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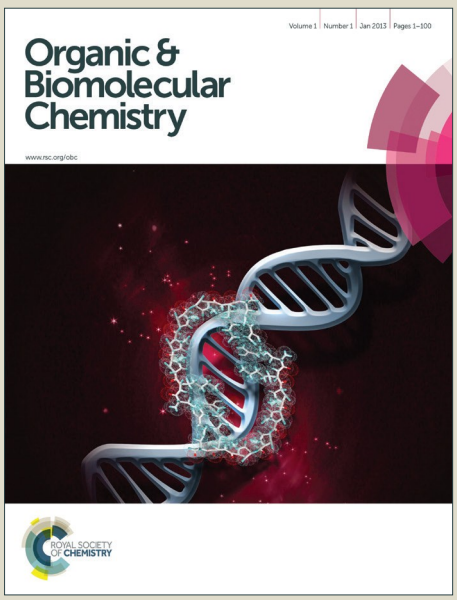

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A selective C–H insertion/olefination protocol for the synthesis of α-methylene-γ-butyrolactone natural products

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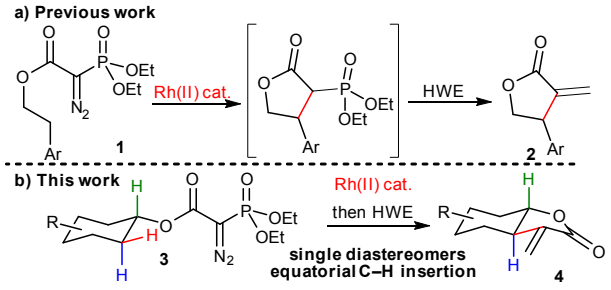
A regio- and stereoselective one-pot C–H insertion/olefination protocol has been developed for the late stage installation of α-methylene-γ-butyrolactones into conformationally restricted cyclohexanol-derivatives. The method has been successfully applied in the total synthesis of eudesmanolide natural product frameworks, including α-cyclocostunolide.

The selective functionalization of sp^3 centres via the activation of unfunctionalised C–H bonds is of much current interest,[1] given that it facilitates the synthesis of complex molecular architectures from relatively simple precursors. Over the last two decades, rhodium(II)-catalysed C–H insertions have become a mainstay in this field; an array of useful reaction modes with well-established reactivity patterns have been developed, including asymmetric variants, based on the C–H insertion of rhodium-stabilised carbenoids.[2] In particular, the donor/acceptor carbenoid systems popularised by Davies have proved to be especially valuable.[2d]

The acceptor/acceptor carbenoid class has received less attention in comparison,[3] although there are prominent exceptions.[4] A useful feature of carbenoids of this type is the fact that the additional acceptor substituent may be used as a handle for further chemical modification; this is exemplified by work published by our own group, in which a one-pot rhodium(II)-catalysed C–H insertion/Horner–Wadsworth–Emmons olefination (HWE) sequence for the conversion of α-diazo-α-(diethoxy)phosphoryl acetates **1** into α-methylene-γ-butyrolactones **2** was reported (Figure 1a).[5] This research focused primarily on substrates with electron rich C–H bonds (*e.g.* benzylic reaction system **1**) that are well-suited to react with electrophilic carbenoids. The work described herein concerns the extension of this method to cyclohexanol derivatives (**3**, Figure 1b). These are much more challenging substrates compared to those examined previously, as there is no electronic bias to direct the C–H insertion, but the products **4** are arguably more important given that a huge number of bioactive cyclohexane-based α-methylene-γ-butyrolactone natural products have been isolated.[6] Our aim (Figure 1b) was to design the cyclohexane precursors so that C–H insertion (and subsequent olefination) occurs exclusively into equatorial C–H bonds,[7] to selectively form fused γ-lactones **4**. The success of this approach, and its application in the total synthesis of three natural product targets and one isomeric analogue, are described.

Figure 1 – C–H insertion/olefination approach to α-methylene-γ-butyrolactones.



