 4-MeO-C ₆ H ₄	$ \begin{array}{c} 0 \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ -$		1
entry	sub.	Rh(II) catalyst	catalyst loading [mol %]	DCM (mL/mmol)	yield (%)
1	10a	$Rh_2(esp)_2$	5	20	64 ^a
2	10b	$Rh_2(esp)_2$	5	20	57 ^a
3	10b	$Rh_2(OAc)_4$	5	20	74 ^a
4	10b	$Rh_2(oct)_4$	5	20	66 ^a
5	10b	$Rh_2(tpa)_4$	5	20	59 ^a
6	10b	$Rh_2(oct)_4$	2	20	70 ^a
7	10b	$Rh_2(oct)_4$	2	200	30 ^{<i>a</i>,<i>c</i>}
8	10b	$Rh_2(OAc)_4$	5	20	77^{b}
9	10b	$Rh_2(OAc)_4$	2	20	71 ^b
10	10b	$Rh_2(oct)_4$	10	20	87^b
11	10b	$Rh_2(oct)_4$	5	20	80^{b}
12	10b	$Rh_2(oct)_4$	2	20	89 ^b
a	-				-

^{*a*}Heated at 45 °C in a round-bottom flask fitted with reflux condenser and argon balloon for 20 h. ^{*b*}Heated at 45 °C in an oven-dried sealable tube flushed with argon for 20 h. ^{*c*}A 51% yield of the product of water insertion [4-methoxyphenethyl 2-(diethoxyphosphoryl)-2-hydroxyacetate (15)] was also isolated in this instance.

oven-dried sealable tube at 45 °C for 20 h with 2 mol % of $Rh_2(oct)_4$ in DCM at a concentration of 20 mL/mmol afforded lactone **11b** in the highest isolated yield (89%, entry 12).

With optimized C–H insertion conditions in hand, attention switched to performing the HWE olefination. As the only byproduct of the cyclization is nitrogen gas, it was expected that this step could be performed in the same reaction vessel without workup or purification. This was achieved by cooling the crude reaction mixture and directly adding KOBu-t (1.2– 1.5 equiv), followed by paraformaldehyde (2 equiv). In some cases a solvent switch (DCM to THF) was made prior to the HWE reaction. Scoping studies were performed on a range of α -diazo- α -(dialkoxyphosphoryl)acetates 10a–10l (which were synthesized as described in Scheme 2) to generate α methylene- γ -butyrolactones 12a–12l (Table 2).

The two-step, one-pot telescoped sequence works well using benzylic substrates 10a-10c; cyclization using the optimized C-H insertion conditions followed by treatment with KOBu-t (1.2 equiv), then paraformaldehyde (2 equiv), resulted in the formation of α -methylene- γ -butyrolactones 12a-12c in good overall yield (Table 2, entries 1-4). The use of more than 1 equiv of base is noteworthy, as related HWE reactions are known to proceed better with substoichiometric amounts of base.^{3,15} Compound 10d reacted smoothly (entries 5-6), demonstrating that insertion into sterically hindered tertiary C-H bonds is viable. There is also scope for the construction of lactones with a high level diastereocontrol; the reaction of dibenzyl substrate 10e resulted in the formation of lactone 12e as a single *trans*-diastereoisomer in excellent overall yield (entry 7). Furthermore, remarkable levels of regiocontrol have been demonstrated; the C-H insertion reaction of unsymmetrical dibenzyl substrate 10f took place exclusively α - to the 4-MeO-C₆H₄ group,¹⁶ clearly highlighting the strong proclivity of such rhodium(II) carbenoids to insert into electron-rich C-H bonds



Table 2. One-Pot C-H Insertion/Olefination Sequence for the Formation of α -Methylene- γ -butyrolactones

^{*a*}(i) 2 mol % Rh₂(oct)₄, DCM, 45 °C, 20 h; (ii) 1.2 equiv of KOBu-*t*, 0 to -78 °C; (iii) 2 equiv of $(CH_2O)_n$, -78 to 0 °C. ^{*b*}Solvent switched from DCM to THF before the HWE. ^{*c*}HWE was done with 1.5 equiv of KOBu-*t* and was warmed to rt.

(entry 8). This furnished lactone **12f** in good overall yield, albeit without the high level of diastereocontrol observed during the formation of its analogue **12e**. Substrate **10g**

underwent cyclization and olefination in in excellent overall yield but resulted in the formation of a 1.45:1 mixture of the desired product 12g and its regioisomer 16, in which C-H insertion has taken place on one of the methyl groups (entry 9). The partial formation of lactone 16 was somewhat surprising given the stereoelectronic bias for insertion into electron-rich C-H bonds, but this is likely to be a result of reduced steric hindrance in the C-H insertion step. Until this point, the formation of lactones 12a-g all involved electronically favorable C-H insertion into benzylic C-H bonds (vide supra). Pleasingly, this assistance to the cyclization is by no means essential: substrates 10h-10i, which are derived from simple aliphatic alcohols, were all compatible with the two-step sequence, affording lactones 12h-12j in comparable yields to those of the preceding benzylic substrates (entries 10-12). Crucially, there was no evidence for the formation of β - or δ lactone products in any of these reactions. Finally, the reaction of cyclopentyl substrate 10k generated spirocyclic lactone 12k in very good overall yield (entry 13).

