Pergamon

Tetrahedron Letters 40 (1999) 5957–5960

TETRAHEDRON LETTERS

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

Francisco Caturla, Carmen Nájera* and Montserrat Varea

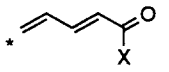
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain; cnajera@ua.es

Received 10 May 1999; accepted 15 June 1999

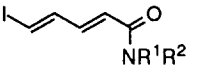
Abstract: (*E*)-5-Tosyl-4-pentenoic acid (**9**), prepared from 4-pentenoic acid by stereoselective *in situ* iodosulfonylation-dehydroiodination, is lithiated at vinylic position and reacts with carbonyl compounds affording stereoselectively 6-hydroxy acids **12**. These acids have been stereoselectively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

Keywords: Lithiation, Sulfones, Dienoates, Lactones

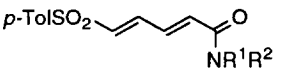
One of the most straightforward approaches to dienic carboxylic acid derivatives is the nucleophilic or electrophilic alkylation at the δ-position of stereodefined δ-acyldienyl cations **1a** or anions **1b** or their equivalents, respectively. This strategy is very useful for transfering the α,β,γ,δ-unsaturated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



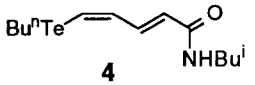
1a, ⋆ = +
1b, ⋆ = -



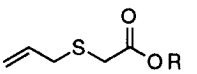
2



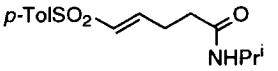
3



4



5

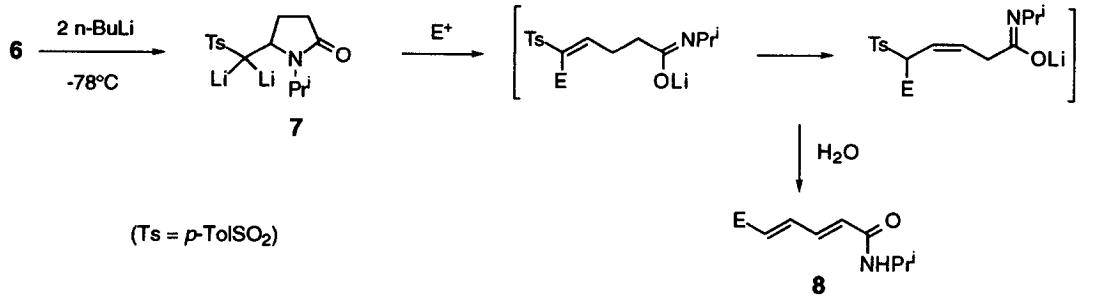


6

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 δ-position affording stereoselectively dienamides **8** through spontaneous ring opening, double bond isomerization and δ-dehydrosulfinylation[7] (Scheme 1). We now describe the lithiation of (*E*)-5-tosyl-4-pentenoic acid (**9**) and its application as a precursor of a δ-acyldienyl anion **1b** equivalent for the synthesis of 6-hydroxydienoates.[8] These esters have been used as intermediates in the synthesis of natural products, for

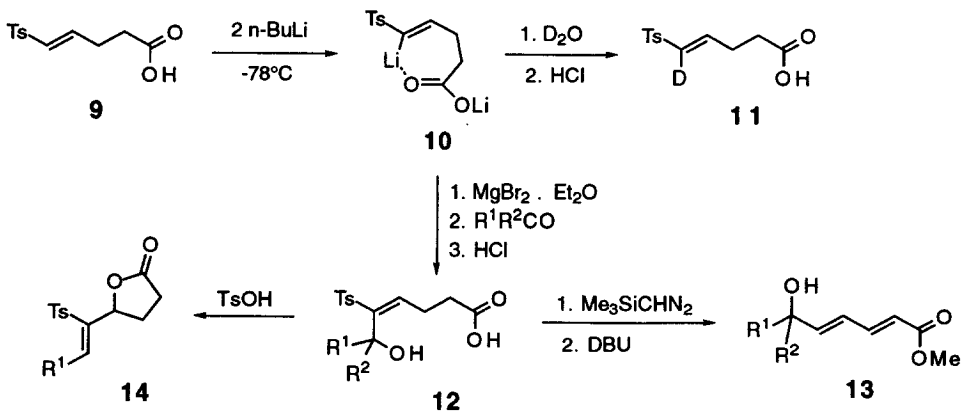
PII: S0040-4039(99)01183-1

instance, macrolactine A,[12] aspicilin,[13] castanospermine,[14] the aglycon of antitumor tetrocarcins (+)-tetronolide[15] and leukotriene B_4.[16]



Scheme 1

The lithiation of (*E*)-5-tosylpent-4-enoic acid (**9**)[17] with *n*-butyllithium at -78°C in THF took place at the vinylic position[18,19] 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.[20] 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[21] 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[23] (Scheme 2 and Table 1).