Our only previous attempt at performing a C–H insertion/olefination of this type was not encouraging; when the diazophosphonate derivative of cyclohexanol (*i.e.* compound **3**, with R = H) was treated under the standard reaction conditions [$Rh_2(oct)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; ii) KOBu-*t*, THF, −78 – 0 °C, 1 h; iii) $(CH_2O)_n$, 0 °C – rt, 1 h][5] a diastereomeric mixture of γ-lactones, as well as some β-lactone product, was obtained (corresponding to insertion into all three of the highlighted C–H bonds in **3**) and the overall yield was low.[5b] It was postulated that the poor selectivity in this case may be related to the flexible nature of the substrate, and that by restricting its conformation, the regio- and stereoselectivity may be improved.

To test this idea, 4-*tert*-butyl cyclohexyl derivatives **5a** and **5b** were formed and reacted under the standard one-pot C–H

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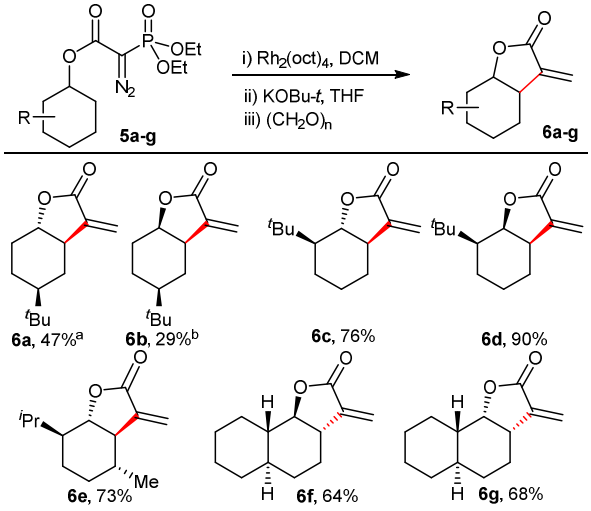
insertion/olefination conditions (Figure 2). The expectation was that the *tert*-butyl group would lock the cyclohexane scaffold in a chair conformation to better distinguish the two γ-C–H insertion sites, and improve the diastereoselectivity. Greater control was indeed observed in both cases; γ-lactones **6a** and **6b** were each isolated as single diastereoisomers, with the stereochemical outcome consistent with insertion into the equatorial C–H bonds. However, in both reactions the overall yield was relatively low, which is partly explained by the formation of β-lactone side-products **7a** and **7b** (not shown, see Supporting Information). Pleasingly, by moving the *tert*-butyl group closer to the C–H insertion site, a significant improvement was observed; 2-*tert*-butyl substrates **5c** and **5d** furnished α-methylene-γ-butyrolactones **6c** and **6d** respectively, with complete diastereoselectivity and a significant increase in isolated yield (76% and 90%), with no β-lactone side-products being formed in either case. The *tert*-butyl group is likely to be playing two roles in these substrates, both fixing the conformation of the cyclohexane ring and providing a steric barrier to competing β-insertion reactions. To further probe this cooperative effect, other 2-subtituted conformationally restricted systems based on menthol and decalinol (**5e**, **5f** and **5g**) were treated under the standard conditions and all afforded the expected γ-lactone products selectively (**6e**, **6f** and **6g**). It is noteworthy that in all cases, there is complete selectivity for equatorial C–H insertion, irrespective of whether the diazoester substituent is itself has an equatorial (**6a**, **6c**, **6e**, **6f**) or axial (**6b**, **6d**, **6g**) configuration.

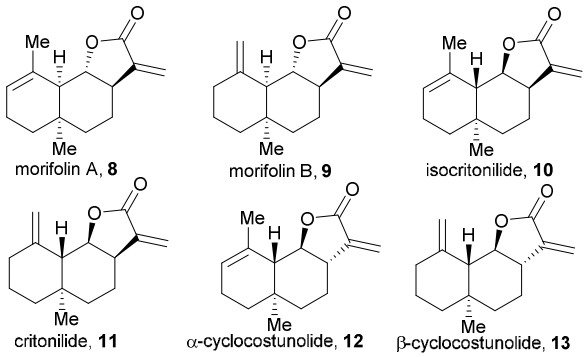
Figure 2 – C–H insertion/olefination sequence for conformationally restricted cyclohexane derivatives **5a-g**.



