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Enantio- and Stereo-controlled Construction of Tertiary and Quaternary Carbon Centers Using Chiral *O*-Benzylglycidol as Template

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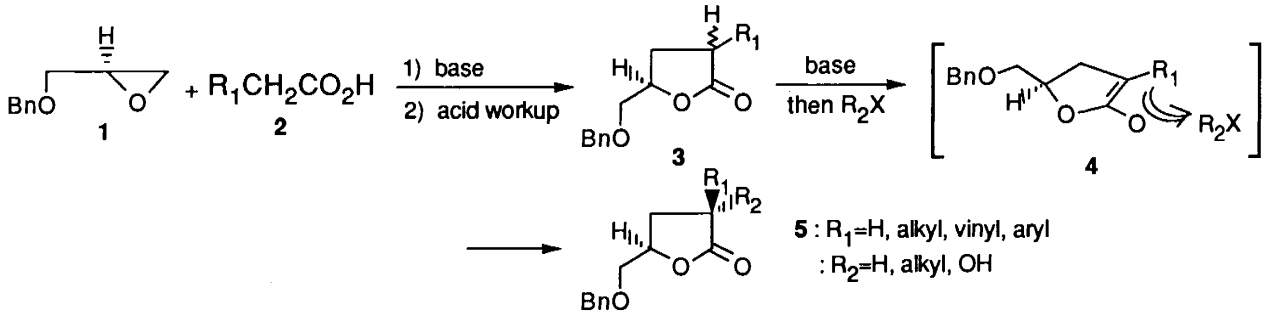
An efficient method for the enantio- and stereo-controlled construction of tertiary and quaternary carbon centers in a highly functionalized system has been developed using chiral *O*-benzylglycidol as template.

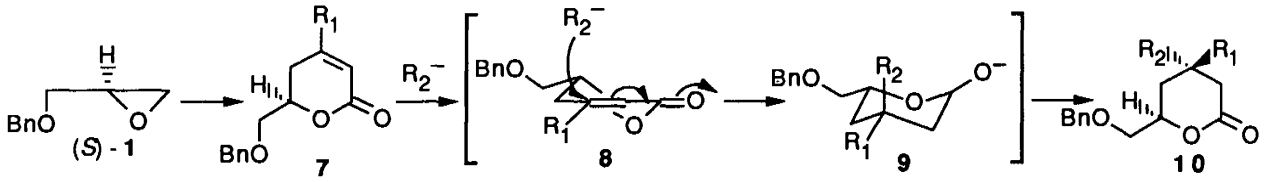
Enantio- and stereo-controlled construction of tertiary and quaternary carbon centers in an appropriately functionalized system is one of the most critical problems in the synthesis of natural products as well as other complex molecules.[1] As a part of utilizing chiral *O*-benzylglycidol[2] (**1**) we have developed a procedure for the construction of tertiary and quaternary centers *via* stereoselective functionalization of a γ-lactone substrate (**3**), prepared by condensation of chiral *O*-benzylglycidol (**1**) and an appropriate carboxylic acid (**2**), which led to formation of a γ-lactone (**5**) bearing tertiary or quaternary carbon at the α position by alkylation, protonation, and hydroxylation.[1b] Although this method using the lactone substrate as nucleophile gave practically satisfactory results in most cases so far examined, complete stereoselection never been observed except one example[3] (Scheme 1). We report herein an alternative methodology for the highly



Scheme 1.

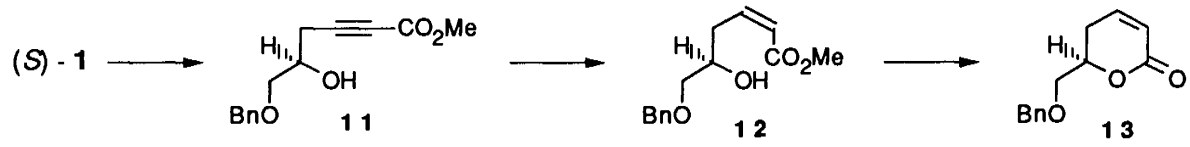
enantio- and stereo-selective construction of tertiary or quaternary carbon center in a functionalized system *via* an electrophilic intermediate using optically active *O*-benzylglycidol (**1**) as template. The principle of the present methodology is based on nucleophilic addition to the α,β-unsaturated δ-substituted δ-lactone substrates (**7**), derived from chiral *O*-benzylglycidol (**1**), which exhibited remarkable stereoselectivity in the formation of both tertiary and quaternary carbon centers in a predictable manner. Although the observed stereoselectivity could be readily expected by the well-

understood stereoelectronic effect of cyclohexenone system,[4] the observed excellent diastereoselection in the conjugate addition was worthy of note (Scheme 2).



