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Application of Chiral Cyclic Diols to Asymmetric Alkylation

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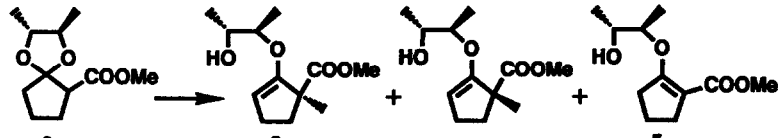
Key Words: 1S,2S-cyclohexanediol; 1R,2R-cycloheptanediol; asymmetric alkylation; chiral cyclic diol, chiral auxiliary, chiral enol ether

Abstract: *Chiral cyclic (6- or 7-membered ring) diols were found to be excellent chiral auxiliaries for asymmetric alkylation of cyclic (or acyclic) β-keto esters.*

It is well known that the selection of a protective group plays an important role in organic synthesis, and many protective groups have been developed for this purpose.[1] Recently, chiral diols having a C_2 axis of symmetry have attracted much attention from the standpoint of asymmetric synthesis,[2] because a single acetal can be derived from a simple carbonyl compound without any other chiral center, and chiral acetal is capable of differentiating between the *re*- and *si*-faces of a neighboring prochiral group. An alternative aspect of the synthetic potential of chiral acetals is that an acetal ring undergoes the Lewis acid-catalyzed opening[3] in a stereo-controlled fashion, in which the high diastereoselectivity can be attributed to specific coordination of the Lewis acid with the acetal oxygen.

In this paper, the authors report that chiral cyclic (6- or 7-membered ring) diols[4] are an excellent chiral auxiliary for asymmetric alkylation of cyclic (or acyclic) β-keto esters to afford a quarternary carbon, and the reaction proceeds in a diastereoselective manner *via* the base-catalyzed opening of chiral 1,2-cylohexanedioxy (or chiral 1,2-cycloheptanedioxy) acetal.

Table I. Effect of the ratio of LDA to alkylation

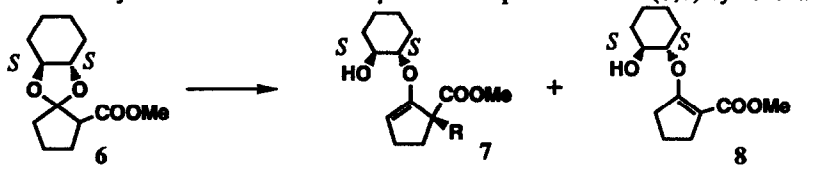


2 3 4 5

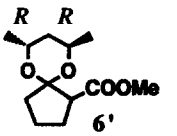
Entry	Eq. (LDA)	Products (%)			Revovery of 2 (%)
		3	4	5	
1	1.0	11	7	28	46
2	2.5	43	21	14	0
3	5.0	59	32	0	0

Reaction conditions: MeI/LDA in THF at -78°C under an Ar atmosphere.

Table II. Alkylation of five-membered β-keto ester protected with (S,S)-cyclohexanediol

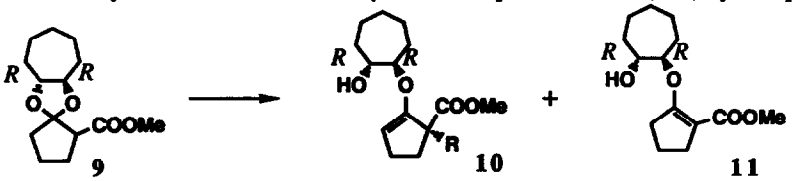


Entry	RX	Products	Yields (%)	de (%)(abs. config.)
1	MeI	7	57	92 (*R*)
		8	8	-
2	$C_9H_{19}Br$	7	66	>99 (*R*)
		8	7	-
3 (Subs.6')	MeI	alkylated enol ether (7-type)	57	73 (*S*)
		conjugated enol ester (8-type)	6	-



Reaction conditions: RX/LDA/HMPA in THF at 78°C under an Ar atmosphere.

