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A two-step, catalytic synthesis of δ-hydroxy-γ-lactones from allylic acetates and bis(trimethylsilyl)ketene acetals

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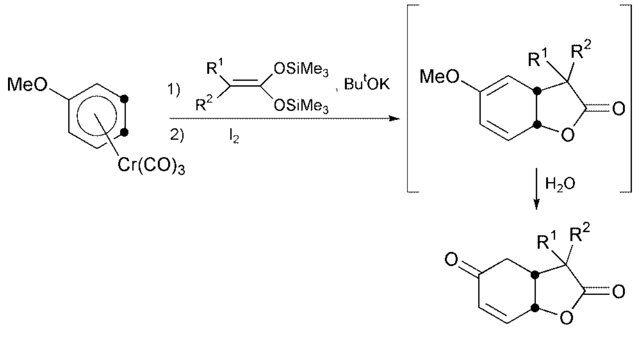
Bis(trimethylsilyl) ketene acetals react successively with allylic acetates, in the presence of Pd(0) then with H_2O_2, in the presence of methyltrioxorhenium, to give δ-hydroxy-γ-lactones *via* γ-unsaturated carboxylic acids.

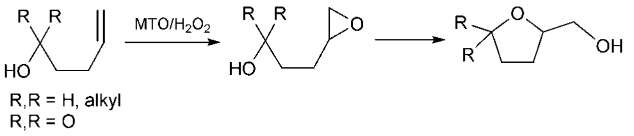
η^3-allyl palladium complexes, formed upon oxidative addition of allylic compounds to Pd(0), have found wide applications, as intermediates, in their reaction with nucleophiles.[1] Much effort has been devoted to the modification of the structure of the allylic moiety, the ligands around the metal, and also of the nucleophiles. It is this last point on which will focus our attention. Indeed, we have shown recently that bis(trimethylsilyl) acetals of ketenes could be used either as nucleophiles or versatile precursors of nucleophiles, when suitably activated, in reactions with a large variety of electrophiles such as carbonyl compounds, organic and organometallic peroxo derivatives,[2] and arene tricarbonyl chromium complexes.[3] These acetals lead *directly*, in contrast to other precursors, to functionalized carboxylic acids in high yield. Moreover, for chromium complexes, a direct double nucleophilic addition of potassium enolates originating from these acetals on a carbon–carbon double bond of anisole (and its derivatives) has been brought to the fore. This one pot reaction leads to functionalized lactones (Scheme 1).

Alkoxy monotrimethylsilyl ketene acetals have already been used in palladium(0) catalyzed alkylations in conjunction with allylic acetates for the preparation of unsaturated esters.[4–6] Under the same conditions, bis(trimethylsilyl) ketene acetals might thus lead to unsaturated carboxylic acids. Moreover, we have shown[7] that γ-unsaturated hydroxyalkenes underwent a high yield catalytic oxidative cyclization to lactols promoted by the system H_2O_2/MTO (methyltrioxorhenium),[8] a reaction which has recently been applied to the transformation of γ-unsaturated carboxylic acids into hydroxylactone (Scheme 2).[9]

Taken together, the interaction of bis(trimethylsilyl) ketene acetals first with allylic acetates to give unsaturated carboxylic acids, then with MTO/H_2O_2 to give hydroxylactones (Scheme 3) would constitute a means for the catalytic addition of two nucleophiles on a carbon–carbon double bond,[10] and would thus parallel, on a formal point of view, the transformation of anisole depicted in Scheme 1. And this indeed turned out to be the case.



Scheme 1



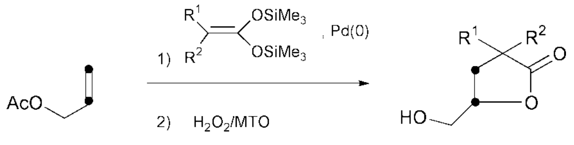
Scheme 2

Depending on the nature of the starting ketene acetals, cyclopropane carboxylic acids could be isolated as secondary products, and epoxycarboxylic acids detected by NMR as intermediates in the lactonization reactions.