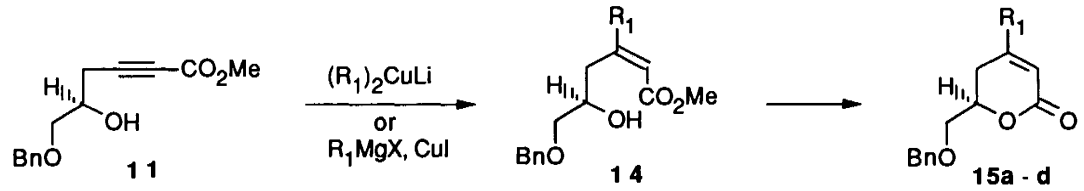
Scheme 2.

The monosubstituted α,β-unsaturated δ-lactone substrate[5] (**13**) for the construction of tertiary carbon center was prepared in 67% overall yield from (*S*)-*O*-benzylglycidol[6] (**1**) by condensation with methyl propiolate in the presence of *n*-butyllithium and boron trifluoride,[7] followed by sequential partial hydrogenation and lactonization[5] (Scheme 3).



Scheme 3.

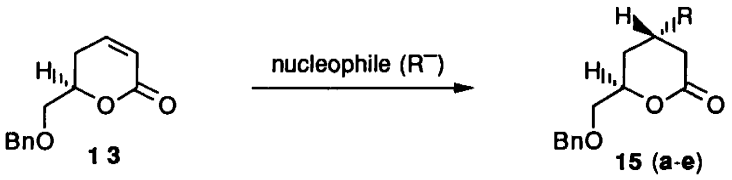
On the other hand, the β,δ-disubstituted-α,β-unsaturated δ-lactone substrates (**15a-d**) for the construction of quaternary center were prepared reasonable overall yields from (*S*)-*O*-benzylglycidol (**1**) *via* the stereospecific conjugate addition[8] of organocuprates to the same intermediate (**11**) followed by lactonization of the resulting olefins (**14**) (Scheme 4 and Table 1).



Scheme 4.

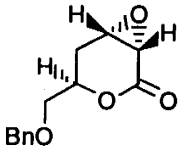
Table 1. Synthesis of the α,β-unsaturated δ-lactones (**15a**) from **11**

Entry	Nucleophile	Product (**15a-d**)	Yield/%
1	Me_2CuLi	**15a** (R_1=Me)	91
2	Ph_2CuLi	**15b** (R_1=Ph)	61
3	EtMgBr, CuI	**15c** (R_1=Et)	59
4	CH_2=CHMgBr, CuI	**15d** (R_1= -CH=CH_2)	72
5	CH_2=CH$(CH_2)_2$MgBr, CuI	**15e** [R_1= -$(CH_2)_2$CH=CH_2)]	80

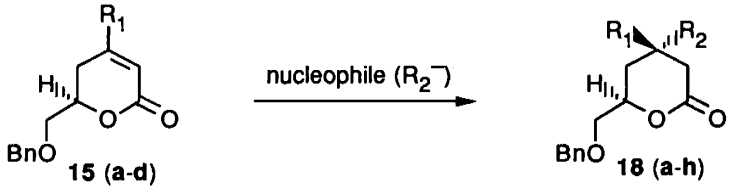


Scheme 5.

Table 2. Reaction of the monosubstituted α,β-unsaturated-δ-lactone (**13**) with nucleophiles

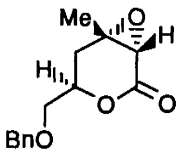
Entry	Nucleophile	Product[a] (**16a-d**), or **17**	Yield/%
1	Me_2CuLi	**16a** (R=Me)	74
2	Ph_2CuLi	**16b** (R=Ph)	74
3	EtMgBr, CuI	**16c** (R=Et)	65
4	^{i}Pr-MgBr, CuI	**16d** (R=^{i}Pr)	66
5	CH_2=CHMgBr, CuI	**16e** (R= -CH=CH_2)	58
6	30% H_2O_2, NaOH	**17**[5] 	73

a) None of diastereomer could be detected.



