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Highly stereoselective additions of cuprates to a polyfunctional enone

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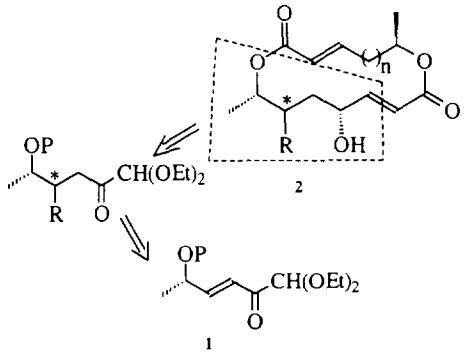
Abstract: The stereoselectivity of the addition of cuprates to a polyfunctional γ-alkoxy enone depended on the γ-hydroxyl protective group. Protection as a blocking silyl ether gave the best results (de=93–95%). An unexpected and original cleavage–oxidation reaction at ambient temperature transformed the addition products into well known lactones well characterized in the literature. Comparison of the spectral data of these lactones with those in the literature allowed the configuration of the new asymmetric centers to be assigned. © 1997 Elsevier Science Ltd

The polyfunctional enone, (3*E*,5*S*)-1,1-diethoxy-5-t-butyldiphenylsilyloxy-hex-3-en-2-one **1**, was synthesized[1] from (*S*)-ethyl lactate as a potential precursor of natural macrodiolides **3** and their analogues. Indeed, the enone function should enable the introduction of many functions to the appropriate positions in the desired analogues. One possible modification was the addition of alkyl or aryl groups in position 4 of the enone by addition of cuprates (Scheme 1).



Scheme 1.

According to our experience, the reaction of the enone **1** with higher order cuprates[2] provoked the formation of 1–2 addition products only. In order to execute these 1–4 addition reactions, we used lower order cyano-cuprates (RCu(CN)Li)[3,4] that we obtained under inert atmosphere in ether medium with two equivalents of copper cyanide per equivalent of lithiated reagent. The cuprates used were of three types: MeCu(CN)Li; nBuCu(CN)Li; PhCu(CN)Li; the stereoselectivity of the reaction depends strongly on the protecting group on the γ-hydroxyl function (Table 1).

It is interesting to note that such additions to α,β-insaturated-γ-alkoxy esters have been extensively studied in the literature[5–7] whereas few examples of addition to γ-alkoxy enones are known. The best des were obtained for the enone **1** having the hydroxyl function protected as a silyl ether. We therefore chose to study more closely the corresponding addition products since for a total synthesis, only des around 90% are acceptable at the first stages. The phenyl group was introduced with low efficiency

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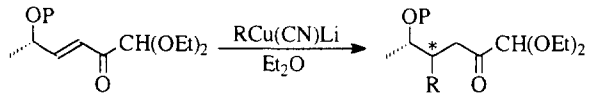
Table 1. Influence of the protective groups on the stereoselectivity of the cuprate additions



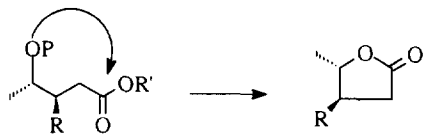
enone **1** **3-5**

Compound	P	R	Temperature (°C)	de*(+,- 3%)	Yields
3a	MEM	Me	-30	40 %	85 %
3b		n-Bu	-50	50 %	80 %
3c		Ph	-50	55 %	48 %
4a	Bn	Me	-30	60 %	78 %
4b		n-Bu	-50	75 %	88 %
4c		Ph	-50	95 %	41 %
5a	$SitBuPh_2$	Me	-30	94 %	88 %
5b		n-Bu	-50	93 %	82 %
5c		Ph	-50	95 %	65 %

because of its steric hindrance. This could be improved by running the reaction at −30°C instead of −50°C, but at the cost of a loss of diastereoselection, which was not the pursued goal.