Thus, a mixture of allyl acetate (10 mmol) and bis(trimethylsilyl)ketene acetal **1a**† (11 mmol) was heated in THF (70 mL) for 24 h in the presence of $Pd(PPh_3)_4$ (0.2 mmol, 2%). Evaporation of the volatiles, under vacuum, left a residue which was diluted in dichloromethane and filtered through a pad of silica gel. Extraction with aqueous sodium hydroxide followed by acidification and extraction with dichloromethane gave a mixture of acids. After cooling the solution to 0 °C, MTO (5% with respect to the unsaturated acids) was added followed by a 30% solution of hydrogen peroxide (1.1 equiv. with respect to the acids). The biphasic mixture was then stirred for three days at room temperature, the excess oxidant destroyed with aqueous sodium bisulfite, and the organic products extracted with dichloromethane. Treatment of the organic layer with dilute sodium hydroxide left an organic phase containing the hydroxylactone (5 mmol). Acidification of the aqueous layer followed by extraction with diethyl ether gave, after evaporation of the solvents, the cyclopropyl acid (1.5 mmol).

The same reactions were carried out on a series of bis(trimethylsilyl) ketene acetals and two allylic acetates.† They led to hydroxylactones and, for the more substituted ketene acetals, to mixtures of lactones and cyclopropyl acids (Table 1).‡

For cinnamyl acetate **2a** (R^3 = Ph) and the ketene acetal **1a** ($R^1 = R^2$ = Me), the two acids **3a** and **4a** resulting, respectively, from S_N2 and S_N2' reactions, were separated by crystallization and by silica gel chromatography. Their oxidation led, respectively, to the lactones **6a** and **7a** (Scheme 4). Whereas the transformation of **3a** into **6a**, obtained as a single isomer was complete within 6 h, the conversion of **4a** into **7a** took three days. This result is in agreement with the difference of epoxidation rate observed for substituted and terminal olefins with the system H_2O_2/MTO.[8]



Scheme 3

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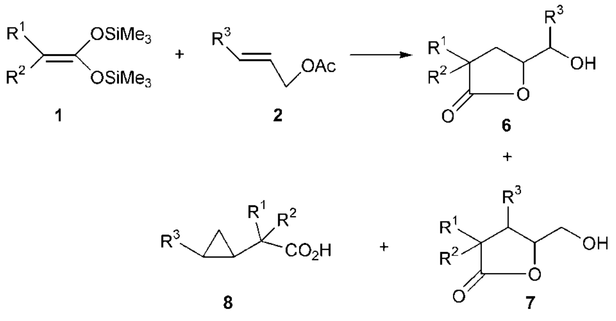
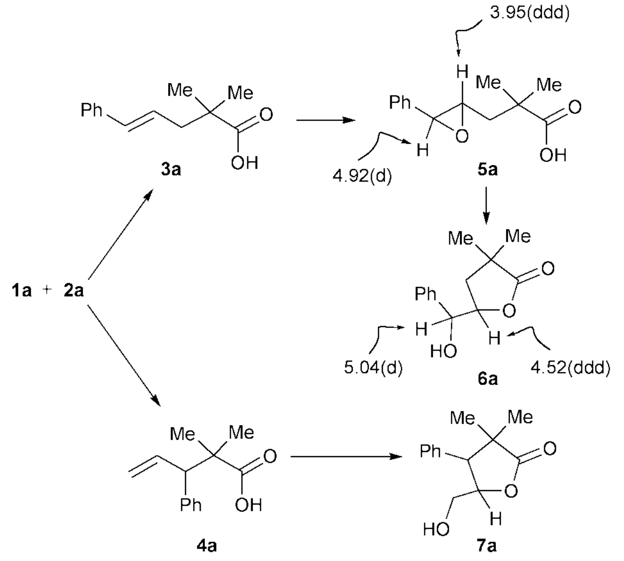
Table 1 Lactones and cyclopropyl carboxylic acids from allylic acetates and bis(trimethylsilyl) ketene acetals. The ratios were obtained from ^{1}H NMR (400 MHz) data, after oxidation. The ratios of **8** *vs.* **6** and **7** was also determined upon isolation of **8**



Entry	1	2	R^1	R^2	R^3	Yield (%)	6	7	8
1	**1a**	**2a**	Me	Me	Ph	69.5	49	27	24
2	**1a**	**2b**	Me	Me	H	26	76	—	24
3	**1b**	**2a**	(CH$_2$)$_5$		Ph	23.5	50	27	23
4	**1b**	**2b**	(CH$_2$)$_5$		H	66	76.5	—	23.5
5	**1c**	**2a**	H	*t*Bu	Ph	29	80	20	—
6	**1d**	**2a**	Ph	Ph	Ph	65	100	—	—
7	**1e**	**2a**	OPh	H	Ph	50	50	50	—