 α -Alkylidene- γ -butyrolactones may also be accessed using the same procedure (Table 3). A range of aromatic aldehydes can

Table 3. One-Pot C-H Insertion/Olefination Sequence for the Formation of α -Alkylidene- γ -butyrolactones

	$\bigcap_{i=1}^{O} \bigcap_{i=1}^{O} OEt \qquad \underbrace{i}_{i=1}^{OEt}$	Rh ₂ (oct) ₄ , DCM KOBu- <i>t</i> , THF RCHO		R S
	År 10b ⊄	Ar = 4-MeO-C ₆ H ₄	Àr	12I-r
entry	R	product	E:Z	yield (%)
1	Ph	12l	1:1	65 ^a
2	$4-NO_2-C_6H_4$	12m	1:1.3	$69^{a,b}$
3	2-F-C ₆ H ₄	12n	1:1.5	91 ^a
4	$4-Ph-C_6H_4$	120	1:1	61 ^{<i>a</i>}
5	3,4-OCH ₂ O-C ₆ H ₃	12p	1:1.2	56 ^{<i>a,c</i>}
6	CH ₃	12q	1.2:1	39 ^a
7	<i>n</i> -butyl	12r	1:3.7	67 ^a
(1) 0		5 45 0 G A A 1 (11)		

^{*a*}(i) 2 mol % Rh₂(oct)₄, DCM, 45 °C, 20 h; (ii) THF; (iii) 1.2 equiv of KOBu-t, 0 to -78 °C; (iv) 2 equiv of RCHO, -78 °C to rt. ^{*b*}HWE at 0 °C. ^{*c*}HWE at reflux.

be used instead of paraformaldehyde in the telescoped twostep, one-pot procedure. The olefination proceeds smoothly at rt when electron-neutral and -deficient benzaldehyde derivatives are used (entries 1–4), but the reaction required heating at reflux when electron-rich piperonal was used (entry 5). In all cases the desired lactones 12l-12p were obtained in good to excellent overall yield. Aliphatic aldehydes are also compatible, as evidenced by the formation of lactones 12q-12r (entries 6– 7).

This method would appear to have great potential in target synthesis, and as a simple demonstration, the synthesis of lactone 17 was completed (Scheme 3). This was the most potent compound found in a recent study of *Staphylococcus aureus* (MRSA) virulence inhibitors.¹⁷ Along with other related α -alkylidene- γ -butyrolactones, it works by binding covalently to the cysteine residues of several binding proteins involved in α -hemolysin expression and, thus, represents a highly promising treatment of antibiotic-resistant *S. aureus* strains. The synthesis commenced by the conversion of commercially available acid **18** into ketone **19** via its Weinreb amide. Subsequent reduction and conversion into the α -diazo- α -(dialkoxyphosphoryl)acetate

Scheme 3. Synthesis of S. aureus Virulence Inhibitor 17



in the usual way furnished precursor **20**. The synthesis was then completed using the standard one-pot C–H insertion/HWE protocol; the desired product **17** was isolated in 49% yield, along with 19% of the regioisomeric lactone **21**. The high level of diastereoselectivity (all *trans*) is noteworthy, as the corresponding *cis*-isomer was found to be a significantly less potent inhibitor.¹⁷

Rhodium(II) carbenoids have therefore been used to convert alcohol derivatives into a range of α -alkylidene- γ -butyrolactones, via a one-pot C–H insertion/olefination sequence in good overall yields.¹⁸ The convenient starting material synthesis and the mild, straightforward experimental conditions should prove valuable in both academic and industrial research settings.

ASSOCIATED CONTENT

S Supporting Information

Synthetic procedures, spectral data, and X-ray data. This material is available free of charge via the Internet at http:// pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: richard.taylor@york.ac.uk.

*E-mail: william.unsworth@york.ac.uk.

Notes

The authors declare no competing financial interest.

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(14) The NMR data of compound **11a** match those reported with the exception of the H-3 resonance: 4.00-4.26 (5 H, m, H-3, 2 × CH₂) [lit. 3.65 (dd, ${}^{3}J_{\rm HH} = 6.5$ Hz, ${}^{3}J_{\rm PH} = 6.0$ Hz, 1H, H-3)]. In view of the fact that the X-ray structure of **11a** was solved it seems likely that there is an error in the previously reported data. Krawczyk, H.; Wasek, K.; Kedzia, J.; Wojciechowski, J.; Wolf, W. M. *Org. Biomol. Chem.* **2008**, *6*, 308.

(15) This has been attributed to the instability of α -methylene- γ -butyrolactones with respect to the base, but in this study, the use of 0.9 equiv of KOBu-*t* led to a lower overall yield in all cases.

(16) The assignment of regioisomer **12f** is supported by HMBC correlation data: H-7 to C-3, H-13 to C-11, H-11 to C-12, no correlation between H-11 and C-6 (see Supporting Information).

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(18) Efforts to develop an asymmetric variant of this reaction using chiral rhodium(II) catalysts are ongoing and will be reported in due course.