Reaction conditions: i) $Rh_2(oct)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; ii) KOBu-*t*, THF, −78 – 0 °C, 1 h; iii) $(CH_2O)_n$, 0 °C – rt, 1 h. Yields of isolated product. [a] β-lactone product **7a**, (12%) was also isolated; [b] β-lactone product **7b**, (19%) was also isolated.

In view of the excellent regio- and stereoselectivity observed in these reactions, attention turned to their application in natural product synthesis. Sesquiterpene lactones are the most common class of α-methylene-γ-butyrolactone found in Nature[6e,8] and selected compounds from a sub-class of this family collectively known as the eudesmanolides, are shown in Figure 3 (**8–13**).

Figure 3 – Eudesmanolide natural products **8–13**.

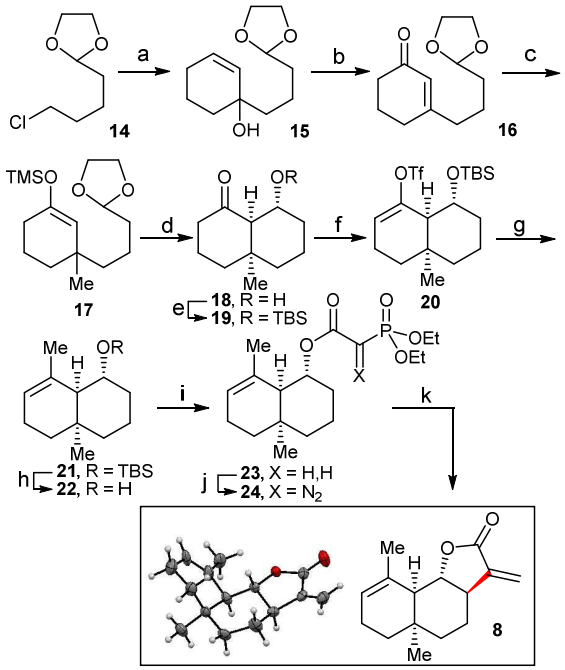


First, compounds **8** and **9** (labelled morifolins A and B, Figure 3) were targeted. As the C–H insertion procedure had not previously been tested on a *cis*-decalin framework (which can potentially ring flip), they were considered to be an interesting challenge to the methodology. An additional reason for performing the synthesis of the morifolins was to clear up confusion that exists in the literature about their structural assignments. In 1985, Dominguez and co-workers isolated a series of sesquiterpene lactones, two of which were named morifolin A and B and assigned the structures **8** and **9** above.[9] However, in a 2004 publication,[10] Herz suggested that these products had been assigned incorrectly, and proposed that they were in fact identical to isocritonilide **10** and critonilide **11**, respectively, described by Bohlmann and co-workers in 1983.[11] The spectral data in the Dominguez publication were insufficient to draw a definitive conclusion, and hence it was decided to complete the total syntheses of lactones **8** and **9** to clarify the anomaly.

The synthesis began with a lithium naphthalenide mediated 1,2-addition of chloride **14** into cyclohexenone,[12] which was followed by oxidative rearrangement with PCC, furnishing α,β-unsaturated ketone **16** (Scheme 1). Next, the 1,4-addition of methylmagnesium chloride under Gilman-type conditions afforded doubly-masked keto-aldehyde **17**. This was followed by an intramolecular aldol reaction under acidic conditions, which furnished *cis*-β-hydroxyketone **18** as a single diastereoisomer, as reported in the literature.[13] Next, silyl protection of the alcohol, vinyl triflate formation and iron-catalysed cross-coupling[14] with methylmagnesium chloride furnished alkene **21** in excellent overall yield. Desilylation using TBAF followed by a T3P-mediated acylation and Regitz diazo transfer reaction, generated the key diazo substrate **24**. This was then primed to undergo the one-pot C–H insertion/olefination sequence, which was performed under the standard conditions, affording α-methylene-γ-butyrolactone **8** in 64% yield with complete stereo- and regiocontrol. The relative configuration of **8** was found to be in line with that observed in the model studies and was assigned

unambiguously by X-ray crystallography.[15] With the identity of our synthetic sample **8** confirmed, its spectral data were then compared with those reported for the natural product morifolin A; significant differences between the ^{1}H NMR data of *cis*-decalin **8** and the natural product were clearly observed, thus confirming that morifolin A had indeed been incorrectly assigned. Thus it appears most likely that the natural isolated material named morifolin A **8** is in fact the same as isocritonilide **10**, as suggested previously by Herz.[10]

