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Efficient and Practical Method for Synthesizing Optically Active γ-Trityloxymethyl-α-alkylidene-γ-butyrolactones Using Ti(II)-Mediated Intramolecular Nucleophilic Acyl Substitution Reaction

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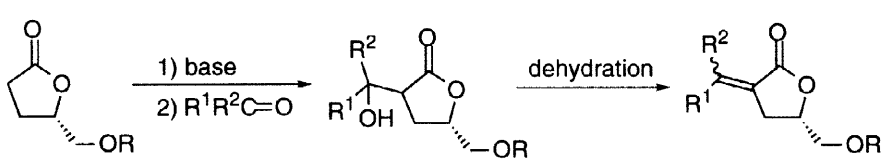
Abstract

An efficient and highly stereoselective method for synthesizing optically active γ-trityloxymethyl-α–alkylidene-γ-butyrolactones having a stereodefined mono or disubstituted exocyclic double bond, starting from commercially available non-racemic glycidyl tritylether has been developed in which a titanium(II)-mediated intramolecular nucleophilic acyl substitution reaction is a key reaction.

Keywords: lactones; epoxides; titanium and compounds; coupling reactions

Optically active stereodefined γ-alkoxymethyl-α-alkylidene-γ-butyrolactones have been accepted as versatile building blocks and intermediates for synthesizing chiral compounds [1]. Among them, γ-trityloxymethyl derivatives have been most effectively used because they attain excellent selectivity in their diastereoselective reactions owing to the sterically demanding trityl protecting group [1c~e]. These lactones usually are prepared from optically active γ-alkoxymethyl-γ-butyrolactone [2] by an aldol reaction with aldehydes or ketones and the following dehydration as illustrated in Scheme 1. However, a problem is incurred in this method in that it affords a stereomeric mixture with regard to the exocyclic double bond which necessitates annoying separation by column chromatography and causes lowering of the yield. We report here an efficient and highly stereoselective entry to



Scheme 1

0040-4039/98/$ - see front matter
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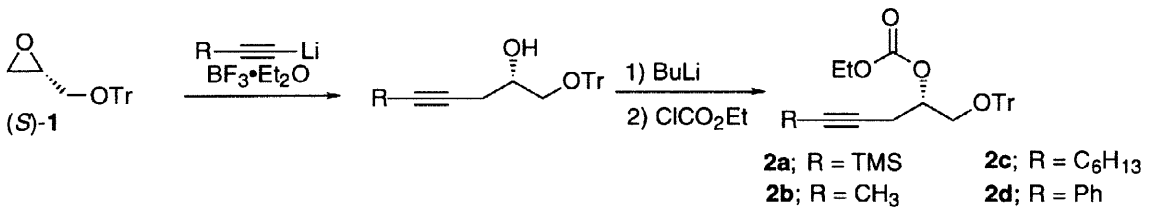
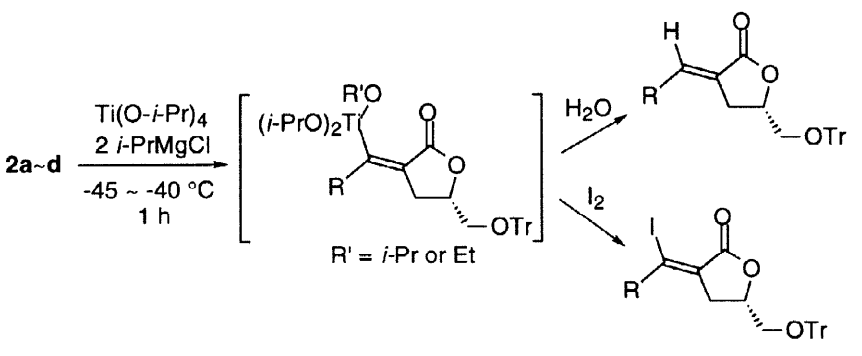
γ-trityloxymethyl-α-alkylidene-γ-butyrolactones starting from commercially available or readily preparable glycidyl tritylether (**1**). Our procedure involves, as a key reaction, a Ti(II)-mediated intramolecular nucleophilic acyl substitution (INAS) reaction [3] of homopropargyl carbonates **2** which can be readily prepared from **1**. Although we used (*S*)-**1** in the present reaction, as its antipode is similarly available, the present process allows access to both enantiomers of γ-trityloxymethyl-α-alkylidene-γ-butyrolactones.

