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AN EXPEDITIOUS ENANTIOSELECTIVE SYNTHESIS OF γ-LACTONES

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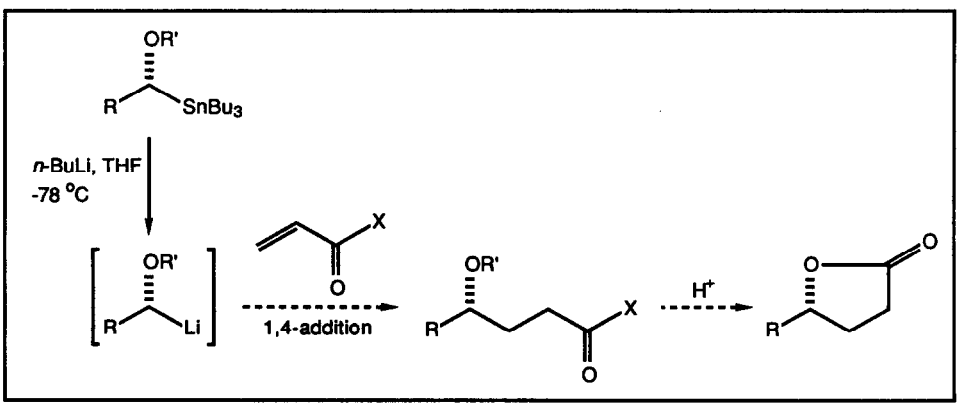
Summary: α-Alkoxyorganolithium reagents react with α,β-unsaturated trimethylhydrazides to give γ-alkoxytrimethylhydrazides in moderate to good yields. Acid hydrolysis of the latter compounds yields γ-lactones. A short enantioselective route to (*S*)-hexanolide is described.

The lactone functionality is prevalent among many natural products.[1] For example, certain γ-lactones are pheromones for several insect species. In addition, the food industry utilizes some lactones as flavouring components. We envisioned an expeditious synthesis of γ-lactones[2] by the 1,4-addition of α-alkoxyorganolithium reagents[3] to α,β-unsaturated carboxylic acid derivatives followed by cyclization of the resulting γ-alkoxyacid derivatives. α-Alkoxyorganolithium reagents can be obtained by transmetalation of α-alkoxyorganostannanes.[3a] Moreover, α-alkoxyorganostannanes can be prepared in enantiomerically enriched form.[4] Thus, an enantioselective route to γ-lactones is feasible as well.

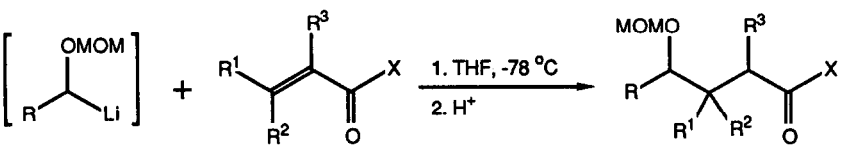


Initial investigations centred on the addition of racemic α-alkoxyorganolithium compounds[5] to α,β-unsaturated amides. Good yields of 1,4-addition product were obtained with the highly hindered acrylic acid tetramethylpiperidide (**2a**)[6] as the Michael acceptor (Table).[7] Unfortunately, attempts to cyclize γ-alkoxyamide **3a** (R=*n*-Bu) to the γ-lactone under acidic conditions (e.g. 3 N HCl, *p*-TsOH, $HClO_4$) were uniformly unsuccessful with no lactone observed.

It is known that alkyllithiums add to α,β-unsaturated trimethylhydrazides in a conjugate fashion.[8] Thus, we examined the reaction of α-alkoxyorganolithiums with various α,β-unsaturated trimethylhydrazides[9] (Table).

Modest yields of 1,4-addition products were obtained with acrylic acid trimethylhydrazide (**2b**) with the principal side reaction being the oligomerization of the intermediate hydrazide lithium enolate with a molecule of **2b**. Yields of 1,4-addition product obtained with crotonic acid trimethylhydrazide (**2c**) were poor to moderate as competing 1,2-addition was occurring.[10] However, much better yields of 1,4-addition product were obtained with methacrylic acid trimethylhydrazide (**2d**); presumably, oligomerization of the intermediate lithium enolate is reduced due to the relatively hindered α-carbon. Not surprisingly, only modest diastereoselection was observed in additions of α-alkoxyorganolithiums to **2c** and **2d**.