Scheme 4

That indeed epoxides were formed as intermediates in these oxidation reactions as for γ-hydroxyalkenes[7] was demonstrated as follows: when the acid **3a** was subjected to the oxidation reaction, a labile precursor could be detected by ^{1}H NMR spectroscopy after 2 h giving a doublet and a multiplet at δ 4.92 and 3.95, respectively attributable to the two hydrogens of the epoxide **5a** (Scheme 4). These signals disappeared progressively in favour of those due to the hydroxylactone **6a** at δ 5.04 (doublet), and δ 4.52 (multiplet). Attempts to isolate the epoxide **5a** by silica gel chromatography failed however, a result which is reminiscent of previous observations.[7]

The results described herein allow the following comments to be made.

As for mono(trialkylsilyl) ketene acetals, no base was required for the interaction with the allylic acetates: the ketene acetals are thus nucleophilic enough to interact as such with the π-allyl complexes of palladium.[6,10]

In addition, these transformations are interesting from a double point of view. First, highly substituted, unsaturated carboxylic acids can be obtained *directly* in the first step of the process. Second, for the disubstituted ketene acetals, cyclopropyl acids are formed, yet, up to now, in rather low yield. Their purification, without the need of chromatography, can easily be achieved by the use of the second step of the process; indeed, the separation of the lactones from the cyclopropyl acids, whenever formed, is possible by a simple extraction process.

The interaction of mono(trialkylsily) ketene acetals with allylic acetates in the presence of complexes of palladium had already been shown to give, besides unsaturated esters, cyclopropyl esters in variable amounts.[5] The reasons behind this dual reactivity of the intermediate π-allyl complexes with the nucleophiles (central *vs.* terminal addition) have not been clearly established since contrasting results have be found in the literature.[12–15] Up to now, no attempts have been made in order to optimize the yields of the reactions described above by modifying the nature of the catalyst and the experimental conditions, or to drive them in one or the other direction. It seems nevertheless likely that steric factors are important both as far as the ligands around the metal and the substituents on the ketene acetals are concerned.

Notes and references

† *Selected data* for **6** [R^{1}R^2 = (CH$_2$)$_5$, R^3 = H], colorless oil; IR(Nujol), 1750 cm^{-1}; δ_H(CDCl$_3$, 400 MHz) 4.52 (m,1H, C*H*O), 3.89 (dd, *J* 12, 2.5 Hz, 1H, C*H*OH), 3.61 (dd, *J* 12, 5.1 Hz, 1 H, C*H*OH), 2.77 (1H, O*H*), 2.24 (dd, *J* 13 and 6.6 Hz, 1H, C*H*H), 1.88 (dd, 1H, *J* 13 and 8 Hz, 1H, CH*H*), 1.81–1.52 (m, 10H, 5 C*H*$_2$); δ_C(CDCl$_3$, 100 MHz) 182.0, 77.84, 63.9, 44.9, 34.1, 34.0, 32.1, 25.26, 22.2, 22.1; HRMS: 185.1178 (M$^+$). For **8** [R^{1}R^2 = (CH$_2$)$_5$, R^3 = H]: colorless oil; δ_H(CDCl$_3$) 2.1–1.07 (m, 10H), 0.87 (m, 1H), 0.18 (m, 4H); δ_C(CDCl$_3$) 183.2, 45.14, 32.18, 25.8, 23.5, 20.9, 0.85; HRMS: 169.122 (M$^+$). For **3a**: white crystals, mp 38 °C, δ_H(CDCl$_3$) 7.11–7.31 (m, 5H, ArH); 6.16 (d, *J* 16 Hz, 1H, PhC*H*=), 6.11 (dt, *J* 16, 7.5 Hz, 1H, =C*H*CH$_2$), 2.39 (d, *J* 7.5 Hz, 2H), 1.17 (s, 6H, 2 Me), δ_C(CDCl$_3$) 184.3, 137.7, 133.7, 128.9, 127.6, 126.5, 126.0, 43.9, 43.0, 25.1. Anal. Calc. For $C_{13}H_{14}O_3$: C, 70.91; H, 7.27. Found: C, 70.71; H, 7.31%.

‡ Satisfactory elemental analyses or HRMS were obtained for the various carboxylic acids and hydroxylactones.

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