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Generation and reaction of an oxiranyl anion derived from α,β-epoxy-γ-butyrolactone

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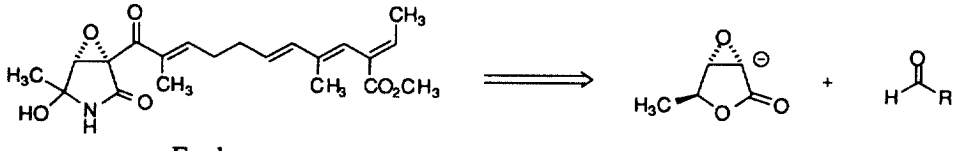
Abstract

Generation and reaction of an oxiranyl anion on a lactone are described. Aldol-type condensation of epoxylactone and aldehydes was accomplished by a two-step procedure via trimethylsilyl epoxylactone. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: oxiranyl anion; β-angelica lactone epoxide; fluoride-catalyzed aldol reaction; epolactaene.

During the course of our investigation towards the synthesis of epolactaene,[2] we became interested in the strategy involving the reaction of an oxiranyl anion derived from epoxylactone and an aldehyde (Scheme 1). Although the oxiranyl anion stabilized by an ethoxycarbonyl group is literature precedented,[3] an oxiranyl anion derived from α,β-epoxy-γ-butyrolactone has not been reported. Such oxiranyl anion derived from epoxylactone is to be localized at the bridgehead because of Bredt's rule,[4] therefore, the reactivity of this anion as well as the method of generation is quite interesting.[5] The present paper focuses on the generation and reaction of the oxiranyl anion, and the accompanying paper describes the application to the synthesis of epolactaene.



Epolactaene

Scheme 1.

First of all, direct condensation of propionaldehyde with an oxiranyl anion generated from epoxylactone was attempted (Table 1). Thus, racemic β-angelica lactone epoxide[6a] ((±)-**1**) was treated with LDA in THF at −78°C, and then propionaldehyde was added to the reaction mixture. However, the desired condensation product **3** could not be obtained, but the dimer **2** was isolated in 16% yield as an identified

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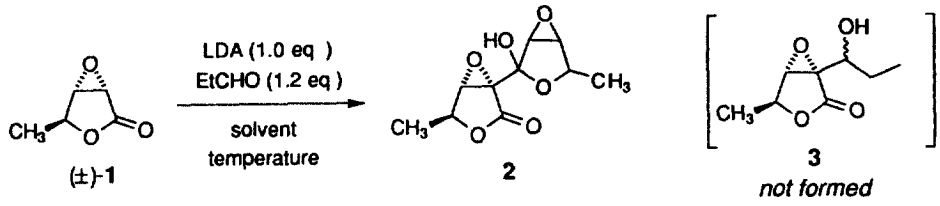
Table 1



Entry	Solvent	Conc. (M)	Temp. (°C)	Yield (%)
1	THF	0.1	-80	16
2	Et_2O	0.02	-110	43
3	Trapp mixture	0.02	-110	65

product (entry 1). Other conditions, such as in ether at lower concentration (0.02 M) at −110°C and in the Trapp mixture[7] (THF:Et_2O:hexane=3:1:1) at −110°C were also unsuccessful, resulting in the undesirable formation of dimer 2 in moderate yields (entries 2 and 3). Although the desired aldol-type product was not obtained, these results clearly indicated that the oxiranyl anion can be generated and that the anion is so reactive that it attacks another epoxylactone during the lithiation step even at −110°C.

We then examined an alternative stepwise approach via α-trimethylsilyl epoxylactone. We reasoned that the reactive oxiranyl anion could be immediately trapped as trimethylsilyl derivative **4** when the deprotonation was carried out in the presence of the excess trimethylsilyl chloride (TMSCl). We also expected that the desired aldol-type condensation might occur when a mixture of trimethylsilyl derivative **4** and an aldehyde was treated with a catalytic amount of a fluoride anion. By this method, generation of the reactive oxiranyl anion becomes possible in the presence of an aldehyde, and the formation of dimer **2** might be prevented.