Conversion of (*S*)-**1** (≥ 98.6% ee) into homopropargyl carbonates **2a~d** was carried out in 80~93% overall yields by the regiospecific epoxide ring-opening with the corresponding alkynyllithium in the presence of BF_3·OEt_2 in THF [4] and the following treatment of the resulting alcohols successively with *n*-BuLi and ethyl chloroformate as shown in Scheme 2.



Scheme 2

As shown in Scheme 3, the INAS reaction of **2a~d** thus prepared with a Ti(O-*i*-Pr)4/2 *i*-PrMgCl reagent in ether proceeded smoothly to afford, after hydrolysis, the corresponding γ-trityloxymethyl-α-alkylidene-γ-butyrolactones with exclusive *E*-olefin geometry, *i.e.*, (*E*)-**3**, -**4**, -**5** and -**6**, in excellent yields [3].



	R	Yield (%)
(*E*)-**3**	TMS	83
(*E*)-**4**	CH_3	80
(*E*)-**5**	C_6H_{13}	83
(*E*)-**6**	Ph	81

	R	Yield (%)
7	TMS	79
8	CH_3	69
9	C_6H_{13}	73
10	Ph	73

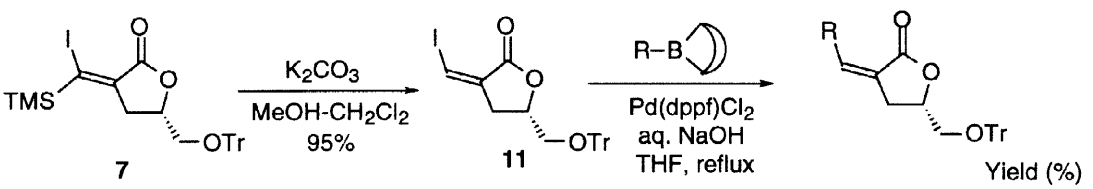
Scheme 3

With a highly efficient method for synthesizing γ-trityloxymethyl-α-alkylidene-γ-butyrolactones having a monosubstituted exocyclic double bond with *E*-geometry in hand, our research effort was then directed to prepare those having *Z*-olefin geometry as well as those having a stereodefined disubstituted exocyclic double bond, and we have succeeded in

developing an efficient method for their synthesis which involves the iodinolysis of the INAS reaction products and the following manipulation of the resulting iodo lactones.

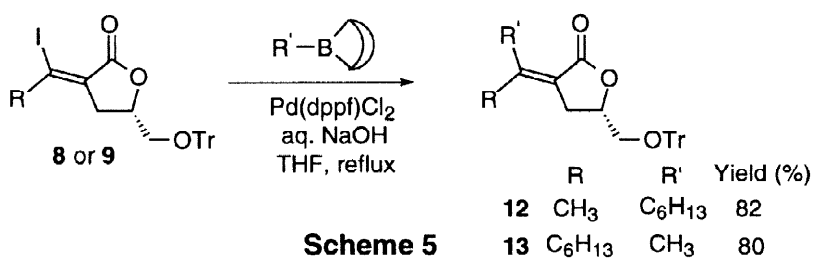
Iodo lactones **7~10** were prepared in high yields by treatment of the reaction mixture of the corresponding **2** and a Ti(O-*i*-Pr)4/2 *i*-PrMgCl reagent with a slight excess of iodine; the results are also summarized in Scheme 3.[1]

Starting from **7**, the butyrolactones having a monosubstituted (*Z*)-exocyclic double bond can be synthesized readily as illustrated in Scheme 4. Thus, protiodesilylation of **7** [5] and the Suzuki-Miyaura coupling [6] of the resulting **11** with *B*-methyl-9-BBN [7], *B*-hexyl-9-BBN [6] or *B*-phenyl-9-BBN [7] provided the corresponding (*Z*)-γ-trityloxymethyl-α-alkylidene-γ-butyrolactones (*Z*)-**4**, -**5** and -**6** in excellent overall yields. The geometric



Scheme 4

purity of the olefinic moiety of butyrolactones thus obtained was confirmed to be more than 99% *Z* by ^1H NMR analysis. Similarly, as shown in Scheme 5, butyrolactone with disubstituted exocyclic double bond **12** and its stereoisomer **13** could be synthesized readily from **8** and **9** and the corresponding organoborane, respectively. It was found from ^1H NMR analysis that the compounds **12** and **13** thus obtained were, respectively, free of production of each other.



