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Asymmetric Alkylation of Chiral α,β-Unsaturated Lactones

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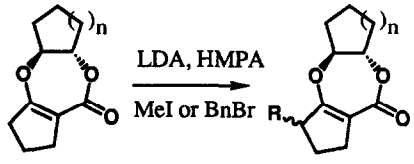
Key Words: (*S,S*)-cyclopenpane-1,2-diol; (*S,S*)-cyclohexane-1,2-diol; asymmetric alkylation; chiral cyclic diol; chiral auxiliary; 2,3-dihydro-1,4-dioxepin-5-one

Abstract: Alkylation of **5**, prepared from six-membered β-keto ester and (*S,S*)-cyclohexane-1,2-diol, proceeded in highly diastereoselective manner to afford a quaternary carbon.

Chiral diols having a C_2 axis of symmetry have attracted much attention from the standpoint of asymmetric synthesis, because these diols are an excellent auxiliary for the preparation of chiral acetal, which is capable of differentiating between the *re*- and *si*-faces of a neighboring prochral group. In a previous paper,[1] we reported that asymmetric alkylation of chiral 1,2-cycloheptanedioxy (or 1,2-cyclohexanedioxy) acetals of five-membered (or acyclic) β-keto esters proceeds in a highly diastereoselective manner to afford a quaternary carbon.

In this paper, we report that asymmetric alkylation of chiral α,β-unsaturated 7-membered lactones prepared from cyclic β-keto esters and chiral diols affords α- or γ-alkylated products diastereoselectively or regioselectively, depending on the ring size. Preparation of substrates (**1**, **2**, **5**) has been readily achieved by reaction with 2-ethoxycarbonyl-cyclopentanone (or -cyclohexanone) and (*S,S*)-cyclopentane (or -cyclohexane)-1,2-diols under azeotropic conditions using *p*-TsOH (1 eq.) in benzene.[2] Alkylation of **1** (or **2**) with RX (5 eq.)/LDA (5 eq.)/HMPA (5 eq.) in THF at -78°C to -40°C afforded, unexpectedly, γ-alkylated products **3** (or **4**) (Table I).[3] Each reaction resulted in low diastereoselectivity (3:1 to 3:2),[4] but it is noteworthy that the alkylation took place in a highly regioselective manner at γ-position of ester carbonyl, and that no α-alkylated or dialkylated products could be detected.

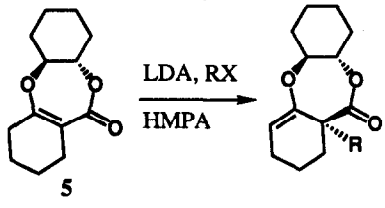
Table I. Alkylation of α,β-unsaturated lactone based on five-membered ring



1(n=1), **2**(n=2)

Substrate	R	Yield (%)		Diastereomeric ratio
1	Me	**3a**	70	3 : 1
1	Bn	**3b**	63	3 : 2
2	Me	**4a**	65	3 : 1
2	Bn	**4b**	67	3 : 2

Table II. Alkylation of α,β-unsaturated lactone based on six-membered ring



5

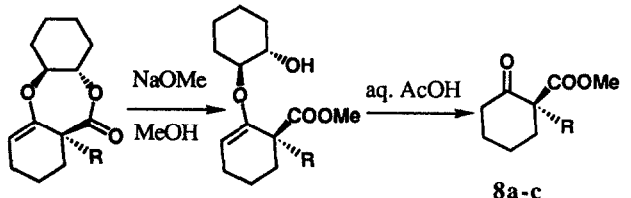
RX	Yield (%)		D.e. (%)	Abs. config.
MeI	**6a**	86	94	*S*
CH_2=$CHCH_2$I	**6b**	51	94	*R*
BnBr	**6c**	52	>99	*R*

On the other hand, alkylation of **5** prepared from 2-ethoxycarbonylcyclohexanone and (*S,S*)-cyclohexane-1,2-diol showed quite different behavior from the case of **1** (or **2**) to afford α-alkylated products (**6a-c**) in highly regio- and diastereo-selective manner (94->99% d.e.)[5] as shown in Table II.[6] It is interesting that the absolute configuration of the newly generated stereogenic center is contrary to that in the cases of alkylation[1] of (*S,S*)-cyclohexane-1,2-dioxy acetal of 2-ethoxycarbonylcyclopentanone, suggesting the difference in the steric course of this reaction.

