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Method for the Parallel Synthesis of α-Methylene-γ-lactones from a Fluorous Acrylate

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α-Methylene-γ-lactone derivatives have attracted much attention over the years, since the α-methylene-γ-lactone ring unit is an important functional structure in a wide range of natural products. Among them, the main representative compounds are sesquiterpene lactones[1] extracted from *Asteraceae* and paraconic acids[2] from lichens, which exhibit particularly relevant cytotoxic or antimicrobial activities. Furthermore, α-methylene-γ-lactones serve as versatile starting materials for other important compounds, such as polyamines,[3] amino acids,[4] terpenes,[5] etc. Because of these interesting properties, solution-phase synthesis of this moiety has stimulated considerable effort,[6] whereas parallel supported synthesis has received very little attention.[7]

However, in recent years, combinatorial chemistry has been widely accepted as a powerful concept in organic synthesis, especially in the search for lead compounds to initiate drug discovery research programs. In this way, the development of new methodologies or the adaptation of already existing ones to make them suitable for parallel synthesis has become a dynamic research field.[8] Thus, fluorous phase organic synthesis (FPOS), which successfully integrates many of the most attractive features of solution- and solid-phase syntheses, has been recently introduced as a "beadless" high-speed synthetic technology.[9] Indeed, perfluoroalkyl chains used as the phase tags allow reactions to be carried out in homogeneous phase. Using those conditions, reactions can be monitored by conventional analytical methods (TLC, NMR, ...), and purification of all intermediates and final products can be performed by solid-phase extraction over reversed-phase fluorous silica gel (F-SPE).[10]

Herein, we investigate the use of FPOS for a sequential Baylis−Hillman (BH) coupling and carbonyl allylation for an easy access to a series of mono- or disubstituted α-methylene-γ-lactones (Scheme 1). This straightforward two-step reaction and its adaptation to fluorous synthesis appear to be a very attractive methodology for parallel synthesis of α-methylene-γ-lactones, since each step allows the introduction of diversity as well as a considerable simplification of purification steps.

First, a fluorous acrylate (**1**) was coupled to an aldehyde via a Baylis−Hillman reaction.[11] This step provided the first diversity in position 4 (R_1). Second, a convenient palladium-catalyzed carbonyl allylation described by Masuyama and co-workers[12] afforded simultaneously (i) the introduction of the second diversity in position 5 (R_2) via the use of a second aldehyde, (ii) the cyclization of the five-membered lactone ring, and (iii) the release of the fluorous tag.
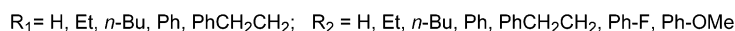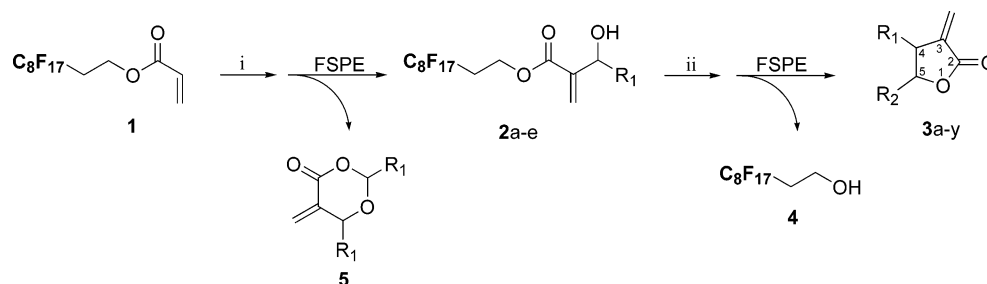
Preparation of Baylis−Hillman Intermediates (2a−e). The best results for the Baylis−Hillman coupling were obtained using DABCO (1 equiv) as tertiary amine with 2 equiv of aldehyde (R_1CHO) and without any solvents[13] at room temperature for 48 h (disappearance of the fluorous acrylate was monitored by TLC). After removal of the amine, purification of BH adduct could be processed by F-SPE. The unreacted aldehyde was eluted using a fluorophobic wash (methanol and water in 80:20 ratio), whereas the fluorous BH adduct was retained onto the SPE cartridge until elution with a fluorophilic solvent (CH_2Cl_2).

^{1}H NMR analyses of the fluorous fraction after F-SPE revealed the presence of the fluorous alcohol (**4**) in addition to the desired fluorous BH adduct. Further investigations revealed that formation of this hydrolysis product is concomitant with the cyclorelease of a dioxanone derivative (**5**). Recently, Price and co-workers proposed a new interpretation of the BH mechanism[14] in which the formation of a hemiacetal would be the rate-determining step. Thus, intramolecular transesterification of this hemiacetal would result in the cyclorelease of this kind of byproducts when the acrylate ester is a reasonable leaving group.[15,16]

However, these two byproducts did not induce further purification steps, since the dioxanone derivative was removed by the fluorophobic wash, and the fluorous alcohol did not interfere in the following step. The ratio of these two latter fluorous compounds was determined by ^{1}H NMR to estimate the yield of BH coupling. Thus, five fluorous-tagged BH adducts (**2a−e**) bearing the first diversity were easily synthesized with a 72−85% yield. As a result, fluorous BH coupling, for which good yield in a reasonable time and without excess of reactants can be reached, is an attractive alternative to other supported BH coupling.[16,17] Subsequently, the BH products were each split and then subjected to further carbonyl allylation.