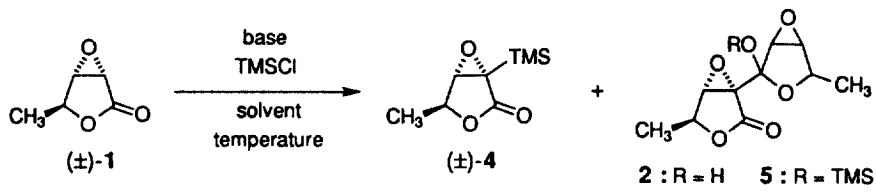
First, according to Eisch's method,[3] a solution of LDA was added to a mixture of epoxylactone (±)-**1** and TMSCl at −110°C. However, silylated product (±)-**4** was not produced and dimers **2** and **5** were isolated (Table 2; entries 1 and 2). Reverse addition was then conducted, and the desired silylated product (±)-**4**[8] was isolated in 70% yield when a solution of epoxylactone in the Trapp mixture was added to a solution of LDA and TMSCl in the Trapp mixture at −110°C (entry 3).

When ether was used as a solvent instead of the Trapp mixture, the dimers **2** and **5** were main products and the yield of (±)-**4** was only 5% (entry 4). The reaction did not proceed when using MHMDS (M=Li, Na and K) as a base, and epoxylactone (±)-**1** was recovered (entry 5).

We next carried out the silylation of chiral *anti*-epoxylactone (+)-**1** and *syn*-epoxylactone (−)-**6** in order to obtain the enantiomerically pure materials and ascertain the structure–reactivity relationships of the bridgehead oxiranyl anion. According to the method reported by Ogawa,[6b] (+)-**1** and (−)-**6** were prepared from D-xylose in a stereoselective manner. Contrary to the case of *anti*-isomer (+)-**1**, *syn*-isomer (−)-**6** afforded the corresponding silylated product (−)-**7**[8] in only 8% yield under the same reaction conditions. The low yield was due to the formation of undesirable oligomers (Scheme 2). The results might be reasonably explained by considering the difference in the steric environment around the lactone carbonyl. Both faces of the lactone carbonyl were blocked by either an epoxide oxygen or a methyl group in the *anti*-isomer **1**, whereas a nucleophile can readily approach from the *re*-face (upper face) of the lactone carbonyl in the case of *syn*-isomer **6**.

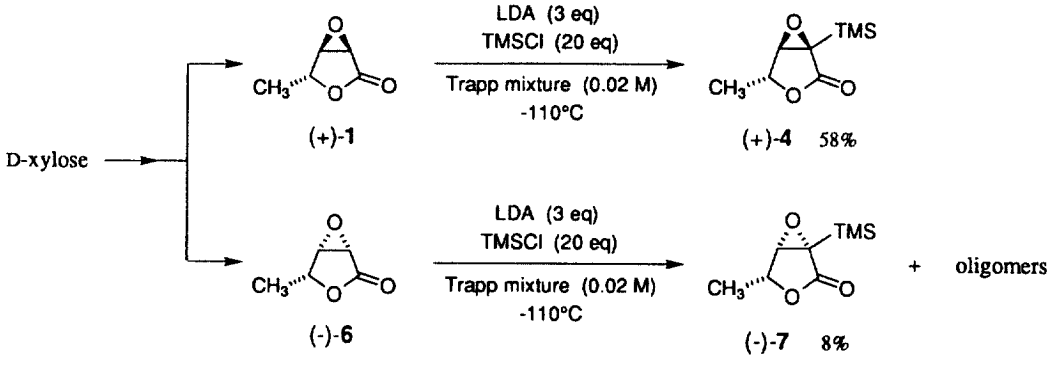
With silylated epoxylactone **4** in hand, condensation of **4** and aldehyde was next attempted. As expected, aldol-type reaction of **4** and propionaldehyde took place in the presence of 0.1 equivalent of tetrabutylammonium fluoride[9] (TBAF) and MS4A [10] in THF to give **10a** in 61% yield after desilylation (aq. HF in CH_3CN) of the initially formed TMS ether **9a** (Table 3; entry 1). Prolonged reaction time

Table 2



Entry[a]	Base (equiv)	TMSCl equiv	Solvent	Conc. M	Yield (%) 4	Dimers
1[b]	LDA (1.2)	5	Ether	0.1	-	**2** 65
2[b]	LDA (1.2)	5	Trapp mixture	0.1	-	**2** 13
						5 58
3	LDA (3.0)	11	Trapp mixture	0.02	70	**2** 6
4	LDA (3.0)	10	Ether	0.02	5	**2** 55
						5 3
5	MHMDS (3.0)	10	Trapp mixture	0.02	No reaction	

[a] Unless otherwise noted, reactions were carried out as follows: Epoxylactone was added to a mixture of a base and TMSCl in the solvent indicated. [b] Solution of LDA was added to a mixture of epoxylactone and TMSCl in the solvent indicated.

