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Expeditious formation of γ-lactones upon palladium-catalyzed double nucleophilic addition of bis(TMS)ketene acetals to vicinal allylacetates

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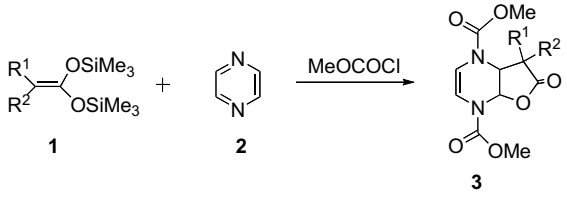
ABSTRACT

Polysubstituted γ-lactones are easily obtained, in one step, upon the interaction of bis(TMS)ketene acetals with vicinal allylic acetates in the presence of catalytic amounts of $Pd(PPh_3)_4$.

Our approaches to the synthesis of polycyclic γ-lactones of biological relevance relied on the use of bis(TMS)ketene acetals **1** as 1,3-dinucleophiles in either transition metal or organic reagent-promoted di-addition reactions.[1]

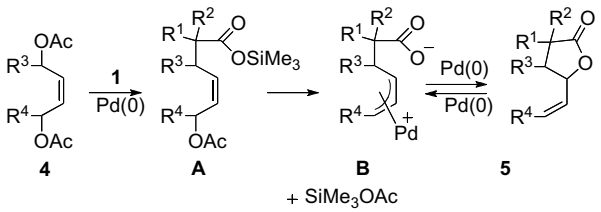
Although we have disclosed a two-step overall catalytic synthesis of such lactones,[2] no catalytic transformation, using this methodology and involving a single metal, has yet been achieved. The purpose of this Letter is to present preliminary results which demonstrate, on a few examples, that this is, however, feasable.

The double nucleophilic addition of both the carbon and the oxygen termini of bis(TMS)ketene acetals to two close, similar electrophilic iminium carbon centers seemed obvious in the case of the methylchloroformate-induced formation of γ-lactones **3** from pyrazine **2**[3a,b] (Scheme 1). However, less obvious would be the addition of the same dinucleophilic species to potential dielectrophiles such as unsaturated diacetates **4**, which might lead successively upon their interaction with palladium(0) and nucleophiles, to disubstitution products via two π-allylic complexes having in common a carbon–carbon double bond. Although the initial step, the addition of carbon–nucleophiles to the first π-allylic complex (**4**→**A**), is well known, both for classical carbon–nucleophiles[4a–i] and for carbon–nucleophiles arising from ketene acetals,[2,5a–c] the second step (**B**→**5**), the formation of a carbon–oxygen bond from **1**, leading to a γ-lactone, although likely to occur, would be more tricky.[6]



Scheme 1.

Indeed, this last step, the formation of the five-membered ring is reversible: the lactone in **5** (Scheme 2) in an allylic position might be prone to react with palladium(0) to give back a π-allyl complex **B**. This property has been used in the synthesis of highly substituted complex organic molecules: such lactones, which could also be synthesized by classical methods, either in the form



Scheme 2.

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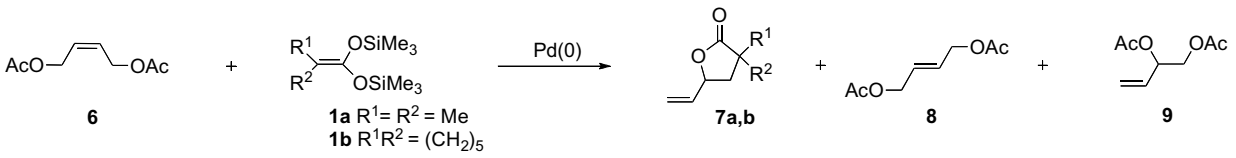
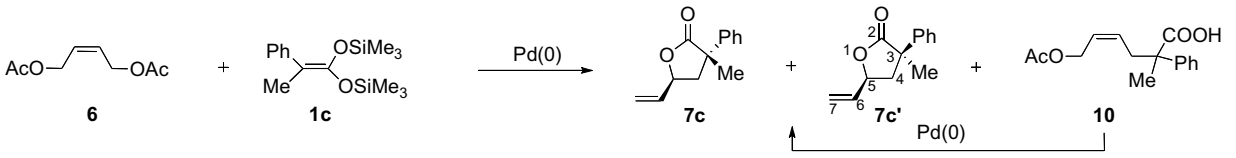


Scheme 3.