Scheme 5

[1] **Typical procedure for the preparation of the iodo lactones 7-10.** To a mixture of Ti(O-*i*-Pr)4 (1.14 g, 4.00 mmol) and **2a** (1.393 g, 2.86 mmol) in ether (44 mL) was added 1.15 M ethereal solution of *i*-PrMgCl (6.48 mL, 7.45 mmol) dropwise at -50 °C. The resulting yellow solution was stirred at -45 - -40 °C for 1 h, after which period the color of the mixture turned to brown. A solution of iodine (3.60 g, 14.2 mmol) in THF (15 mL) was added to the reaction mixture at -60 °C and stirred at -50 - -40 °C for 1 h, then 0 °C for 0.5 h. The resulted mixture was quenched with HCl (0.5 N, 50 mL) at 0 °C and stirred at room temperature for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ and aqueous saturated $NaHCO_3$, and dried over $MgSO_4$. After concentration *in vacuo*, the residue was recrystallized (hexane-dichloromethane) to afford the iodo lactone **7** (1.28 g, 79%).

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Some physical constants and ^{1}H NMR data (selected). *(E)*-**3.** mp 132-133 °C, $[\alpha]^{25}_D$ +76.2° (*c* 0.82, $CHCl_3$). ^{1}H NMR δ 7.00 (t, *J*= 3.0 Hz, 1 H), 4.67 (m, 1 H), 3.45 (dd, J_1= 10.2, J_2= 3.3 Hz, 1 H), 3.09 (dd, J_1= 10.2, J_2= 4.1 Hz, 1 H), 2.93 (ddd, J_1= 17.4, J_2= 8.4, J_3= 3.0 Hz, 1 H), 2.78 (ddd, J_1= 17.4, J_2= 4.5, J_3= 2.7 Hz, 1 H), 0.16 (s, 9 H). *(E)*-**4.** mp 165-166 °C, $[\alpha]^{25}_D$ +59.1° (*c* 0.49, $CHCl_3$). ^{1}H NMR δ 6.84 (qt, J_1= 7.2, J_2= 3.3 Hz, 1 H), 4.67 (m, 1 H), 3.39 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 3.15 (dd, J_1= 10.2, J_2= 4.5 Hz, 1 H), 2.83 (m, 1 H), 2.65 (m, 1 H), 1.84 (dt, J_1= 7.2, J_2= 1.8 Hz, 3 H). *(Z)*-**4.** mp 109.5-111 °C, lit.[1d] 110-112 °C; $[\alpha]^{25}_D$ +27.3° (*c* 0.50, $CHCl_3$), lit.[1d] $[\alpha]^{25}_D$ +27.5°. ^{1}H NMR δ 6.27 (qt, J_1= 7.2, J_2= 2.4 Hz, 1 H), 4.58 (m, 1 H), 3.37 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 3.13 (dd, J_1= 10.2, J_2= 4.2 Hz, 1 H), 2.89 (dddq, J_1= 16.1, J_2= 8.6, J_3= J_4= 2.4 Hz, 1 H), 2.69 (ddq, J_1= 16.1, J_2=J_3= 2.4 Hz, 1 H), 2.22 (dt, J_1= 7.2, J_2= 2.4 Hz, 3 H). *(E)*-**5.** mp 72-73 °C, $[\alpha]^{25}_D$ +49.0° (*c* 0.62, $CHCl_3$). ^{1}H NMR δ 6.78 (tt, J_1= 7.7, J_2= 3.0 Hz, 1 H) 4.64 (m, 1 H), 3.40 (dd, J_1= 10.2, J_2= 3.3 Hz, 1 H), 3.12 (dd, J_1= 10.2, J_2= 4.2 Hz, 1 H), 2.81 (dd, J_1= 16.8, J_2= 8.7 Hz, 1 H), 2.65 (d, *J*= 16.8, 1 H), 2.16 (m, 2 H). *(Z)*-**5.