Preparation of the α-Methylene-γ-lactones Array (3a−y). The fluorous BH adduct was coupled to a second aldehyde (R_2CHO) in the presence of $SnCl_2$ and PdCl$_2$-(PhCN)$_2$ in a catalytic amount. The reaction was carried out under nitrogen in a mixture of *N*-methylpyrrolidinone (NMP) and water (1/0.1) at 80 °C for 48 h. After dilution in diethyl ether, the crude mixture was filtered over diatomaceous earth and washed with water to remove the majority of the catalyst and NMP. The residue was then purified by F-SPE to afford the substituted α-methylene-γ-lactones in the fluorophobic wash and complete removal of fluorous products in the fluorophilic wash. The efficiency of this purification step is

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Scheme 1. Fluorous-Phase Synthesis of Disubstituted α-Methylene-γ-Lactones[a]

R$_1$= H, Et, *n*-Bu, Ph, PhCH$_2$CH$_2$; R$_2$ = H, Et, *n*-Bu, Ph, PhCH$_2$CH$_2$, Ph-F, Ph-OMe

[a] Reagents and conditions: (i) R$_1$-CHO (2 equiv), DABCO (1 equiv), rt, 48 h; (ii) R$_2$-CHO (0.9 equiv), PdCl$_2$(PhCN)$_2$ (0.1 equiv), SnCl$_2$ (2 equiv), NMP−H$_2$O, N$_2$, 80 °C, 48 h.
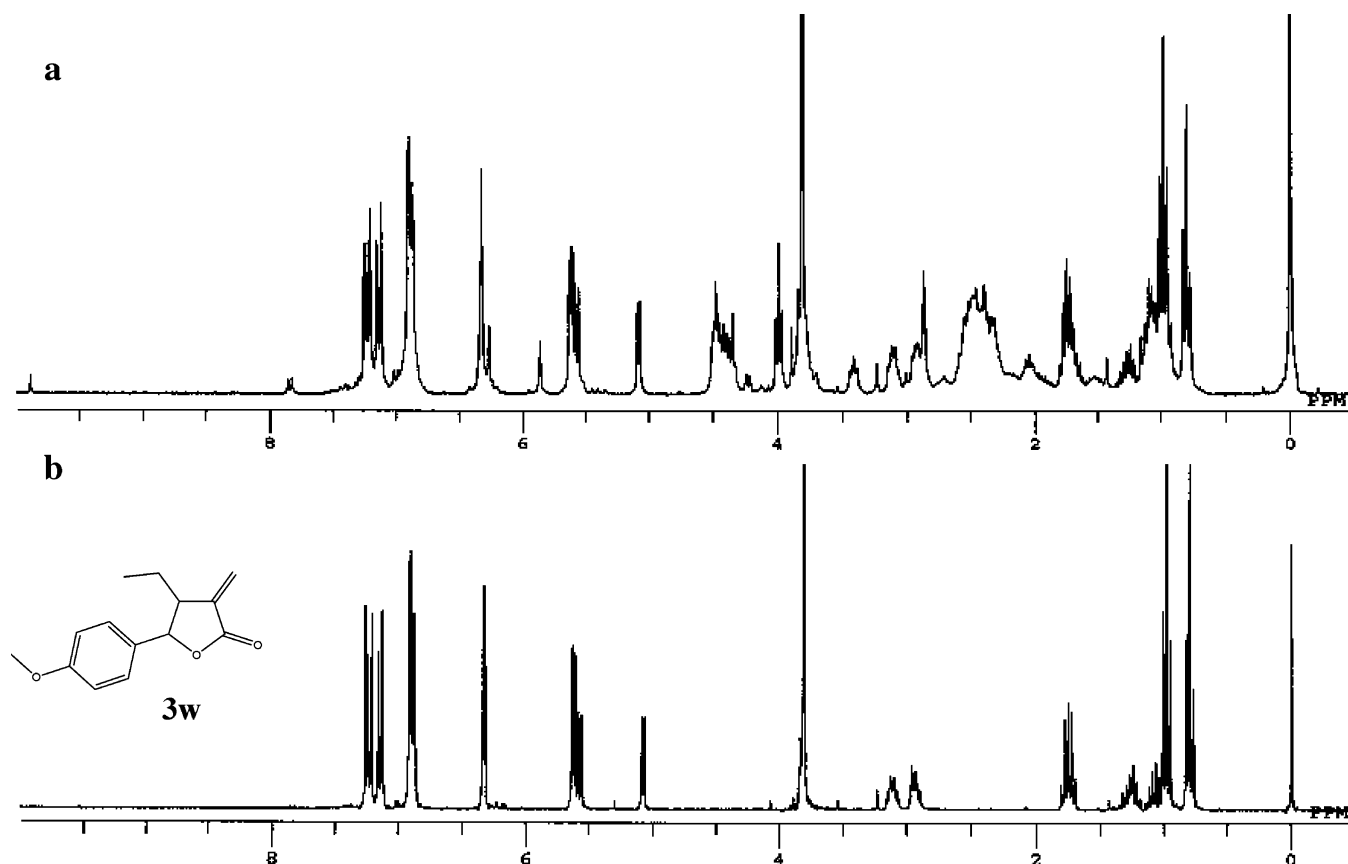

