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3-Substituted-γ-butyrolactones from 5-Trimethylsilyl-2-cyclohexenone. Synthesis of (-)-Enterolactone

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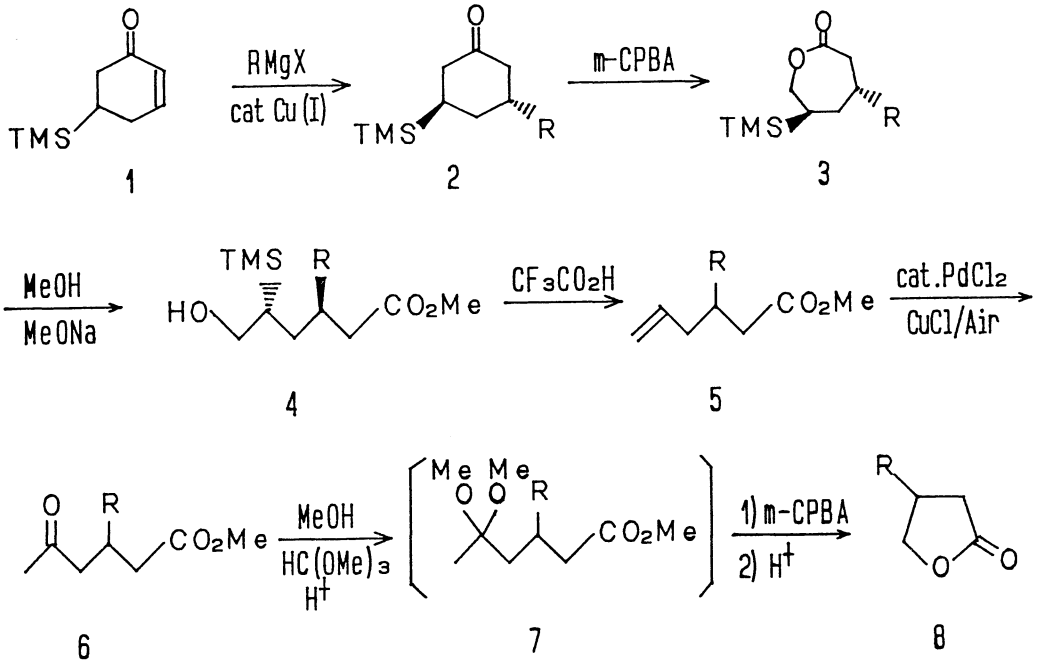
1,4-Adducts of 5-trimethylsilyl-2-cyclohexenone (**1**) with Grignard reagents were converted to various hexanoate derivatives and γ-butyrolactones. Starting from optically pure **1**, (-)-enterolactone (Factor X) was synthesized.

In the preceding paper[1] we reported the synthesis and optical resolution of 5-trimethylsilyl-2-cyclohexenone (**1**). Highly stereoselective 1,4-addition of some Grignard reagents to **1** and concomitant application of the adducts (**2**) to the synthesis of some chiral molecules were also described. In this communication, we will focus on the synthesis of 3-substituted-γ-butyrolactones, since some of them are known to be important precursors of lignans which are isolated from a variety of plants or animals and have a wide variety of interesting activities.[2]

For the synthesis of lignan precursors, 1,4-addition of benzyl type Grignard reagents to the enone **1** is required. Surprisingly, such type of Grignard reagents showed low stereoselectivity in 1,4-addition to **1** (entries 6, 8, and 10), under the same reaction conditions used for the other types of Grignard reagents[1] which gave trans adducts exclusively.



1 2 3 4 5 6 7 8

Fortunately, the ratios were improved by lowering the reaction temperature to -100 °C and by changing the addition mode, i.e., a mixture of **1** and TMSCl in THF was added to a mixture of CuBr-Me_2S, HMPA, and Grignard reagent (entries 9 and 11).

TMS group directed Baeyer-Villiger reaction[3] was chosen for the conversion of the adducts **2** to acyclic derivatives. The reaction proceeded smoothly to give 7-membered lactones **3**. It is noteworthy that all the 7-membered lactones **3** except p-methoxybenzyl derivatives were obtained as crystalline products, therefore diastereoisomerically pure materials are available at this stage by recrystallization even if the precursor (**2**) contains a small amount of diastereoisomer. Ring opening with MeONa in MeOH at rt for 0.5-2 h and subsequent treatment with CF_3CO_2H at rt for 1 min afforded 3-substituted hexenoic acid ester **5**. Oxidation of **5** with a catalyst system of $PdCl_2/CuCl/O_2$[4] furnished the 5-oxohexanoate (**6**). As shown in the table, yield of every step of the reaction sequence **1**-**2**-**3**-**5**-**6** is high for the various substituents. Next, we examined conversion of **6** to γ-butyrolactones. Double Baeyer-Villiger oxidation[5] of **6** via acetal **7** followed by acid hydrolysis gave 3-substituted-γ-lactones **8** in moderate yields. These results are also listed in Table 1. The yield of **8** decreased when methoxy group was introduced to benzene nuclei (entries 4, 7, 9, and 11), presumably due to the increase of electrophilic side reactions to the nuclei.