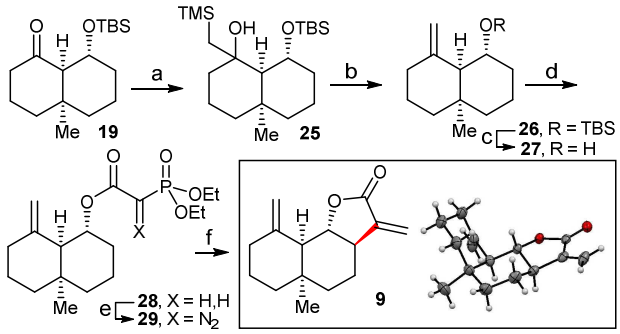
Scheme 1 – Synthesis of α-methylene-γ-butyrolactone **8**.



Scheme 1 Reagents and conditions: (a) (1) **14**, Li, naphthalene, THF, –78 °C; (2) 2-cyclohexen-1-one, –78 °C – rt, 100%; (b) PCC, Al_2O_3, CH_2Cl_2, 0 °C – rt, 52 %; (c) CuI, LiCl, TMSCl, MeMgCl, THF, –78 °C – rt, 98%; (d) 10% aq. HCl, MeOH, 80 °C, 65%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C – rt, 99%; (f) LHMDS, Tf_2O, THF, –40 °C, 80%; (g) $Fe(acac)_3$, MeMgCl, THF:NMP (1:3), 82%; (h) TBAF, THF, 65 °C, 88%; (i) DEPAA, DIPEA, T3P, PhMe, rt, 100%; (j) LHMDS, *p*-ABSA, THF, –78 °C – rt, 89%; (k) (1) $Rh_2(oct)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (2) KOBu-*t*, THF, 0 °C, 1 h; (3) $(CH_2O)_n$, –78 °C – rt, 1 h, 64%

The synthesis of the proposed structure of morifolin B **9** started with a common intermediate from the morifolin A route, ketone **19**, which was treated with $TMSCH_2Li$ to form alcohol **25** (Scheme 2). This was followed by a base-mediated Peterson olefination to generate exocyclic alkene **26**, and subsequent desilylation, acylation and diazotization as before, to generate diazo substrate **29** in excellent overall yield. Then, $Rh_2(OAc)_4$ catalysed C–H insertion[16] and olefination in the usual way, furnished lactone **9** as a single diastereoisomer (which was again verified by X-ray crystallography),[15] along with a small amount of a cyclopropane side-product **30** (not shown, see Supporting Information). The ^{1}H NMR data of synthetic material **9** were again significantly different to those published for the natural product,[9] confirming that morifolin B was also incorrectly assigned in the literature. Therefore, similarly to morifolin A, it again seems most likely that the isolated material named morifolin B **9** is in fact the same as critonilide **11**, again as suggested previously by Herz.[10]

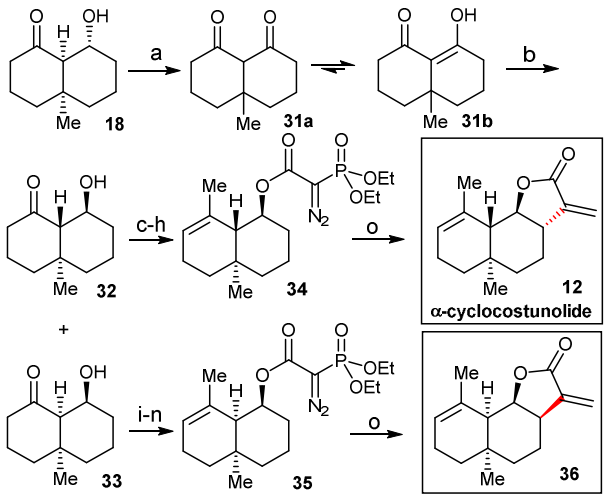
Scheme 2 – Synthesis of α-methylene-γ-butyrolactone **9**.