Figure 1. ^{1}H NMR spectra of representative library member (**3w**) before (a) and after (b) F-SPE.

illustrated by the ^{1}H NMR spectra (Figure 1) of a representative compound, **3w**, before and after F-SPE, which distinctly show the disappearance of fluorous alcohol signals (released by cycloelimination of the lactone) and the excellent purity of the isolated lactone. Thus, 25 aromatic or alkyl mono- or disubstituted α-methylene-γ-lactones (**3a**−**y**) were obtained using this methodology. Yields, purities, and diastereoisomeric ratios of crude products are reported in Table 1. Determination of the cis/trans ratio was performed using ^{1}H NMR by comparison of the integration of the H$_5$ or methylene signals, or both. Syn diastereoselectivity was observed in all cases except for the coupling with 4-methoxybenzaldehyde, which surprisingly did not induce any diastereoselectivity. The syn addition probably proceeded via an acyclic antiperiplanar transition state[18] to afford the cis α-methylene-γ-lactone as the major product (80 to ~100%), confirmed by measurement of the H$_4$−H$_5$ constant coupling

(^3J = 7−8 Hz) and NOESY experiments. Yields of carbonyl allylation ranged from 20 to 100% to give moderate or good overall yields. The efficiency of F-SPE is clearly demonstrated, affording after a fast and simple purification step most compounds with good or excellent purities (>85%) that are sufficient for a biological screening. Last, we could notice that as expected, reaction conditions described in the literature were easily adaptable to FPOS to give comparable or better yields.

In summary, 25 mono- or disubstituted α-methylene-γ-lactones were easily synthesized via a straightforward two-step reaction, in the course of which each step allowed the introduction of diversity via the use of various aliphatic and aromatic aldehydes. The combination of this reaction scheme and FPOS represents an attractive method that has potential for automated sample processing to produce libraries of compounds for high-throughput screening. Cytotoxic evalu-

Table 1. Yields, Purities, and Diastereoisomeric Ratios for the Crude α-Methylene-γ-lactone Array

entry	R₁	R₂	overall yield (%)	cis/trans ratio (%)[a]	purity (%)[b]
a	n-Bu	H	43		90
b	H	n-Bu	60		89
c	H	Ph	80		94
d	(CH₂)₂Ph	H	56		95
e	H	(CH₂)₂Ph	68		92
f	n-Bu	n-Bu	58	90/10	90
g	Et	n-Bu	60	90/10	88
h	n-Bu	Et	29	85/15	81
i	Et	Ph	45	~100	92
j	Et	(CH₂)₂Ph	60	85/15	89
k	(CH₂)₂Ph	Et	41	85/15	87
l	n-Bu	Ph	55	95/5	84
m	Ph	n-Bu	25	~100	53[c]
n	(CH₂)₂Ph	n-Bu	46	90/10	90
o	n-Bu	(CH₂)₂Ph	48	85/15	87
p	(CH₂)₂Ph	Ph	70	95/5	90
q	Ph	Ph	21	~100	65[c]
r	(CH₂)₂Ph	(CH₂)₂Ph	60	85/15	85
s	Et	Ph-F	38	~100	86
t	n-Bu	Ph-F	32	~100	80
u	Ph	Ph-F	17	~100	80
v	(CH₂)₂Ph	Ph-F	50	~100	61[c]
w	Et	Ph-OMe	55	55/45	97
x	n-Bu	Ph-OMe	25	55/45	90
y	(CH₂)₂Ph	Ph-OMe	44	60/40	90

[a] Diastereoisomer ratios were determined by ^{1}H NMR. [b] Purity was determined by reversed-phase HPLC with UV detection at 220 nm. [c] For entry which exhibited HPLC purity under 80%, a flash chromatography using Si-SPE with CH_2Cl_2 had easily afforded pure product (>95%).

ation of some compounds on a human melanoma cell line is still in progress.

Supporting Information Available. Details of experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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