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Asymmetric Synthesis of α-Substituted-γ-butyrolactone Empolying Prolinol Type of Auxiliaries

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Abstract: Eleven (*S*)-(-)-bishydrocarbyl-(1-alkanoylpyrrolidin-2-yl)-methanol derivatives of three types were synthesized from L-proline, asymmtrically selective alkylation products were obtained by LDA treatment and alkylation using methyl 2-bromoethyl ether, and three types of chiral α-substituted-γ-butyrolactones were obtained by hydrolyzing the alkylation products, with %e.e. being up to 89 percent.

Keywords: Asymmetric synthesis, α-substituted-γ-butyrolactone.

Chiral α-substituted-γ-butyrolactone is an important block of naturally existing bioactive molecules and natural medicaments[1]. Meyers *et al.*[2,3] reported a method for synthesizing α-substituted-γ-butyrolactone in which oxazoline was used as chiral auxiliary. This paper employs proline type of chiral auxiliaries in the asymmetric synthesis of α-substituted-γ-butyrolactones. The new method provides a useful tool in organic synthesis. (*S*)-(-)-Bishydrocarbyl-(1-alkanoyl-pyrrolidin-2-yl)-methanol derivatives of three types were synthesized from L-proline, asymmtrically selective alkylation products were obtained by LDA treatment at –78°C and alkylation *via* a transition state in which metal ion takes part, and three types of chiral α-substituted-γ-butyrolactones were obtained by cleaving ether bond of the alkylation products using BBr_3 followed by hydrolyzing under conditions of 1mol/L HCl and at 100 °C (**Scheme 1** and **Table 1**).

Chiral lactones can be prepared *via* (S)-(-)-bishydrocarbyl-(1-alkanoylpyrrolidin-2-yl) methanol. We found that the bulkiness of R group in the compounds **3a-k** did affect the diastereoselectivity of the alkylation reaction (**Table 2**). It is quite evident that when R=Ph, the final butyrolactones showed higher enantioselectivity (87-89%, see **Table 3**), and when R=CH_3 or CH_2Ph, the final butyrolactones showed lower selectivity (19-47%).

Our proposed transition state (see **Figure 1**) might be as **Figure 1**. Evans[4] approved that alkylation reaction took place preferentially from *Si*-face of an intermediate carrying a proline chiral auxiliary. Thus the ratio of two configurations of the double bond in the transition state greatly affects the selectivity of the asymmetric alkylation. Phenyl is a secondary radical which is larger than the primary radicals of methyl or benzyl, therefore its stereoselectivity is higher than latters.

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Table 1 Synthesis of substrates (S)-(-)-**3a-k** bearing with a chiral auxiliary

Substrate	R′	R	mp. (°C)	Yield (%)	$[\alpha]_D^{20}$ (EtOAc)
3a	CH_3	CH_3	Viscous liquid	75	-36.4 (c,1.0)
3b	CH_3	CH_3CH_2	Viscous liquid	70	-66.1 (c,1.6)
3c	CH_3	C_6H_{13}	Viscous liquid	76	-43.2 (c,2.2)
3d	CH_3	CH_2Ph	Viscous liquid	80	
3e	CH_3	Ph	106-7	73	-182.1 (c,2.0)
3f	CH_3CH_2	CH_3	Viscous liquid	22	-74.0 (c,1.4)
3g	CH_3CH_2	CH_2Ph	Viscous liquid	30	-53.2 (c,1.5)
3h	CH_3CH_2	Ph	Viscous liquid	44	-63.6 (c,1.6)
3i	Ph	CH_3	68.5-70.2	52	-138.0 (c,1.3)
3j	Ph	CH_2Ph	130-1	50	-118.3 (c,1.5)
3k	Ph	Ph	117-8	68	-92.6 (c,1.4)