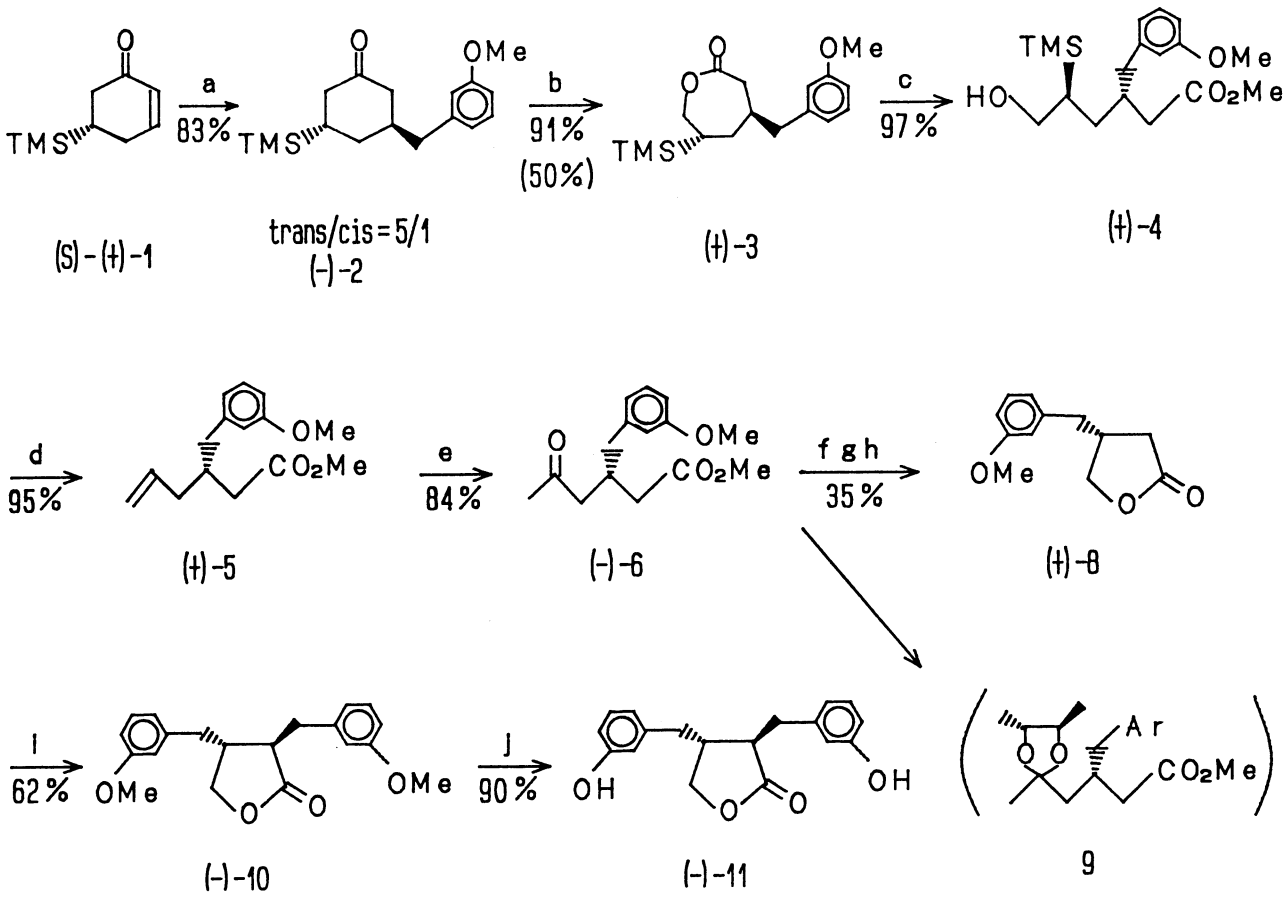
Table 1. Synthesis of 3-substituted hexanoates and γ-butyrolactones