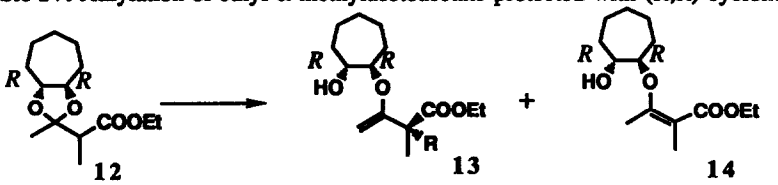
Table III. Alkylation of five-membered β-keto ester protected with (R,R)-cycloheptanediol



Entry	RX	Products	Yields (%)	de (%)(abs. config.)
1	MeI	**10**	54	>99 (*S*)
		11	36	-
2	$C_9H_{19}Br$	**10**	74	>99 (*S*)

Reaction conditions: the same as the case of Table II.

Table IV. Alkylation of ethyl α-methylacetoacetate protected with (R,R)-cycloheptanediol



Entry	RX	Products	Yields (%)	de (%)(abs. config.)
1	$PhCH_2Br$	**13**	78	>99 (*R*)
		14	11	-
2	CH_2=$CHCH_2Br$	**13**	48	>99 (*R*)
		14	7	-

Reaction conditions: the same as the case of Table II.
When (*S*,*S*)-1,2-cyclohexanediol was employed instead of (*R*,*R*)-1,2-cycloheptanediol, the alkylated product (R=$PhCH_2$) of 94% de (S) was obtained.

Acetalization of a five-membered cyclic β-keto ester (**1**) (or acyclic α-methyl-β-keto ester) with chiral diols such as (*R,R*)-2,3-butanediol, (*R,R*)-2,4-pentanediol, (*S,S*)-1,2-cyclohexanediol, and (*R,R*)-1,2-cycloheptanediol under azeotropic conditions using *p*-TsOH/benzene afforded the corresponding acetals, which are an inseparable mixture[5] of two diastereomers. As shown in Table I, alkylation[6] of **2** with MeI at -78°C afforded better yield of **3** and **4** as the ratio of LDA (5.0 eq.) was increased, and the yield of α,β-unsaturated ester (**5**) was reduced. It is noteworthy that, in this alkylation, the alkylated product retaining the original acetal structure intact was not obtained at all, but the enol ether formed by cleavage of the acetal ring was obtained.[7] Alkylation of **6** (or **9**) protected with (*S,S*)-1,2-cyclohexanediol[4] or (*R,R*)-1,2-cycloheptanediol[4] with RX/LDA(5eq)/HMPA (5eq) in THF at -78°C proceeded in a highly diastereoselective fashion,[8] as shown in Table II and III, while alkylation of five membered cyclic β-keto ester protected with (*R,R*)-2,4-pentanediol under the same conditions resulted in only 73% de (50% yield). The above results suggest that cyclic chiral diols, in particular, (*R,R*)-1,2-cycloheptanediol (Table III) are superior as temporary chiral auxiliaries to acyclic chiral diols such as chiral 2,3-butanediol and 2,4-pentanediol. Next, acyclic α-methyl-β-keto ester (ethyl α-methylacetoacetate) with cyclic chiral diol as a chiral auxiliary was subjected to the above described alkylation reaction. In accord with our expectation, alkylation of the acyclic ring protected with (*R,R*)-1,2-cycloheptanediol also afforded an excellent result ,[9,10] as shown in Table IV.

Typical examples (entry 3, Table II): A solution of n-BuLi in hexane (15% solution, 0.91ml, 1.46 mmol) was added dropwise to a stirred solution of diisopropylamine (147 mg, 1.46 mmol) in THF (5 ml) at -78° C under an Ar atmosphere. After 10 min, HMPA (261 mg, 1.46 mmol) in THF (0.5 ml) and **6** (70 mg, 0.29 mmol) in THF (0.5 ml) were successively added at -78°C, and the whole was stirred for 10 min, then $C_9H_{19}Br$ (302 mg, 1.46 mmol) in THF (0.5 ml) was added. After being stirred for 3 h at -78°C, and for 12 h at -40°C, the reaction mixture was diluted with an aqueous solution saturated with NH_4Cl (10 ml), then extracted with AcOEt. The oily residue was purified by flash chromatography to afford **7** (70 mg, 66%, elution with 2% AcOEt in hexane) and **8** (7 mg, elution with 16% AcOEt in hexane).