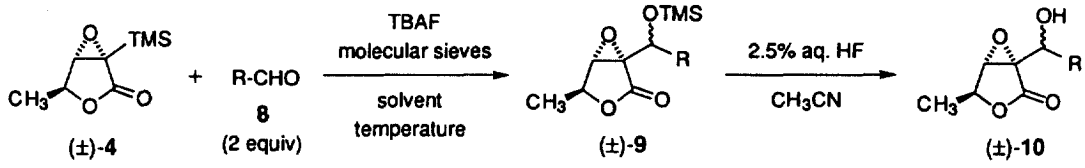


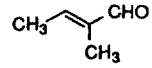
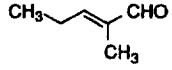
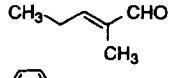
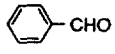
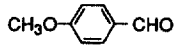
Scheme 2.

was found necessary for long-chain aliphatic aldehyde and α-methylated-α,β-unsaturated aldehyde. For example, **10e** was obtained in a total of 23% yield by the treatment of **4** and **8e** with TBAF three times.[11] The use of an equimolar amount of TBAF resulted in the formation of a complex mixture of products, and the use of a catalytic amount of a fluoride anion source seemed essential for the present reaction. Other fluoride anion sources or the presence of a co-additive such as trimethylsilyl fluoride[12] were not effective. We finally found that the condensation proceeded moderately in THF:hexane=1:1 (entry 5 versus entry 6). Condensation of **4** with aromatic aldehydes were also examined to obtain the corresponding condensation products. In this case, interesting diastereoselectivity was observed (entries 7 and 8).

In summary, we were able to achieve the aldol-type condensation of epoxylactone and aldehyde by a two-step procedure via trimethylsilyl epoxylactone. Although the reaction is not fully optimized, the present approach provides the first example of the generation and reaction of a highly reactive oxiranyl anion derived from epoxylactone. Synthetic applications for the total synthesis of epolactaene are described in the following paper.

Table 3



Entry	RCHO	8	Solvent	Temp. °C	Time hr	Yield (10) % (ds[b])
1	CH_3CH_2CHO	8a	THF	0→r.t.	6	61 (*ca.* 1 : 1)
2	$CH_3(CH_2)_4CHO$	8b	THF	r.t.	11	50 (*ca.* 1 : 1)
3	$CH_3(CH_2)_{10}CHO$	8c	THF : hexane = 1 : 1	r.t.	24	43 (*ca.* 1 : 1)
4		8d	THF	r.t.	24	57 (*ca.* 1 : 1)
5		8e	THF	r.t.	3 x 24h[a]	23 (*ca.* 1 : 1)
6		8e	THF : hexane = 1 : 1	r.t.	24	57 (*ca.* 1 : 1)
7		8f	THF : hexane = 1 : 1	r.t.	25	44 (*ca.* 3 : 1)
8		8g	THF : hexane = 1 : 1	r.t.	25	62 (single isomer)

[a] Reaction was carried out 3 times. [b] Diastereoselectivity was determined by ^{1}H-NMR.

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8. ^{1}H NMR (270 MHz) spectra are as follows: **4**: δ 0.22 (9H, s), 1.35 (3H, d, *J*=6.6 Hz), 3.72 (1H, s), 4.69 (1H, q, *J*=6.6 Hz). **7**: δ 0.21 (9H, s), 1.47 (3H, d, *J*=6.6 Hz), 3.83 (1H, d, *J*=1.7 Hz), 4.54 (1H, dq, *J*=1.7, 6.6 Hz).
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10. Molecular sieves 4A was added to remove H_2O present in commercial THF solution of TBAF. We found that the addition of molecular sieves 3A instead of 4A was not effective affording 6% of **10e** and 78% of the recovered **4**.
11. Without purification and separation, the crude mixture (**4**, aldehyde, and **9**) was retreated with TBAF and MS4A, and this operation was repeated.
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