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DIASTEREOSPECIFIC ADDITION OF ORGANOMETALLICS TO (S)-2-ALKOXY-1-(1,3-DITHIAN-2-YL)-1-PROPANONES AND ITS APPLICATION TO THE SYNTHESIS OF (-)-TRACHELANTHIC ACID

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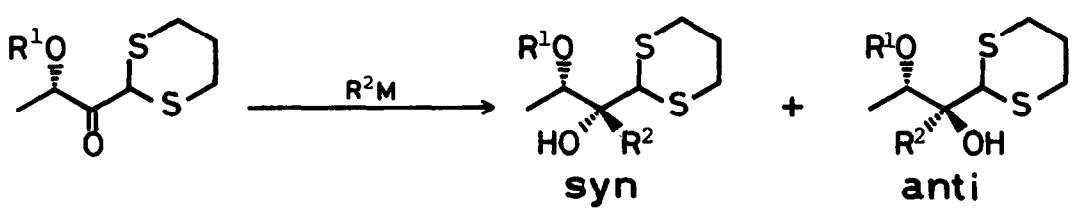
Summary: *Nucleophilic addition of organometallics to (S)-2-alkoxy-1-(1,3-dithian-2-yl)-1-propanones afforded preferentially (1R,2S)-2-alkoxy-1-alkyl-1-(1,3-dithian-2-yl)-1-propanols. The utility of the present reaction was demonstrated in the synthesis of (2R,3S)-trachelanthic acid.*

1,2-Asymmetric induction by nucleophilic addition of organometallics to chiral α-alkoxy carbonyl compounds has provided the efficient methods for the synthesis of chiral 1,2-diol derivatives. The stereochemistry of the adducts is generally explained by Cram's chelation model or non-chelation (Felkin-Anh or Conforth) model, which depends on the nature of organometallics and the protecting group of α-hydroxyl group employed.[1,2] Although the coordination ability of the sulfur atom in 1,3-oxathiane ring is known to be lower than that of the oxygen atom,[3] α-alkylthio carbonyl compounds are also capable of chelation or non-chelation control by changing nucleophilic reagents and / or Lewis acidic additives.[4] Recently we have observed unusual diastereoselective reduction of (S)-1-(1,3-dithian-2-yl)-2-hydroxy-1-propanone (**1d**) to *syn*-**4d** with zinc borohydride[5,6] which is well known to be an effective chelating hydride reagent to furnish *anti*-diols.[7] Herein, we wish to describe diastereospecific addition of organometallics to **1** leading into *syn*-1,2-diol derivatives of **2** and **3** with a chiral quaternary carbon, and its application to enantioselective synthesis of (-)-trachelanthic acid (**9**).

Optically active (S)-2-alkoxy-1-(1,3-dithian-2-yl)-1-propanones **1a ~ c** were prepared by the reaction of the corresponding O-protected methyl (S)-lactate with 2-lithio-1,3-dithiane in THF at -90 ~ -30 °C for 3 h in 48, 70, and 76%



1a: R^1 = $Me_2{}^tBuSi$
b: R^1 = MeO~O~
c: R^1 = $PhCH_2$
d: R^1 = H

2a ~ d R^2 = Me
3a ~ d R^2 = ^iPr
4d R^2 = H

yields, respectively. For the protecting group R^1 in keto dithianes **1**, t-butyldimethylsilyl, methoxyethoxymethyl and benzyl ones were chosen and **1a ~ c** were alkylated with several kinds of methyl- and isopropylmetals to give the corresponding tertiary carbinols, **2** and **3**, as listed in Table 1. The *syn* and *anti* stereochemistry of methylated product **2a** was determined by converting **2a** *via* **2d** into ethyl (2R,3S)-2,3-O-isopropylidene-2,3-dihydroxy-2-methylbutanoate (**7**) and its isomer of which ^{1}H-NMR spectra and GLC analysis were compared with those of a racemic authentic sample prepared from ethyl tiglate *via* osmium tetroxide oxidation.[8] Conversion of **2b** into **2d**, **2d** into **2c** defined the stereochemistry of those addition products. The absolute configuration of **3** was ascertained by the synthesis of (-)-trachelanthic acid (**9**) *via* **8** (*vide infra*), which also proved no racemization during the process from (S)-lactate.

