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Synthesis of Functionalized γ-and δ-Lactones *via* Polymer-Bound Epoxides

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Abstract: Solid phase synthesis of epoxides from alkenoic acids followed by ring-opening reactions with sodium azide or thiophenols and subsequent cleavage from the polymeric support afford γ-and δ-lactones in good yields and high purity. © 1997 Published by Elsevier Science Ltd.

Interest in the application of solid phase synthesis in drug research increased rapidly in the past few years.[1,2] Undoubtedly, there is a growing need to expand the number of efficient organic reactions for the synthesis of small molecule libraries.[3]

The importance of epoxides in organic synthesis is well known and their nucleophilic ring opening has been extensively studied as a convenient route to create new carbon-carbon or carbon-heteroatom bonds.[4] We report herein our investigations concerning the synthesis of polymer-bound epoxides from alkenoic acids and their use as convenient precursors of functionalized γ-and δ-lactones.[5] These subunits are commonly encountered in many natural products and are of importance in insect pheromones,[6] antifungal substances, flavor components or in the essential oils of plants.[7] Additionally γ-butyrolactones serve as versatile starting materials for other important products such as furans, cyclopentenones, etc.[8]

We first selected four commercially available alkenoic acids as starting material. The carboxyl group both provides a convenient site for attachment onto a solid support and a useful functionality for a further cyclisation step. The Solid phase synthesis was initiated by coupling acids **1a-d** to Merrifield resin (1.7 mmol of Cl/g, 1% DVB) according to a literature procedure.[9] Epoxidation with m-chloroperbenzoic acid in

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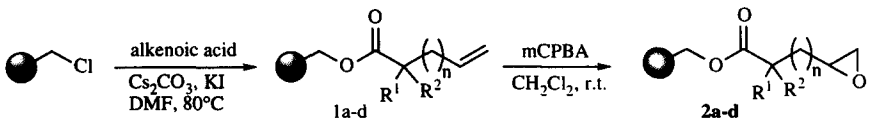
methylene chloride at room temperature furnished oxiranes **2a-d**.[10] FTIR was successfully used in reaction monitoring since disappearance of absorption at 1640 cm^{-1} ensured complete conversion of the alkene function. The observation of a band at 1730 cm^{-1} indicates that the ester moiety was still present (Figure 1).



a n=1 R^1=H R^2=H **c** n=1 R^1=Me R^2=Me
b n=1 R^1=H R^2=Me **d** n=2 R^1=H R^2=H

Scheme 1

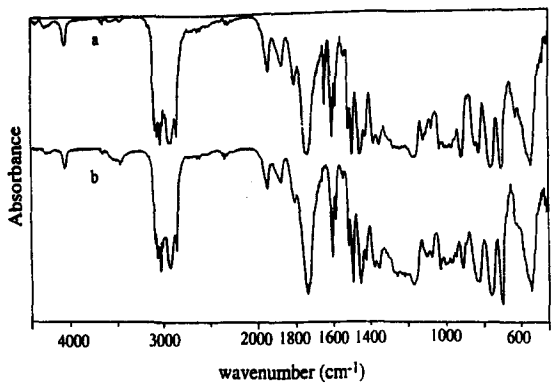
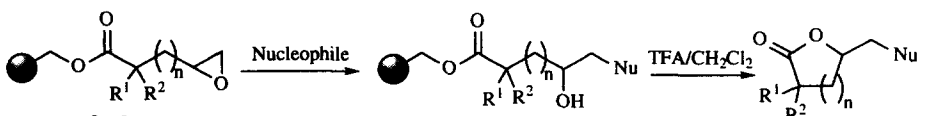


Figure 1: FTIR spectra of **1a** before (a) and after epoxidation (b).

We first investigated the azidolysis of **2** under usual conditions, i.e. NaN_3/NH_4Cl in DMF.[11] The reaction was carefully monitored by FTIR spectroscopy to avoid cyclisation during the opening of the epoxide ring. TFA-treatment of **3** caused spontaneous lactonization and cleavage from the resin. The desired compounds **5-8** were obtained in good yields and purities. In a similar way, sodium thiolates reacted with **2** at room temperature in DMF to afford the β-hydroxy thioethers **4**. As for the azido derivatives, lactones **9-12** were directly obtained after treatment with trifluoroacetic acid (Scheme 2, Table 1).[12] Examination of the resin by FTIR showed no absorption at 1730 cm^{-1} indicating that cleavage has been completely achieved.