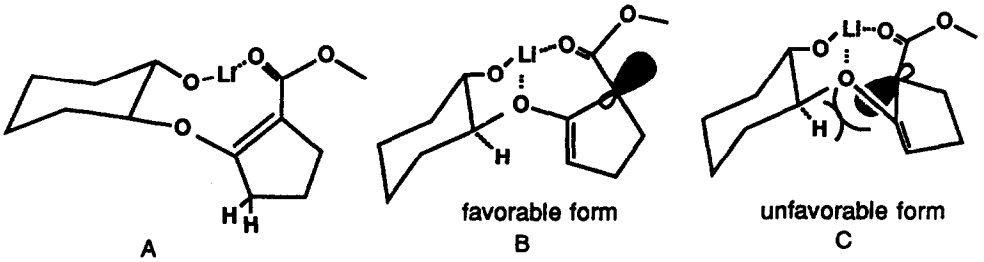
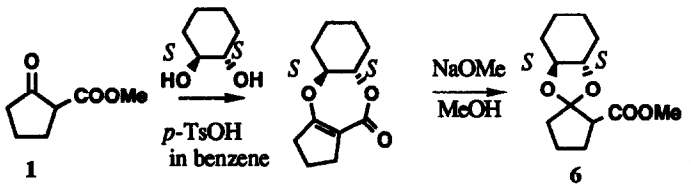


Fig.

As shown in Fig. A, the enol ester may be first formed by opening of the acetal under strong basic conditions. In the next step, it is reasonable that the excess of base (5 eq.) affords the deconjugated enol ether (Fig. B or Fig. C) *via* the abstraction of hydrogen at the γ-position (Fig. A). Examination using the stereomodel (Dreiding) indicates that Fig. B is the prefable form to Fig. C, because the resulted anion lobe in Fig. C occupies a sterically crowded space. Thus, high diastereoselectivity in the alkylation of five-membered ring β-keto ester protected with chiral 1,2-cyclohexanediol or 1,2-cycloheptanediol may be rationalized by considering the intermediate shown in Fig. B.

References and notes

1. Greene, T.W. Protective Groups in Organic Synthesis , John Wiley & Sons (Canada), 1981.
2. Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry*, **1990**, 1, 477.
3. Kaino, M.; Naruse, Y.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.*, **1990**, 55, 5814.
4. Chiral diols can be prepared by enzymatic procedure. See Xie, Z.-F.; Suemune, H.; Sakai,K. *J. Chem. Commun.*, **1987**, 838: Xie, Z.-F., Suemune, H.; Nakamura, I.; Sakai, K. *Chem. Pharm. Bull.*, **1987**, 35, 4454: Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Commun.*, **1988**, 966.
5. In the acetalization of five-membered ring β-keto ester (1) using (*S,S*)-1,2-cyclohexanediol in the presence of *p*-TsOH in refluxing benzene, usual acetal was not obtained, but the seven-membered ring lactone converted to 6 by treatment with NaOMe was obtained.



1 6

6. Absolute configuration of each product was determined by comparison with the stereochemically known compounds after deprotection with aq. AcOH. Deprotection of **7** (R=C_9H_{19}, entry 2 in Table II) afforded an intermediate for the synthesis of (-)-malyngolide. For both absolute configuration and synthesis of (-)-malyngolide, see Sato, T.; Maeno, H.; Noro, T.; Fujisawa, T. *Chem. Lett.*, **1988**, 1739.
7. Selected spectroscopic data of representative products.