All the diastereomeric excesses could be calculated by the analysis of the ^1H NMR (400 MHz, $CDCl_3$) spectra thanks to the splitting of the acetal proton signals. In order to find the absolute configuration of these addition products, we transformed them into molecules known in the literature.

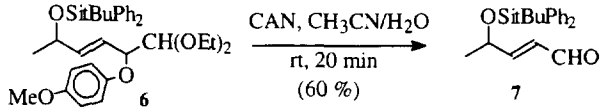
In the case of 1–4 additions of cuprates to α,β-insaturated γ-alkoxy esters, the hydroxyl function of the addition product is deprotected and cyclises directly on the ester function to give the corresponding lactones (Scheme 2).[5]



Scheme 2.

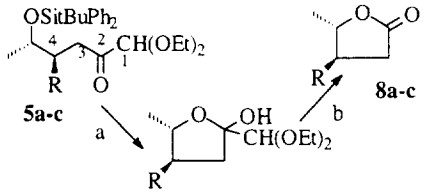
In the case of the addition products of the enone, deprotection of the alcohol function did not give a lactone directly but a cyclic hemiacetal.

An error of manipulation at the time of the cleavage of a para anisyl ether by the CAN in aqueous acetonitrile medium, allowed us to observe that at ambient temperature, this reagent provoked an oxidative cleavage. Indeed, the secondary protected alcohol function of compound **6** afforded in these conditions an aldehyde **7**[8] with a shorter skeleton (Scheme 3).



Scheme 3.

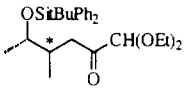
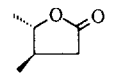
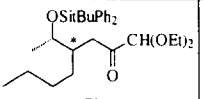
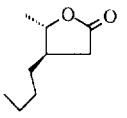
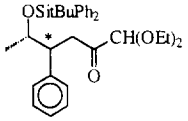
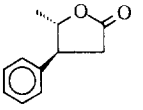
Some reactions of this type had been already observed by Trahanosky et al.[9] in the case of tertiary alcohols. We thus had the idea to apply this method to the hemiacetals previously obtained. The quaternary carbon had to be transformed into a carbonyl function in order to produce the lactones known in the literature (Scheme 4). Table 2 summarizes the results obtained and it appears that the new stereogenic carbons created had the R configuration.



a) $nBu_4N^+F^-$, 4 eq, THF, rt, 4days ; b) CAN, 3 eq, CH_3CN/H_2O (3/1), 20 min, rt.

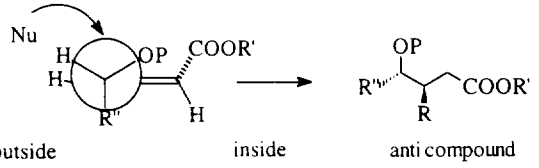
Scheme 4.

Table 2.

Cuprates	Addition product		lactones		Configuration
	Product[10]	de (%)[a]	structure[b]	yields[c]	
MeCu(CN)Li	 **5a**	94 %	 **8a**	50 %	C_4 (R)
nBuCu(CN)Li	 **5b**	93 %	 **8b**	40 %	C_4 (R)
PhCu(CN)Li	 **5c**	95 %	 **8c**	40 %	C_4 (R)

a- diastereomeric excesses were determined by ^1H NMR (400 MHz, $CDCl_3$)
b- The lactone structures were determined by comparison with the analytical data of the literature and comfirmed by NOE studies
c- Global yields from the addition products (**5a-c**)

All these conclusions were in agreement with the hypotheses of Yamagushi[5,6] and Morokuma.[7] Indeed the modified Felkin–Ahn models they used anticipated an anti addition for some α,β-unsaturated esters with a trans configuration (Scheme 5).



Scheme 5.

These cuprate additions allowed us to obtain precursor compounds of macrodiolides with a high diastereomeric purity. In order to prove the configuration of the new asymmetric centers, an unexpected oxidative cleavage transformed the addition products into lactones fully characterized in the literature.