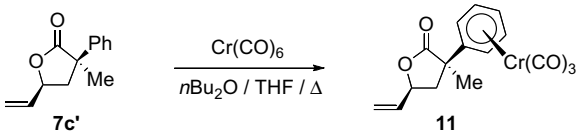


Scheme 4.

of racemates or in enantiomerically pure forms, were used as the starting material for the stereocontrolled synthesis of acyclic scaffolds in the presence of Pd(0) and suitable nucleophiles.[6,7a–d] We nevertheless attempted the reaction with the simplest potential di-π-allyl complex precursor, diacetate **6**. In order to take the less chances for this subsequent ring-reopening to occur (**5**→**B**), we first used highly substituted bis(TMS)ketene acetals such as **1a** ($R_1 = R_2 = Me$), **1b** (R_1–$R_2 = (CH_2)_5$), and **1c** (R_1 = Ph, R_2 = Me), which might act favorably in the second step on the grounds of the Thorp-Ingold effect, and carried out the reactions at room temperature[8a,b] (see Schemes 3 and 4).

Thus, when the ketene acetal **1a** (1.1 equiv) was added dropwise to a solution of diacetate **6** (1 equiv) and $Pd(PPh_3)_4$ (5%) and the mixture stirred at room temperature for two days, then, according to TLC, the formation of a new, less polar product **7a** was observed. Silica gel column chromatography allowed to isolate the new compound as a white solid, mp 30 °C, in 47% yield besides some more polar isomerized starting diacetates **8** and **9**. The ^{13}C NMR spectrum of **7a** was in agreement with the presence of a γ-lactone, with a signal at δ 181.68 ppm, of a monosubstituted carbon–carbon double bond according to a DEPT sequence, with signals at δ 136.02 (CH) and 117.67 (CH_2) ppm. The ^1H NMR spectrum confirmed these data and also depicted a deshielded signal for one proton at δ 4.82 ppm as a quartet of triplets, J = 6.3 and 1.1 Hz. An HMQC sequence allowed to assign this signal to a proton linked to a carbon at δ 77.12 ppm. Moreover, signals as doublets of doublets for two geminated protons were also apparent at δ 2.21 and 1.84 ppm. Finally, the two methyl groups gave a singlet at δ 1.24 ppm. It is therefore clear that the expected double nucleophilic addition took place leading to a γ-lactone. The ketene acetal **1b** behaved similarly and gave the same type of lactone **7b**, again as a solid (71% yield, mp 31 °C). However, confirmation of the structure of these new lactones by an X-ray analysis could not be achieved due to the poor quality and the low melting points of crystals of **7a** and **7b**. In the case of the ketene acetal **1c**, the same procedure led however to a more complex mixture of three compounds, two of them having almost the same polarity. Careful silica gel column chromatography allowed the separation, besides the starting isomerized diacetates, of three compounds. To the less polar compound, isolated in 10% yield as a solid, mp 37 °C, was assigned structure **7c** on the grounds of its NMR data, which were very close to those of **7a** (except for the presence of a phenyl group). A slightly more polar product **7c′**, obtained as a liquid, in 5% yield, showed almost the same ^{13}C NMR spectrum as **7c,** but as far as the ^1H NMR spectrum was concerned, differences in the chemical shifts of the protons of both the methylene group and of the proton H-5 could be noticed. Finally, a much more polar product was also isolated as a viscous liquid in 23% yield. The NMR data agreed fully with a structure such as **10** and depicted the presence, besides a disubstituted carbon–carbon double bond, of a phenyl group and of a methyl group as a singlet, of an acid and of a methylester. They gave signals, respectively, at δ 181.50 ppm and 170.95, the latter confirmed by the presence of a signal for a methyl group at δ 2.01 ppm and of a doublet J = 5.2 Hz at δ 4.44. Accordingly, **10** was therefore the monoaddition product of the ketene acetal **1c** to diacetate **6**, having suffered hydrolysis of the TMS ester function. Since carboxylic acids are also excellent nucleophiles for π-allyl complexes of palladium,[9] we submitted compound **10** to a catalytic amount of Pd(0): a fast reaction took place leading after one night at room temperature to a mixture of the expected lactones **7c** and **7c′**, in the same ratio as for the direct double addition reaction. The observation of the monoadduct **10**, which exists in the reaction mixture, before workup, as the TMS ester, might be ascribed to its lower reactivity toward the catalyst. The presence of bulky substituents and especially of the TMS group would considerably slow down the second addition reaction, and thus allow the isolation of the monoaddition product. The presence of a phenyl group in lactones **7c** and **7c′** gave us the opportunity to convert the more polar liquid lactone **7c′** into an arenetricarbonylchromium complex upon its heating for two days in the presence of an excess of chromium hexacarbonyl in a refluxing mixture of dibutylether/THF (Scheme 5). A silica gel column chromatography allowed us to purify that complex and, after recrystallization from dichloromethane/hexane solutions, to get yellow crystals of **11** (37% yield, mp 150 °C) suitable for an X-ray structure determination.[10] The ^1H NMR spectrum confirmed the coordination of the arene group to the metal, all the signals for the aromatic protons being shifted toward higher field. As shown (Fig. 1) the phenyl group, coordinated to $Cr(CO)_3$, is cis with respect to the vinyl group. Therefore, in the less polar solid lactone **7c** these two substituents are trans.