Scheme 6.

Table 3. Reaction of the disubstituted α,β-unsaturated-δ-lactones (**15a-d**) with nucleophiles

Entry	Substrate (**15a-d**)	Nucleophile	Product[a] (**18a-h**), or **19**	Yield/%
1	**15a** (R_1=Me)	Ph_2CuLi	**18a** (R_1=Me; R_2=Ph)	53
2	**15a** (R_1=Me)	EtMgBr, CuI	**18b** (R_1=Me; R_2=Et)	77
3	**15a** (R_1=Me)	CH_2=CHMgBr, CuI	**18c** (R_1=Me; R_2= -CH=CH_2)	73
4	**15a** (R_1=Me)	$H_2(PtO_2)$	**18d** (R_1=Me; R_2=H)	82
5	**15b** (R_1=Ph)	Me_2CuLi	**18e** (R_1=Ph; R_2=Me)	61
6	**15b** (R_1=Ph)	$H_2(PtO_2)$	**18f** (R_1=Ph; R_2=H)	62
7	**15d** (R_1=Et)	CH_2=CHMgBr, CuBr·Me_2S	**18g** (R_1=Et; R_2= -CH=CH_2)	70
8	**16d** (R_1= $(CH_2)_2CH$=CH_2)	EtMgBr, CuI	**18h** (R_1= -$(CH_2)_2CH$=CH_2; R=Et)	90
9	**15a** (R_1=Me)	30% H_2O_2, NaOH	**19** 	70

a) None of diastereomer could be detected.

As shown, the monosubstituted lactone (**13**) afforded the saturated lactones (**16a-d**) and **17** bearing newly generated tertiary carbon center at β-position with *anti* configuration to the δ-substituent, exclusively, regardless of the nucleophiles used (Scheme 5 and Table 2).

Quite similarly, all of the disubstituted lactones (**15**) furnished the corresponding saturated lactones (**18a-c, e, g, h**) and **19** bearing quaternary carbon center at β-position by introduction of nucleophiles exclusively from the *anti* face to the δ-substituent (Scheme 6 and Table 3). Hydrogenation also took place in the same way to form the tertiary carbon center selectively (Entries 4 and 6) which were opposite stereochemistry to those generated by nucleophilic addition (Table 2; Entries 1 and 2). The present procedure also allows arbitrary construction with respect to quaternary carbon centers regardless of the configuration of the chiral template used as exemplified by the formation of **18a** and **18e** (Table 3; Entries 1 and 5).

Since the δ-lactones bearing tertiary and quaternary carbon centers thus obtained possess high functionalities such as lactone carbonyl and 1,2-glycol unit in the molecules as well as latent structural symmetry of the molecules, they may be potentially useful as versatile chiral building blocks for the enantio-controlled synthesis of a variety of natural products. We have already completed the syntheses of *cis*- and *trans*-rose oxides, (+)- and (–)-mevalonolactones, phytol, α-tocopherol, and bakuchiol employing the present methodology which will be published elsewhere.

References

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3) S. Takano, M. Tanaka, K. Seo, M. Hirama, and K. Ogasawara, *J. Org. Chem.*, **50**, 931 (1985).

4) Cf. P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon, Oxford (1983), p. 209.

5) S. Takano, Y. Shimazaki, Y. Sekiguchi, and K. Ogasawara, *Synthesis*, **1989**, 539.

6) S. Takano, K. Seya, E. Goto, M. Hirama, and K. Ogasawara, *Synthesis*, **1983**, 116; S. Takano, M. Akiyama, and K. Ogasawara, *ibid.*, **1985**, 503.

7) Cf. S. P. Munt and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, **1989**, 480.

8) Cf. E. J. Corey and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 1851 (1969); J. B. Sidall, M. Biskup, and J. H. Fried, *ibid.*, **91**, 1853 (1969).

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