   Table II (entry 2, R=C_9H_{19}): $[\alpha]_D^{26}$ +55.6 (c=1.00, $CHCl_3$); ν max/cm^{-1} 3550, 1740, 1665, 1250; ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J/Hz 7, CH_3), 1.26 (16H, br s), 1.59-1.88 (6H, m), 2.05-2.33 (6H, m), 3.48-3.70 (2H, m, OCH), 3.63 (1H, br s, OH), 3.69 (3H, s, OCH_3), 4.64 (1H, br s, =CH); ^{13}C NMR ($CDCl_3$) δ 176.6 (CO), 157.3 (=C-O), 96.9 (=CH), 84.4 (O-CH), 73.7 (OCH), 58.1 (quaternary carbon), 52.1 (OCH_3), 35.2, 32.9, 32.5, 31.9, 30.0, 29.5, 29.4, 29.3, 26.4, 25.8, 24.4, 24.3, 23.9, 22.7 (CH_2), 14.3 (CH_3); *m/z* 366 (M^+, 5), 191 (8), 142 (100), 110 (21), 69 (14).

   Table III (entry 1, R=Me): $[\alpha]_D^{26}$ -63.6 (c=0.33, $CHCl_3$); ν max/cm^{-1} 3500, 1720, 1640, 1440, 1100 ; ^1H NMR ($CDCl_3$) δ 1.35 (3H, s, CH_3), 1.50-1.98 (11H, m), 2.27-2.41 (3H, m), 3.38 (1H, brs, OH), 3.70 (3H, s, OCH_3), 3.64-3.81 (2H, m, OCH), 4.52 (1H, br s, =CH); ^{13}C NMR ($CDCl_3$) δ 176.8 (CO), 158.5 (=C-O), 95.9 (=CH), 86.5 (OCH), 75.8 (OCH), 54.0 (quaternary carbon), 52.2 (OCH_3), 35.7, 31.6, 28.5, 27.4, 26.2, 22.5, 22.2 (CH_2), 21.9 (CH_3); *m/z* 268 (M+, 30), 167 (86), 156 (93), 124 (95), 97 (81), 83 (34), 69 (95), 55 (100).

   Table IV (entry 2, R=CH_2=CH-CH_2): $[\alpha]_D^{26}$ -69.6 (c=0.77, $CHCl_3$); ν max/ cm^{-1} 3450, 1710, 1660, 1640, 1440, 1100; ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J/Hz 7, -CH3), 1.30 (3H, s, CH_3), 1.46-1.97 (10H, m), 2.43 (1H, dd, J/Hz 14, 8, CH-C=C), 2.65 (1H, dd, J/Hz 14, 6, CH-C=C), 3.01(1H, br s, OH), 3.64-3.72 (1H, m, OCH), 3.82-3.89 (1H, m, OCH), 4.04 (1H, d, J/Hz 3, CH=C-O), 4.11 (1H, d, J/Hz 3, CH=C-O), 4.10-4.22 (2H, m, OCH_2-C), 5.03 (1H, s, C=CH), 5.08 (1H, d, J/Hz 4, C=CH), 5.58-5.68 (1H, m, C=CH-C); ^{13}C NMR ($CDCl_3$) δ 175.3 (CO), 161.2 (=C-O), 133.7 (-CH=), 118.1 (=CH_2), 83.3 (OCH), 83.0 (CH_2=), 75.6 (OCH), 61.2 (OCH_2), 50.8 (quaternary carbon), 40.3, 31.8, 27.8, 22.5, 22.3 (CH_2), 20.9 (CH_3), 14.2 (CH_3); *m/z* 296 (M^+, 1), 281 (2), 155 (58), 142 (24), 114 (17), 95 (51), 43 (100).
8. Diastereo excess (de) was determined by the examination of ^1H-NMR spectroscopy using a chiral shift reagent (Eu(hfc)$_3$).
9. For absolute configuration, see Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.*, **1984**, 106, 2718.
10. Formation of *R*-configuration, in contrast to the case of Table III, is due only to the CIP selection rules, and not to the steric course of the reaction.

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