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## Lithiated (E)-5-Tosyl-4-pentenoic Acid: A New δ-Acyldienyl Anion Equivalent

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Abstract: (E)-5-Tosyl-4-pentenoic acid (9), prepared from 4-pentenoic acid by stereoselective in situ iodosulfonylation-dehydroiodination, is lithiated at vinylic position and reacts with carbonyl compounds affording stereoselectively 6-hydroxy acids 12. These acids have been stereoselectively transformed into methyl (2E,4E)-6-hydroxydienoates 13, by esterification with trimethylsilyldiazomethane followed by  $\delta$ -dehydrosulfinylation with DBU, or into (Z)- $\gamma$ -lactones 14 by heating in the presence of p-toluenesulfonic acid. © 1999 Elsevier Science Ltd. All rights reserved.

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One of the most straightforward approaches to dienic carboxylic acid derivatives is the nucleophilic or electrophilic alkylation at the  $\delta$ -position of stereodefined  $\delta$ -acyldienyl cations **1a** or anions **1b** or their equivalents, respectively. This strategy is very useful for transfering the  $\alpha, \beta, \gamma, \delta$ -unsaturated functionality present in many natural products.<sup>1,2</sup> Representative precursors of cationic synthons are  $\delta$ -iodo **2**<sup>3</sup> and  $\delta$ -tosyl **3**<sup>4</sup> dienamides, which undergo vinylic nucleophilic substitution by carba- and heteronucleophiles providing regio and stereoselectively naturally occurring dienamides.<sup>2</sup> The generation of the umpoled d<sup>5</sup> carbanionic reagents **1b** have been recently achieved by tellurium-lithium exchange in the case of dienamide **4**.<sup>5</sup> As  $\delta$ -acyldienyl anion equivalents only dianions derived from  $\alpha$ -(allylthio)acetates **5**<sup>6</sup> have been used for the synthesis of (2*E*,4*E*)-dienoates, and (*E*)-*N*-isopropyl-5-tosyl-4-pentenamide **6**<sup>7</sup> for dienamides.



The vinyl sulfone 6, prepared by *in situ* iodosulfonylation-dehydroiodination of 4-pentenoic acid, gives dilithiated lactam 7 after reaction with 2 equiv of *n*-butyllithium. Intermediate dianion 7 reacts with electrophiles at the  $\delta$ -position affording stereoselectively dienamides 8 through spontaneous ring opening, double bond isomerization and  $\delta$ -dehydrosulfinylation? (Scheme 1). We now describe the lithiation of (*E*)-5-tosyl-4-pentenoic acid (9) and its application as a precursor of a  $\delta$ -acyldienyl anion 1b equivalent for the synthesis of 6-hydroxydienoates.<sup>8</sup> These esters have been used as intermediates in the synthesis of natural products, for

instance, macrolactine A,<sup>12</sup> aspicilin,<sup>13</sup> castanospermine,<sup>14</sup> the aglycon of antitumor tetrocarcins (+)tetronolide<sup>15</sup> and leukotriene  $B_{4,16}$ 



The lithiation of (*E*)-5-tosylpent-4-enoic acid (9)<sup>17</sup> with *n*-butyllithium at -78°C in THF took place at the vinylic position <sup>18,19</sup> affording intermediate **10** instead of intramolecular Michael addition as in the case of the amide **6**. This dianion **10** was chemically characterized after reaction with deuterium oxide as its deuterated derivative **11**, which was isolated in 93% yield and 96% of deuterium incorporation.<sup>20</sup> The reaction of the lithiated intermediate **10** with carbonyl compounds gave tosylated 6-hydroxy acids **12** in poor yields. However, better results were obtained by addition of magnesium bromide etherate<sup>21</sup> to dianion **10** prior to the reaction with the carbonyl compound. The corresponding hydroxy acids **12** were isolated after hydrolysis with 2M hydrochloric acid and transformed without further purification into hydroxy esters by reaction with trimethylsilyldiazomethane in a 1/1: methanol/ether mixture at room temperature for 1 d. When benzaldehyde was used as the electrophile, the corresponding hydroxy acid **12d** (Table 1, entry 4) suffered decomposition under the esterification conditions. Final treatment of esters, derived from acids **12**, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at room temperature for 1 d provides diastereoselectively methyl (2*E*,4*E*)-6-hydroxydienoates **13** after δ-elimination of *p*-toluenesulfinic acid<sup>23</sup> (Scheme 2 and Table 1).