Table. 1,4-Addition of α-Alkoxyorganolithium Reagents to 2.



2a: R^1,R^2,R^3=H; X=—N

3a-d

2b: R^1,R^2,R^3=H; X=N(Me)NMe_2

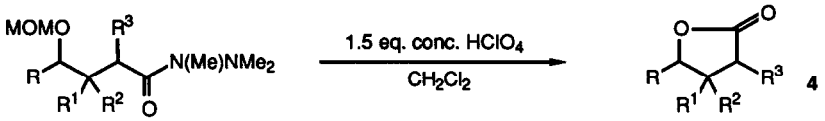
2c: R^1=Me; R^2,R^3=H; X=N(Me)NMe_2

2d: R^1,R^2=H; R^3=Me; X=N(Me)NMe_2

	Isolated Yields, %[a]			
R	3a	3b	3c[b,c]	3d[b]
Et	75	50	49 (51:49)	70 (67:33)
i-Pr	65	49	37 (54:46)	65 (71:29)
n-Bu	68	40	53 (71:29)	71 (61:39)
c-C_6H_{11}	65	42	37 (72:28)	73 (66:34)[d]
$PhCH_2CH_2$	69	52	61 (60:40)[d]	70 (61:39)

[a] All new compounds exhibited satisfactory spectroscopic and analytical data. [b] Numbers in parentheses refer to the diastereomeric ratio determined by GC analyses. [c] 16-40% yield of 1,2-addition product observed. [d] The major diastereomer was assigned as *syn* on the basis of its conversion to the γ-lactone. The chemical shift of H_5 of the γ-lactone was diagnostic.[2] For **4c** (R=$PhCH_2CH_2$), *cis* δH_5= 4.41 ppm, *trans* δH_5= 3.99 ppm. For **4d** (R=*c*-C_6H_{11}), *cis* δH_5= 4.23 ppm, *trans* δH_5= 4.05 ppm.

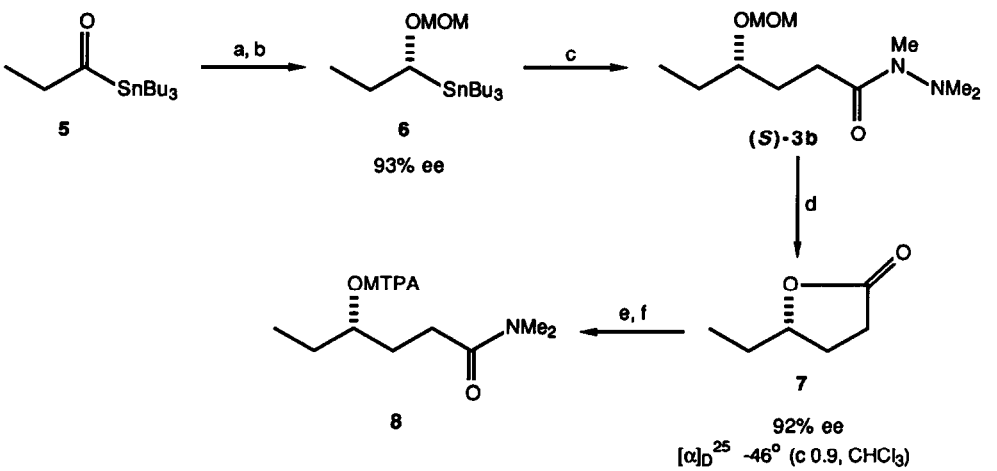
In contrast to the tetramethylpiperidides **3a**, cyclizations of the resulting γ-alkoxy-hydrazides **3b-3d** to the γ-lactones **4** proceeded smoothly and in good yields. Exposure of the hydrazide to $HClO_4$ (1.5 eq) in CH_2Cl_2 (rt, 8 h) afforded the expected γ-lactone as the exclusive product. Some results are tabulated below. Hence, although yields of 1,4-addition product are only moderate, the overall synthesis of substituted γ-lactones is expedient (two steps) and simple.