Table 2 Synthesis of diastereoisomers (-)-**4a-i**

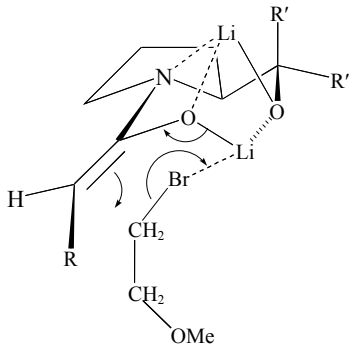
Compound	R′	R	Yield (%)	$[\alpha]_D^{20}$ (EtOAc)	Diastereoisomeric ratio
4a	CH_3	CH_3	55	-84.4 (c,1.0)	73:27
4b	CH_3	CH_2P	59	-63.7 (c,1.5)	74:26
4c	CH_3	Ph	85	-108.3 (c,2.7)	99:1
4d	CH_3C	CH_3	31	-55.4 (c,1.0)	75:25
4e	CH_3C	CH_2P	68	-61.4 (c,2.0)	79:21
4f	CH_3C	Ph	54	-102.2 (c,1.0)	98:2
4g	Ph	CH_3	67	-99.6 (c,1.2)	82:18
4h	Ph	CH_2P	29	-104.1 (c,1.6)	75:25
4i	Ph	Ph	52	-107.3 (c,1.0)	>99:1

Table 3 Synthesis results of α-substituted-γ-butyrolactone

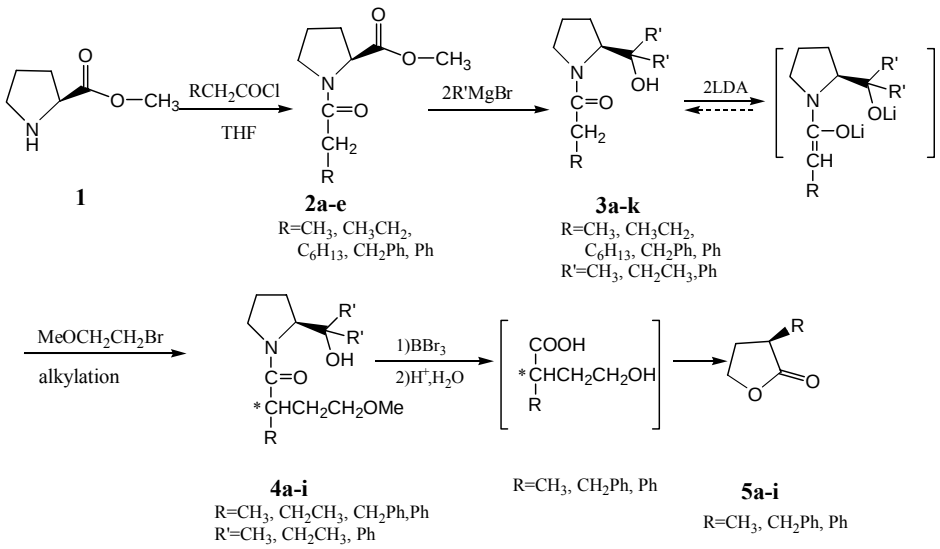
Compound	R′	R	Yield (%)	$[\alpha]_D^{20}$ (EtOAc)	% e.e.*
5a	CH_3	CH_3	71	+11.6 (c,1.0)	47
5b	CH_3	CH_2Ph	61	+20.4 (c,1.5)	41
5c	CH_3	Ph	57	-1.69 (c,2.0)	89
5d	CH_3CH_2	CH_3			
5e	CH_3CH_2	CH_2Ph	76	+14.3 (c,1.0)	32
5f	CH_3CH_2	Ph	72	-1.32 (c,1.0)	87
5g	Ph	CH_3	58	+8.9 (c,0.5)	36
5h	Ph	CH_2Ph	75	+12.1 (c,1.5)	19
5i	Ph	Ph	64	-1.67 (c,1.0)	88

*HPLC 1100 Chiralcel OD, 254nm, Hexane:isopropanol=95:5

Figure 1 The proposed transition state of (-)-**4a-i**



Scheme 1 Route of synthesis of **5a-i**



The present work characterized the synthesized compounds through ^{1}HNMR, ^{13}CNMR, MS, HRMS, rotational analysis, and/or HPLC chiralcel OD column.

α-Substituted-γ-butyrolactones were synthesized stereo selectively by the new route, with %e.e. being up to near 90%. This work showed that the more bulky substituent, the higher the stereoselectivity.

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