Scheme 2 Reagents and conditions: (a) $TMSCH_2Li$, THF, –78 °C, 84%; (b) NaH, THF, 65 °C, 100%; (c) TBAF, THF, 65 °C, 81%; (d) DEPAA, DIPEA, T3P, PhMe, rt, 82%; (e) LHMDS, *p*-ABSA, THF, –78 °C – rt, 78%; (f) (1) $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, 45 °C, 16 h; (2) KOBu-*t*, THF, 0 °C, 1 h; (3) $(CH_2O)_n$, –78 °C – rt, 1 h, 45% (**9**) and 11% (**30**).

Next, attention turned to the synthesis of α-cyclocostunolide **12**,[17] a cytotoxic[18] *trans*-decalin eudesmanolide natural product with anti-trypanosomal[19] and anti-coagulant activity.[20] Its synthesis began with a two-step epimerisation of *cis*-β-hydroxyketone **18** *via* an oxidation-reduction sequence, which provided the desired *trans*-β-hydroxyketone **32**, in addition to diastereoisomeric *cis*-β-hydroxyketone **33** (Scheme 3).[21]

Scheme 3 – Synthesis of (±)-α-cyclocostunolide **12** and α-methylene-γ-butyrolactone **36**.



Scheme 3 Reagents and conditions: (a) DMP, CH_2Cl_2, 0 °C, 80%; (b) $NaBH_4$, MeOH, 0 °C, 10% (**32**), 16% (**33**); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C – rt, 100%; (d) Tf_2O, DTBMP, CH_2Cl_2, rt, 67%; (e) $Fe(acac)_3$, MeMgCl, THF:NMP (1:3), 92%; (f) TBAF, THF, 65 °C, 92%; (g) DEPAA, DIPEA, T3P, PhMe, rt, 99%; (h) LHMDS, *p*-ABSA, THF, –78 °C – rt, 88%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C – rt, 96%; (j) LHMDS, Tf_2O, THF, –40 °C, 62%; (k) $Fe(acac)_3$, MeMgCl, THF:NMP (1:3), 59%; (l) TBAF, THF, 65 °C, 71%; (m) DEPAA, DIPEA, T3P, PhMe, rt, 63%; (n) LHMDS, *p*-ABSA, THF, –78 °C – rt, 75%; (o) (1) $Rh_2(oct)_4$ (2

mol%), CH_2Cl_2, 45 °C, 16 h; (2) KOBu-*t*, THF, 0 °C, 1 h; (3) $(CH_2O)_n$, −78 °C – rt, 1 h, 52% (**12** from **34**) and 66% (**36** from **35**).

Then, the same sequence shown in Scheme 2 was performed on each of these β-hydroxyketones, affording diazo substrates **34** and **35** without complication. We were then pleased to isolate α-cyclocostunolide as the sole product from the reaction of diazophosphonate **34** under the standard one-pot C–H insertion/olefination conditions, with its spectral data fully matching those of natural α-cyclocostunolide.[17] In addition, diastereomeric lactone **36** was also isolated from diazophosphonate **35**, and was again formed in good yield, via selective equatorial C–H insertion.[22]

In summary, a highly regio- and stereoselective one-pot C–H insertion/olefination protocol for the late-stage functionalisation of conformationally restricted cyclohexanol-derivatives has been developed. Exclusive formation of γ-lactones via insertion into equatorial C–H bonds was observed and the method was validated in natural product synthesis. Eudesmanolide sesquiterpene natural product α-cyclocostunolide **12** was synthesised in racemic form in high yield using this protocol. In addition, structures **8** and **9**, originally assigned to the natural products morifolin B and morifolin A, were prepared and it was demonstrated unambiguously that the original structural assignments were in error. Finally, a fourth isomeric α-methylene-γ-butyrolactone **36**, which is apparently novel, was also prepared.[22] This chemistry is expected to be applicable to a variety of synthetic targets possessing the α-methylene-γ-butyrolactone motif.

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21 The relative stereochemistry of compounds **32** and **33** were assigned retrospectively based on an X-ray crystal structure

of a TBS-protected derivative of **32** (**S8**); see CCDC 1421164 and the Supporting Information for details.

22 To the best of our knowledge, isomer **36** is novel and has not yet been found in Nature, although in view of the high number of related natural products known, it is not inconceivable that it occurs naturally.