	Isolated Yields, %
3b (R=Et)	**4b** (R=Et) 85
3b (R=*c*-C_6H_{11})	**4b** (R=*c*-C_6H_{11}) 84
3b (R=$PhCH_2CH_2$)	**4b** (R=$PhCH_2CH_2$) 80
3c (R=$PhCH_2CH_2$)	**4c** (R=$PhCH_2CH_2$) 90
3d (R=*c*-C_6H_{11})	**4d** (R=*c*-C_6H_{11}) 92

Attention was then turned to the enantioselective synthesis of a γ-lactone (Scheme). Retention of configuration in the 1,4-addition of an α-alkoxyorganolithium reagent to an α,β-unsaturated acid derivative has not been previously demonstrated. Starting with the enantiomerically enriched α-alkoxyorganostannane **6**,[11] (*S*)-hexanolide[12] (**7**) was prepared in two steps. The enantiomeric purity of **7** was determined by its optical rotation[13] and by ^{13}C NMR analysis of Mosher ester **8**,[14] obtained by derivatization of **7**. Since the enantiomeric purities of **6** and **7** are the same, then the conjugate addition of the α-alkoxyorganolithium reagent to the unsaturated trimethylhydrazide occurred with retention of configuration.

Scheme. Enantioselective Synthesis of (*S*)-Hexanolide (7).



Key: (a) (*S*)-BINAL-H, THF, -78 °C. (b) MOM-Cl, *i*-Pr_2NEt, CH_2Cl_2, 59% from **5**.
(c) *n*-BuLi, THF, -78 °C, 10 min then **2**, 1 h, 50%.
(d) 1.5 eq conc. $HClO_4$, CH_2Cl_2, rt, overnight, 85%.
(e) Me_2NH, Et_3N, -20 °C --> RT. (f) (*R*)-MTPA-Cl, Et_3N, DMAP, CH_2Cl_2.

Thus, we have described an efficacious route to substituted γ-lactones and to enantiomerically enriched γ-alkyl-γ-lactones. The latter compounds may be prepared in four steps (ca. 25% overall yield) from acylstannanes. Of the previously described enantioselective routes to γ-alkyl-γ-lactones,[15] that of Silverstein's is perhaps the most general and economical (four steps from *D*- or *L*-glutamic acid, ca. 9-19% overall yields).[1] However, it is incapable of accessing branched γ-alkyl-γ-lactones (*e.g.* **3b**, R=*i*-Pr or *c*-C_6H_{11}) since the key step involves displacement of a primary tosylate (*i.e.* **4**, R=CH_2OTs; R^1,R^2,R^3=H) with an organocuprate reagent. The present method allows one to prepare straight-chain and branched γ-alkyl-γ-lactones enantioselectively.

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References and Notes

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9. Prepared by addition of an equimolar mixture of trimethylhydrazine (Beltrami, R. T.; Bissell, E. R. *J. Am. Chem. Soc.* **1956**, *78*, 2467) and triethylamine to the unsaturated acid chloride in ether at -78 °C. Yields of **2b**, **2c**, and **2d** were 45, 35, and 82%, respectively.
10. In fact, with hydrazide **2e** [R^1=TMS; R^2,R^3=H; X=N(Me)NMe_2], only the product of 1,2-addition was observed with **1** (R=*i*-Pr) (49% yield). With *n*-BuLi, **2e** affords only the 1,4-addition product (66% yield). Perhaps stabilization of the tetrahedral intermediate arising from 1,2-addition by the alkoxy group [cf: additions to N-methoxyamides (Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, *22*, 3815)] causes 1,2-addition to be more favourable when α-alkoxy-organolithiums **1** are used.
11. Detailed experimental procedures for the preparation of compounds **5** and **6** are available: Chong, J. M.; Mar, E. K. *Tetrahedron*, **1989**, *45*, 7709.
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