Entry	R	Yield/%[c]					
		2	trans/cis	**3**	**5**	**6**	**8**
1	Me-	88	a)	88	-	-	-
2	Ph-	90	a)	95	92	91	70
3	p-Tolyl-	92	a)	94	94	90	62
4	p-$MeOC_6H_4$-	92	a)	92	99	96	49
5	$PhCH_2CH_2$-	92	a)	91	92	89	65
6	Benzyl-	89	3/1	91	93	92	66
7	p-MeO-benzyl-	74	>10/1	90	92	84	45
8	m-MeO-benzyl-	76	1/1	-	-	-	-
9		89	>10/1[b]	89	96	85	38
10	3,4-dimethoxybenzyl-	83	1/1	-	-	-	-
11		89	>10/1[b]	88	79[d]	89	35

a) No cis-isomer was detected by ^{13}C-NMR; see Ref. 1. b) A mixture of enone **1** and TMSCl was added to a solution of CuBr-Me_2S and HMPA in THF at -100 °C. c) All the reactions were carried out in 0.5-2.0 mmol scale. d) Corresponding alcohol (**4**) was treated with concd HCl instead of CF_3CO_2H.

Apparently, the compounds **5**, **6**, and **8** with high optical purities are available by the above sequence when optically pure **1** is used as a starting material. To demonstrate the utility of the reaction sequence, synthesis of optically active (-)-enterolactone[6] [(-)-**11**] via 3-substituted-γ-butyrolactone was carried out.

1,4-Addition of m-methoxybenzylmagnesium chloride to optically pure S-(+)-**1** gave ca. 5 to 1 mixture of trans and cis adducts (-)-**2**[7] as an oil which gave 7-membered lactone (+)-**3** contaminated by a diastereoisomer in 91% yield upon treatment with m-CPBA.



a) m-methoxybenzylmagnesium chloride, cat. CuBr-Me_2S, TMSCl, HMPA, -100 °C; b) m-CPBA, Na_2HPO_4, H_2O-CH_2Cl_2, 0 °C; c) MeOH-MeONa; d) CF_3CO_2H(neat), rt 1 min; e) air, cat $PdCl_2$, CuCl, DMF-H_2O, rt ovn; f) MeOH-$CH(OMe)_3$, H^+, rt; g) m-CPBA, rt 6.5 h; h) AcOH-H_2O, cat. TsOH, △ ; i) LDA, THF, m-methoxybenzyl bromide, -78 °C; j) BBr_3, CH_2Cl_2, 0 °C 2 days.

Recrystallization of the diastereoisomeric mixture of the lactone from hexane gave diastereoisomerically and optically pure (+)-**3** [50% from (-)-**2**, $[\alpha]_D^{26}$+45.3°(c 2.00, $CHCl_3$), mp 66°C], which was treated with NaOMe (1 equiv.) in MeOH at rt for 1 h to give (+)-**4** [97%, oil, $[\alpha]_D^{23}$+19.6°(c 2.37, benzene)]. Treatment of (+)-**4** with CF_3CO_2H at rt for 1 min gave (+)-**5** [95%, oil, $[\alpha]_D^{23}$+8.93°(c 4.03, $CHCl_3$)]. Oxidation of (+)-**5** with $PdCl_2$ (0.1 equiv.) and CuCl (1.0 equiv.) in DMF-H_2O (2:1) with bubbling air gave (-)-**6** [84%, oil, $[\alpha]_D^{23}$-8.33° (c 3.60, benzene)][8]. Presence of antipode was not discernible as long as estimated by ^{13}C-NMR after conversion to the acetal of chiral diol (**9**). Acetalization, double Baeyer-Villiger reaction with 4 equiv. of m-CPBA at rt for 6.5 h, and subsequent hydrolysis gave (+)-**8** [35%, oil, $[\alpha]_D^{24}$+6.06°(c 7.92, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$+6.4°(c 1, $CHCl_3$)]. Alkylation of the lactone gave disubstituted butyrolactone (-)-**10** [62%, oil, $[\alpha]_D^{26}$-42.9°(c 3.81, $CHCl_3$)]. Demethylation with BBr_3 at 0 °C for 2 days gave (-)-enterolactone [Factor X, (-)-**11**] as a gum [90%, Ms:M^+=298, $[\alpha]_D^{19}$-40.3°(c 0.553, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$-38.4°(c 0.5, $CHCl_3$)].

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7) The reaction was carried out in 36 mmol scale.
8) In the synthesis of optically active 3-phenyl- and 3-p-tolyl-5-oxohexanoates by the same sequence, the products were found to be contaminated with 2-3% of unidentified impurities which caused 30-40% decrease of the specific rotation of them. Therefore, this product, (-)-**6**, might also contain similar impurities.
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