Scheme 2

		producta					
entry	electrophile	no.	<b>R</b> 1	R <sup>2</sup>	yield (%) <sup>b</sup>	$mp (^{\circ}C)^{\circ} \text{ or } R_{f^{d}}$	
1	EtCHO	1 <b>3a</b>	Et	Н	47	0.66	
2	PriCHO	13b	Pri	Н	49	0.45	
3	BuiCHO	13c	Bu <sup>i</sup>	н	57	0.67	
4	PhCHO	12d°	Ph	н	75f	115-116	
5	PhCH <sub>2</sub> CHO	13e	PhCH <sub>2</sub>	н	48	0.58	
6	(CH <sub>2</sub> ) <sub>4</sub> CO	1 <b>3f</b>	-(CH <sub>2</sub>	)4-	34	0.75	
7	(CH <sub>2</sub> ) <sub>5</sub> CO	13g	-(CH <sub>2</sub>	)5-	40	0.76	

Table 1. Synthesis of Methyl (2E,4E)-6-Hydroxydienoates 13

All products were pure (TLC, 300MHz <sup>1</sup>H NMR) and gave satisfactory spectral data (IR, <sup>1</sup>H and <sup>13</sup>C NMR, and mass spectra).
Isolated yield based on acid 9, after column chromatography on silica gel. <sup>c</sup> Hexane/EtOAc.
Hexane/EtOAc: 1/1. <sup>e</sup> This hydroxy acid decomposed during the esterification step. <sup>f</sup> Isolated crude yield.

Treatment of the crude hydroxy acids 12 with 2 equiv of *p*-toluenesulfonic acid under toluene reflux for 1 d yielded steroselectively  $\gamma$ -lactones 14 (Scheme 2 and Table 2), which were formed by intramolecular Michael addition of the acid function to the vinyl sulfone followed by dehydration. The lactones obtained showed mainly the Z-configuration according to <sup>1</sup>H NMR data for the olefinic hydrogens, with  $\delta$  values between 6.09 and 6.37 ppm typical for  $\beta$ -hydrogens *trans* relative to the sulfone group. In the case of compound 14c difference NOE measurements also confirmed the Z-configuration.

In summary, we have found that the dilithiation of (E)-5-tosyl-4-pentenoic acid, readily accessible from 4-pentenoic acid, and further reaction with carbonyl compounds is an adequate strategy to prepare stereoselectively 6-hydroxy-substituted (2E, 4E)-dienoates. The dianion of this sulfone is acting as a  $\delta$ acyldienyl anion equivalent.

Table	2.	Synthesis	of	Lactones	14ª
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no.	R1	yield (%) <sup>b</sup>	R <sub>f</sub> c	
 14b	Pr <sup>i</sup>	33	0.54	-
14c	Bu <sup>i</sup>	40	0.56	
14d	Ph	36	0.58	

\* All products were pure (TLC, 300MHz <sup>1</sup>H NMR) and gave satisfactory spectral data (IR, <sup>1</sup>H and <sup>13</sup>C NMR, and mass spectra). <sup>b</sup> Isolated yield based on acid 9, after column chromatography on silica gel. <sup>c</sup> Hexane/EtOAc: 1/1. Acknowlegments. We are very grateful to the DCICYT, Spain (Project no. PB97-0123) for financial support. M. V. thanks ASAC Pharmaceutical International S. A. for a fellowship.

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