Finally, we carried out the same reaction by using two monosubstituted bis(TMS)ketene acetals, **1d** (R_1 = H, R_2 = Me) and **1e** (R_1 = H, R_2 = *i*Pr). The reason behind this choice was that lactone



Scheme 5.

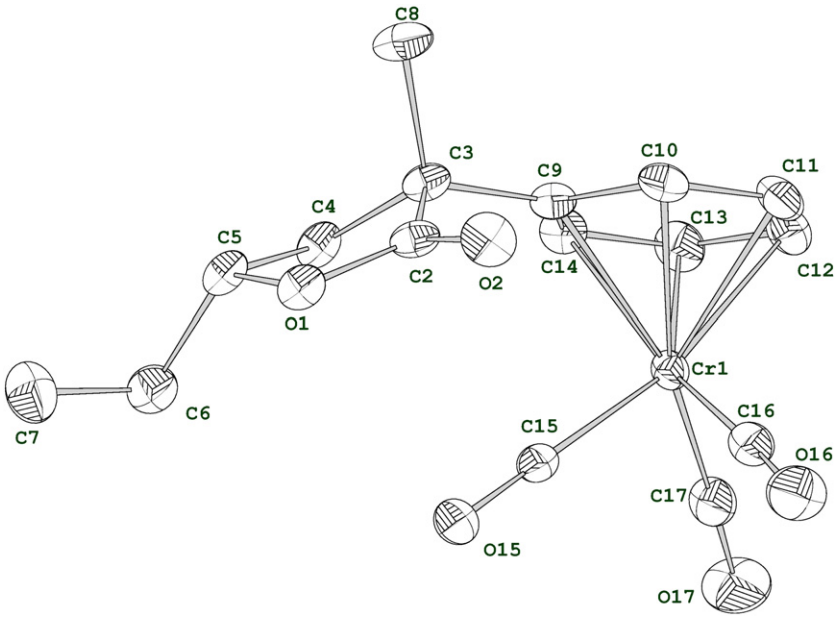


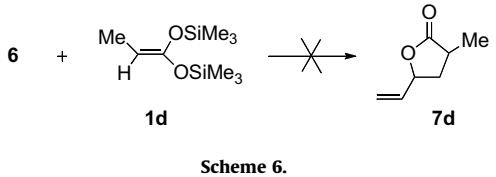
Figure 1. X-ray structure of compound **11**.

7d which might be formed upon the interaction of **1d** with diacetate **6** is known from the literature.[11]

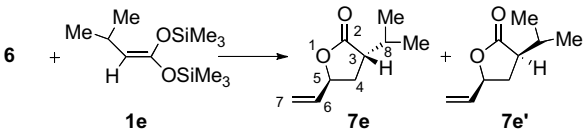
However, to our surprise and in spite of many efforts to achieve this goal, only trace amounts of the expected lactone **7d** could be detected by NMR: only isomerization of the starting diacetate to the more stable trans diacetate **8** took place (Scheme 6).

However, under the same conditions **1e** led to a 2:1 mixture of the expected isomeric lactones **7e** and **7e′** in 42% yield (Scheme 7). They could also be partially separated. Their NMR data agreed with the suggested structures (see the Supplementary data). Indications that indeed the catalyst reacted with, and was deactivated by the ketene acetal **1e** were obtained: a yellow precipitate, the nature of which has not yet been established forms rapidly in the absence of diacetate **6**. No such a interaction took place with for example **1b**: stirring a dichloromethane solution of **1b** in the presence of the catalyst for one day did not induce its deactivation since the addition of diacetate **6** led to the expected lactone **7b**.

As a conclusion, the expected di-addition reactions leading to satisfactory yields of γ-lactones took place as expected, provided that two rather bulky substituents were present on the bis(TMS)-ketene acetals **2**. In the case of monosubstituted acetals, and depending on the size of the substituent either a partial or a complete deactivation of the catalyst was observed. Extensions of the reaction to structurally different diacetates able to give rise to two successive π-allyl complexes, and involving also different achiral and chiral catalysts, which might improve the stereoselectivity of these transformations, and introduce enantioselectivity are in progress.



Scheme 6.



Scheme 7.

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Supplementary data

Experimental section and physical data for compounds **7a**, **7b**, **7c**, **7c′**, **10**, **11**, **7e**, **7e′** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.111.

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10. Crystal data for **11**: $C_{16}H_{14}CrO_5$, M = 338, monoclinic, space group $P2_1/n$, a = 10.3919(6) Å, b = 13.7841(8) Å, c = 11.4571(8) Å, V = 1516.65(17) Å^3, Z = 4, D_c = 1.48 g cm^{-3}, μ = 0.774 mm^{-1} (Mo Kα, λ = 0.71073) T = 250 K, R_1 (0.034), wR_2 [$I > 3\sigma(I)$] = 0.037; R_1 (0.0538), wR_2 (all data) = 0.0491, CCDC-687772.
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