References

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(8) Analytical data of compound **7**: Colorless oil, Rf=0.80 E/PE (50/50), MS (CI, NH_3) m/z 356.5, 339.3, 281.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz): 9.51 (d, *J*=7.6, 1H), 7.38 (m, 10H), 6.73 (dd, *J*=15.8, 4.6, 1H), 6.25 (ddd, *J*=15.3, 7.6, 1.5, 1H), 4.56 (m, 1H), 1.19 (d, *J*=6.1, 3H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.2, 23.1, 26.9, 68.7, 127.7, 129.9, 133.2, 133.7, 135.7, 135.8, 160.5, 193.8.
(9) Trahanovsky, W. S.; Macaulay, D. B. *J. Org. Chem.* **1973**, 38, 1497–99.
(10) Analytical data of compounds **5a–c**: **5a**: Colorless oil, Calcd anal for $C_{27}H_{40}O_4Si$: C: 71.01%, H: 8.83%; Found: C: 71.24%, H: 8.92%. $[\alpha]^{25}_D$=+2.8 (*c* 1.07 CH_2Cl_2). Rf=0.60 E/PE (50/50). IR (film): 1728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz): 7.80–7.30 (m, 10H), 4.49 (s, 1H), 3.75–3.40 (m, 5H), 2.72 (dd, *J*=17.8, 4.1, 1H), 2.39 (dd, *J*=17.8, 9.2, 1H), 2.19 (m, 1H), 1.23, 1.20 (2t, *J*=7.1, 6H), 1.04 (s, 9H), 0.94 (d, *J*=6.1, 3H), 0.90 (d, *J*=7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.1, 15.4, 19.4, 19.6, 27.0, 35.4, 39.9, 63.1, 63.2, 72.7, 102.7, 127.4, 127.5, 129.4, 129.5, 134.0, 134.9, 135.9, 205.6. **5b**: Colorless oil, Calcd anal for $C_{30}H_{46}O_4Si$: C: 72.24%, H: 9.30%; Found: C: 72.06%, H: 9.16%. $[\alpha]^{25}_D$=−3.3 (*c* 2.77 CH_2Cl_2). Rf=0.70 E/PE (20/80). IR (film): 1729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz): 7.80–7.30 (m, 10H), 4.51 (s, 1H), 3.86 (m, 1H), 3.70–3.40 (m, 4H), 2.73 (dd, *J*=18.3, 5.6, 1H), 2.51 (dd, *J*=18.3, 7.1, 1H), 2.01 (m, 1H), 1.50–1.10 (m, 6H), 1.24, 1.21 (2t, *J*=7.1, 6H), 1.04 (s, 9H), 0.94 (d, *J*=6.1, 3H), 0.83 (t, *J*=7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 15.1, 19.4, 20.4, 22.9, 27.1, 29.6, 30.5, 37.7, 40.1, 63.2, 63.3, 70.6, 102.8, 127.3, 127.5, 129.4, 129.5, 133.9, 134.9, 135.9, 206.1. **5c**: Colorless oil, Calcd anal for $C_{32}H_{42}O_4Si$: C: 74.09%, H: 8.17%; Found: C: 74.32%, H: 8.11%. $[\alpha]^{25}_D$=+11.5 (*c* 1.91 CH_2Cl_2). Rf=0.60 E/PE (20/80). IR (film): 1731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz): 7.70–7.30 (m, 10H), 7.25–7.05 (m, 5H), 4.35 (s, 1H), 3.96 (m, 1H), 3.60–3.05 (m, 7H), 1.17 and 1.11 (2t, *J*=7.1, 6H), 1.03 (s, 9H), 0.80 (d, *J*=6.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.0, 15.1, 19.4, 21.5, 27.0, 39.4, 48.3, 62.9, 73.1, 102.6, 126.4–141.9, 205.2.

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