2a-d

3 Nu=N_3
4 Nu=SAr

5-12

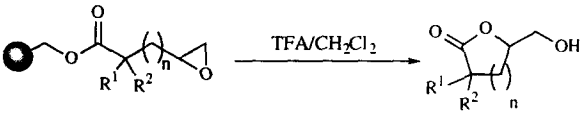
Scheme 2

Table 1. Lactones **5-12** from nucleophilic ring opening of polymer-bound epoxides

Epoxide	Nucleophile	n	R^1	R^2	Lactone	Purity[a]	Yield(%)[b]
2a	NaN_3,NH_4Cl	1	H	H	**5**	90	60
2b	NaN_3,NH_4Cl	1	CH_3	H	**6**	87	55[c]
2c	NaN_3,NH_4Cl	1	CH_3	CH_3	**7**	75	48
2d	NaN_3,NH_4Cl	2	H	H	**8**	80	56[d]
2a	PhSNa	1	H	H	**9**	>95	67
2b	PhSNa	1	CH_3	H	**10**	90	50[c]
2d	PhSNa	2	H	H	**11**	75	65[d]
2a	*p*-CH_3PhSNa	1	H	H	**12**	95	45[e]

[a] Purity estimated by GC and NMR analysis after cleavage.[b] Isolated yield (based upon loading of initial Merrifield Resin) after flash chromatography. All the new products were identified by ^1H NMR,^{13}C NMR and mass spectroscopy. [c] 1/1 Mixture of diastereoisomers. [d] Crude yield. [e] The corresponding β-hydroxy thioether **4** was not isolated.

If the resin **2** was directly treated with trifluoroacetic acid[13] in methylene chloride as before, lactones **13-16** were isolated in moderate to good yields (Scheme 3). GC and NMR analysis of the crude reaction mixture obtained after cleavage showed purities ranging from 70% (n=2, R^1=R^2=H) to 90% (n=1, R^1=R^2=H) (Table 2).[12]



2a-d **13-16**

Scheme 3

Table 2. Synthesis of lactones **13-16**

Epoxide	n	R^1	R^2	Lactone	Purity[a]	Yield(%)[b]
2a	1	H	H	**13**	90	57
2b	1	CH_3	H	**14**	85	60[c]
2c	1	CH_3	CH_3	**15**	87	60
2d	2	H	H	**16**	70	56[d]

[a] Purity determined by GC and NMR analysis. [b] Isolated yield (based upon loading of initial Merrifield Resin) after chromatography. All the new products were identified by ^1H NMR,^{13}C NMR and mass spectroscopy. [c] 1/1 Mixture of diastereoisomers. [d] Crude yield.

In summary, these results establish the utility of supported epoxides in solid phase approaches to functionalized γ-and δ-lactones. The ample choice of easily available reagents compatible with this two step sequence show its potential in combinatorial chemistry. Further investigations concerning asymmetric epoxidation and ring opening with other nucleophiles are currently in progress in our laboratory.

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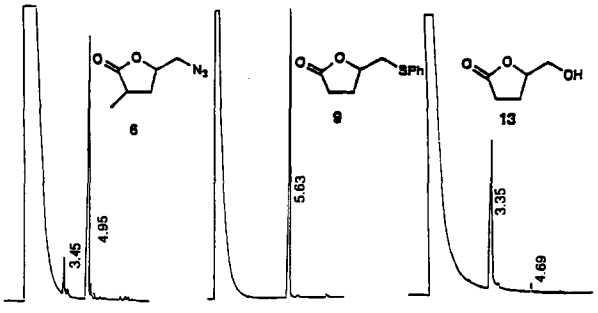
12. Procedure for synthesis of lactones: A solution of mCPBA (5 equiv) in dry CH_2Cl_2 (15 mL) was slowly added to a suspension of resin **1** (600 mg, 1.02 mmol) in dry CH_2Cl_2 (3 mL) at room temperature under nitrogen. After mixing for 48h, the reaction mixture was filtered, and the resin **2** was washed and dried in vacuo.
    -->To the resin **2b** (600 mg, 1.02 mmol) in dry DMF (3 mL) was added NaN_3 (5 equiv) and NH_4Cl (5 equiv) in dry DMF (25 mL). The resulting mixture was heated at 100°C for 2h. After cleavage with 50% TFA/CH_2Cl_2 (16 mL, r.t., 2h), the solution is filtered from the resin, concentrated to dryness and analyzed by GC. Purification of the residue by chromatography on silica gel eluting with 20% ethyl acetate in methylene chloride gave pure **6** ; yield 55%.
    -->PhSNa (3 equiv) generated by treatment of NaH in dry DMF with an excess of PhSH was added to the resin **2a** (600 mg, 1.02 mmol) in dry DMF (8 mL) at 0°C and shaken for 12h at room temperature. Compound **9** was obtained in 67% yield and in high purity by application of the described procedure for cleavage.
    --> Trifluoroacetic acid (50% in CH_2Cl_2, 16 mL) was added to the resin **2a** and shaken for 2h. The resulting solution is filtered from the resin, concentrated to dryness and analyzed by GC. Purification of the residue by chromatography on silica gel eluting with 20% methylene chloride in ethyl acetate gave pure **13** ; yield 57%.



Gas chromatographic analyses of crude product **6**, **9**, **13** obtained after cleavage.
No diastereoisomeric separation of **6** was observed under these GC conditions.[14]

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14. GC analysis was performed using a commercial Carlo Erba 4160, SE 52 capillary column, 25mx 0,32mm I.D. Program : 120°C during 2 min., then 120 to 240°C at a rate of 10°C/min. For **9**, 180°C during 2 min, then 180 to 240°C at a rate of 10°C/min.

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