Typical examples: A solution of n-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mmol) in THF (8 ml) at -78 °C under an Ar atmosphere. After 10 min, HMPA (403 mg, 2.25 mmol) in THF (1 ml) and **5** (100mg, 0.45 mmol) in THF (1 ml) were added, the whole was stirred for 10 min, then benzyl bromide (385 mg, 2.25 mmol) in THF (0.5 ml) was added. After being stirred for 3 h at -78°C, then 12 h at -40°C, usual work-up and subsequent flash chromatography afforded **6c** (75 mg, 52%), and recovered **5** (15 mg, 15%).

References and Notes

1. Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.*, **1992**, 33, 247-250. References cited therein.
2. Usual acetalization of ethoxycarbonyl-cyclopentanone (or -cyclohexanone) using cyclopentanediol (or cyclohexanediol) in the presence of *p*-TsOH (1 eq.) affords exclusively the unsaturated lactones (**1, 2, 5**) in 50-60% yields, and the usual acetal is not obtained. However, this reaction depends on the ring size of cyclic diol. (*S,S*)-Cycloheptane-1,2-diol yielded only the acetal, and the corresponding α,β-unsaturated lactone was not obtained. Examination of this reaction process using TLC indicated that **1, 2,** and **5** might be formed *via* corresponding acetals.
3. Alkylation of α,β-unsaturated lactone prepared from 2-ethoxycarbonylcyclohexanone and (*S,S*)-cyclopentane-1,2-diol under the same reaction conditions gave a mixture of γ-alkylated product and α-alkylated product in 59% and 26% yields, respectively .
4. Diastereomeric ratio was estimated by 270MHz ^{1}H-NMR. Absolute configurations of **3, 4** are not determined.
5. Products **6a-c**[6] were converted to corresponding hydroxy esters **7a-c**[6] with NaOMe in MeOH, and subsequent acid treatment afforded **8a-c**,[6] which are configurationally known compounds (Scheme 1). See Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.*, **1984**, 106, 2718. Diastereomeric excess was determined by the examination of 270MHz ^{1}H-NMR spectroscopy using a chiral shift reagent (Eu(hfc)$_3$).



6a-c **7a-c** Scheme 1 **8a-c**

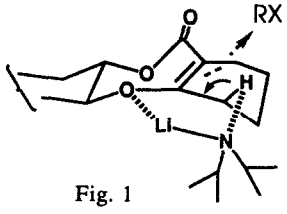


Fig. 1

6. Formation of *S*-configuration in **6a** (Table II), in contrast to the case of **6b** and **6c**, is due only to the CIP selection rules, and not to the steric course of the reaction. The alkylation mechanism is tentatively proposed as Fig. 1. The reaction starts presumably with abstraction of allyl β-hydrogen to afford α-alkylated product. Spectroscopic data of **6c**: $[\alpha]_D^{27}$ +17.6 (c 0.8, $CHCl_3$); ν max/cm^{-1} 1720, 1660, 1445, 1220; ^{1}H NMR ($CDCl_3$) 2.96, 3.39 (1H each, d, *J*/Hz 13, CH_2Ph), 3.85 (1H, m, O-CH), 4.53 (1H, m, COO-CH), 5.47 (1H, t, *J*/Hz 4, CH=), 7.21-7.29 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$) 175.0 (C=O), 147.4 (=C-O), 136.8 (4° Ar), 130.8, 128.4, 126.5 (Ar-CH), 118.8 (=CH), 80.9, 77.3 (O-CH), 53.4 (4°), 44.4, 33.2, 31.8, 31.5, 23.9, 23.6, 23.3, 19.1 (CH_2); *m/z* 312 (M^+, 7), 180 (64), 107 (98), 92 (100).

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