** $[\alpha]^{25}_D$ +9.1° (*c* 0.65, $CHCl_3$). ^{1}H NMR δ 6.19 (tt, J_1= 7.7, J_2= 2.3 Hz, 3 H), 4.58 (m, 1 H), 3.36 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 3.14 (dd, J_1= 10.2, J_2= 4.2 Hz, 1 H), 2.83-2.95 (m, 1 H), 2.60-2.81 (m, 3 H). *(E)*-**6.** mp 138-139 °C, $[\alpha]^{25}_D$ +114.0 °C (*c* 0.84, $CHCl_3$). ^{1}H NMR δ 7.61 (t, *J*= 3.0, 1 H), 4.76 (m, 1 H), 3.47 (dd, J_1= 10.5, J_2= 3.6 Hz, 1 H), 3.21 (ddd, J_1= 17.6, J_2= 5.2, J_3= 3.0 Hz, 1 H), 3.20 (dd, J_1= 10.5, J_2= 4.2 Hz, 1 H), 3.00 (ddd, J_1= 17.6, J_2= 4.1, J_3= 3.0 Hz, 1 H). *(Z)*-**6.** mp 157-158 °C, $[\alpha]^{25}_D$ -67.0° (*c* 0.80, $CHCl_3$). ^{1}H NMR δ 6.97 (dd, *J*= 2.7, J_2= 2.1 Hz, 1 H), 4.66 (m, 1 H), 3.47 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 3.16 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 3.15 (ddd, J_1= 16.8, J_2= 8.3, J_3= 2.7 Hz, 1 H), 2.94 (ddd, J_1= 16.8, J_2= 4.5, J_3= 2.1 Hz, 1 H). **7.** mp 246-247 °C, $[\alpha]^{25}_D$ -20.3° (*c* 1.02, $CHCl_3$). ^{1}H NMR δ 4.51 (m, 1 H), 3.55 (dd, J_1= 10.5, J_2= 3.0 Hz, 1 H), 2.99 (dd, J_1= 10.5, J_2= 3.0 Hz, 1 H), 2.91 (d, *J*= 4.5 Hz, 1 H), 2.89 (d, *J*= 0.9 Hz, 1 H), 0.29 (s, 9 H). **8.** mp 202-203 °C, $[\alpha]^{25}_D$ -23.2° (*c* 0.59, $CHCl_3$). ^{1}H NMR δ 4.51 (m, 1 H), 3.46 (dd, J_1= 10.2, J_2= 3.3 Hz, 1 H), 3.09 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 2.96 (ddq, J_1= 16.8, J_2= 8.7, J_3=1.5 Hz, 1 H), 2.80 (ddq, J_1= 16.8, J_2= 3.9, J_3= 1.5 Hz, 1 H), 2.70 (t, *J*= 1.5 Hz, 3 H). **9.** mp 114-115 °C, $[\alpha]^{25}_D$ -20.5.0° (*c* 0.66, $CHCl_3$). ^{1}H NMR δ 4.48 (m, 1 H), 3.49 (dd, J_1= 10.2, J_2= 3.0 Hz, 1 H), 3.01 (dd, J_1= 10.2, J_2= 3.3 Hz, 1 H), 2.93 (dd, J_1= 16.5, J_2= 8.4 Hz, 1 H), 2.80 (dd, J_1= 16.5, J_2= 3.9 Hz, 1 H), 2.68 (td, J_1= 7.7, J_2= 3.6 Hz, 2 H). **10.** mp 197.5-199 °C, $[\alpha]^{25}_D$ +12.6° (*c* 0.81, $CHCl_3$). ^{1}H NMR δ 4.45 (m, 1 H), 3.50 (dd, J_1= 10.5, J_2= 3.0 Hz, 1 H), 2.95 (dd, J_1= 10.5, J_2= 3.0 Hz, 1 H), 2.90 (dd, J_1= 16.8, J_2= 8.7 Hz, 1 H), 2.68 (dd, J_1= 16.8, J_2= 3.8 Hz, 1 H). **12.** $[\alpha]^{25}_D$ +20.5° (*c* 1.05, $CHCl_3$). ^{1}H NMR δ 4.56 (m, 1 H), 3.34 (dd, J_1= 10.2, J_2= 3.9 Hz, 1 H), 3.13 (dd, J_1= 10.2, J_2= 4.5 Hz, 1 H), 2.69-2.89 (m, 3 H), 2.56-2.69 (m, 1 H), 1.84 (bs, 3 H). **13.** $[\alpha]^{25}_D$ +35.7° (*c* 1.56, $CHCl_3$). ^{1}H NMR δ 4.56 (m, 1 H), 3.37 (dd, J_1= 10.2, J_2= 3.6 Hz, 1 H), 3.10 (dd, J_1= 10.2, J_2= 4.2 Hz, 1 H), 2.87 (ddq, J_1= 16.2, J_2= 8.4, J_3= 2.0 Hz, 1 H), 2.66 (dq, J_1= 16.2, J_2= 2.0 Hz, 1 H), 2.29 (t, *J*= 2.0 Hz, 3 H), 2.10 (t, *J*= 7.5 Hz, 2 H).

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