Scheme 2

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

		product[a]				
entry	electrophile	no.	R^1	R^2	yield (%)[b]	mp (°C)[c] or R_f[d]
1	EtCHO	**13a**	Et	H	47	0.66
2	Pr^{i}CHO	**13b**	Pr^i	H	49	0.45
3	Bu^{i}CHO	**13c**	Bu^i	H	57	0.67
4	PhCHO	**12d**[e]	Ph	H	75[f]	115-116
5	$PhCH_2CHO$	**13e**	$PhCH_2$	H	48	0.58
6	$(CH_2)_4CO$	**13f**	$-(CH_2)_4-$		34	0.75
7	$(CH_2)_5CO$	**13g**	$-(CH_2)_5-$		40	0.76

[a] All products were pure (TLC, 300MHz ^1H NMR) and gave satisfactory spectral data (IR, ^1H and ^{13}C NMR, and mass spectra). [b] Isolated yield based on acid **9**, after column chromatography on silica gel. [c] Hexane/EtOAc. [d] Hexane/EtOAc: 1/1. [e] This hydroxy acid decomposed during the esterification step. [f] 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 γ-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 ^1H NMR data for the olefinic hydrogens, with δ values between 6.09 and 6.37 ppm typical for β-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 (2*E*,4*E*)-dienoates. The dianion of this sulfone is acting as a δ-acyldienyl anion equivalent.

Table 2. Synthesis of Lactones **14**[a]

no.	R^1	yield (%)[b]	R_f[c]
14b	Pr^i	33	0.54
14c	Bu^i	40	0.56
14d	Ph	36	0.58

[a] All products were pure (TLC, 300MHz ^1H NMR) and gave satisfactory spectral data (IR, ^1H and ^{13}C NMR, and mass spectra). [b] Isolated yield based on acid **9**, after column chromatography on silica gel. [c] 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.

REFERENCES AND NOTES

1. For recent reviews about polyene macrolide antibiotics see: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021-2040. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041-2114.
2. For a recent review about natural products with polyene amide structures see: Nájera, C.; Yus, M. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science, Vol. 21 in the press.
3. Babudri, F.; Fiandanese, V.; Naso, F.; Punzi, A. *Tetrahedron Lett.* **1994**, *35*, 2067-2070.
4. Bernabeu, M. C.; Chinchilla, R.; Nájera, C. *Tetrahedron Lett.* **1995**, *36*, 3901-3904.
5. Huang, Y. Z.; Mo, X. S. *Synlett* **1998**, 93-95.
6. These dianions are alkylated at the allylic position, the resulting thioesters afforded (2*E*,4*E*)-dienoates after LDA-promoted [2.3]-sigmatropic rearrangement to the 2-mercaptocarboxylic esters and *S*-methylation and oxidation to the sulfoxides followed by thermal dehydrosulfenylation: Tanaka, K.; Terauchi, M.; Kaji, A. *Chem. Lett.* **1981**, 315-318.
7. (a) Caturla, F.; Nájera, C. *Tetrahedron Lett.* **1996**, *37*, 2833-2836. (b) Caturla, F.; Nájera, C. *Tetrahedron* **1998**, *54*, 11255-11270.
8. The 6-hydroxy dienoate unit is present in natural products such as the plant hormone absicic acid,[9] the *xenia* diterpenoid xeniatine A[10] and in the antitumoral and fungicide reveromycins.[11]
9. Beale, M. H.; Chen, A.; Harrison, P. A.; Willis, C. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3061-3064.
10. Iwagawa, T.; Amano, Y.; Hase, T.; Shiro, M. *Chem. Lett.* **1995**, 695-696.
11. McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196-1197.
12. Benvegnu, T.; Schio, L.; Le Floc'h, Y.; Greé, R. *S ynlett* **1994**, 505-506.
13. Quinkert, G.; Becker, H.; Dürner, G. *Tetrahedron Lett.* **1991**, *32*, 7397-7400.
14. Kim, N. S.; Choi, J. R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096-7099.
15. Boeckman, R. K., Jr.; Wrobleski, S. T. *J. Org. Chem.* **1996**, *61*, 7238-7239.
16. Nunu, K.; Mosset, P.; Greé, R.; Saalfrank, R. W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1188-1189.
17. Prepared by *in situ* iodosulfonylation-dehydroiodination of 4-pentenoic acid in 71% yield.[7]
18. For our last work on lithiated vinyl sulfones see: Caturla, F.; Nájera, C. *Tetrahedron* **1997**, *53*, 11449-11464.
19. For a recent review about synthetic applications of functionalized sulfones as carbanionic reagents see: Nájera, C.; Sansano, J. M. *Recent Res. Devel. in Organic Chem.* **1998**, *2*, 637-683.
20. Deduced by ^{1}H NMR (300 MHz).
21. The interchange lithium-magnesium is a efficient way for improving the reactivity of sulfonyl substituted vinyl carbanions.[22]
22. (a) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 3279-3280. (b) Nájera, C.; Yus, M. *J. Org. Chem.* **1989**, *54*, 1491-1499.
23. When hydroxy acids **12** were treated directly with DBU the dehydrosulfinylation reaction failed.[7a]