t-Butyldimethylsilyl group is frequently employed as a protecting group to be incapable of chelation.[9,10] Thus, methylation of **2a** with methyllithium and cerium reagent gave expectedly non-chelation product of *syn*-**2a** (entries 1 and 2). Both methyl Grignard reagent and methyltitanium triisopropoxide, however, gave *anti*-**2a** (entries 3 and 4). The latter result was in sharp contrast to that obtained in the reaction of methyltitanium triisopropoxide with 2-t-

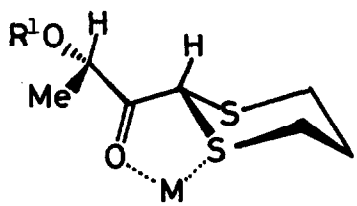
Table 1. Addition of Organometallics (R^2M) to Ketone **1a ~ d**

Entry	Ketone	R^2M[a]	Solvent	Temp (°C)	Time (h)	Product	Yield[b] (%)	*syn* : *anti*
1	**1a**	MeLi	Et_2O	-78→ rt	17	**2a**	40	80 : 20[c]
2		$MeCeCl_2$	THF	-78→ 0	24		67	94 : 6[c]
3		MeMgBr	THF	-78→-50	5		86	35 : 65[c]
4		$MeTi(O^iPr)_3$	CH_2Cl_2	rt	72		40	19 : 81[c]
5		^iPrLi	Et_2O	-78→-15	5	**3a**	74	97 : 3[c]
6		$^iPrCeCl_2$	THF	-78→ rt	15		65	97 : 3[c]
7	**1b**	MeLi	Et_2O	-78→-20	6	**2b**	81	94 : 6[d]
8		$MeCeCl_2$	THF	-78→ 0	18		20	79 : 21[d]
9		$MeMgBr\text{-}ZnCl_2$	Et_2O	-78→ 0	48		37	55 : 45[d]
10		^iPrLi	Et_2O	-78→ rt	50	**3b**	11	>98 : <2[d]
11		$^iPrCeCl_2$	THF	-78→ rt	30		30	>98 : <2[d]
12	**1c**	MeLi	Et_2O	-78→-60	4	**2c**	95	99 : 1[c]
13		MeLi	THF	-78→ -5	10		27	75 : 25[c]
14		MeMgBr	THF	-78→ rt	7		75	37 : 62[c]
15		^iPrLi	Et_2O	-78→ rt	18	**3c**	36	83 : 17[c]
16		$^iPrCeCl_2$	THF	-78→-60	5		83	86 : 14[c]
17	**1d**	MeMgBr	THF	-78→-30	9	**2d**	26	68 : 32[c]

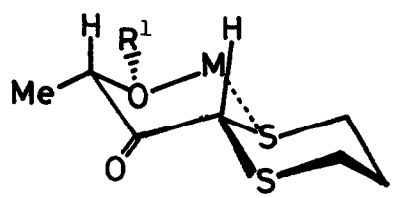
[a] All reactions were performed using 1.2 ~ 1.5 equiv of R^2M except entry 14 (2.2 equiv. of MeMgBr). [b] Isolated yield. [c] Determined by separation of each diastereomer by silica gel TLC (hexane : AcOEt = 6 : 1). [d] Determined by ^{1}H NMR.

butyldimethylsiloxy-3-pentanone leading exclusively to the corresponding *syn* product reported by Reetz and Hüllmann.[10] Whereas the protecting groups in 1 were capable of chelation, *i.e.*, methoxyethoxymethyl and benzyl ones,[12,13,14] methyllithium, Grignard reagent, Grignard reagent-zinc chloride[13] and cerium reagent preferred *syn*-**2b** and **2c** similarly in the reaction with **1a** (entries 7, 8, 9, and 12 except entry 14). Of methylmetals investigated, methyllithium or methylcerium reagent, prepared from methyllithium and cerium trichloride,[11] showed good diastereofacial selectivity of over 94% in the reaction with **1a ~ c** (entries 2, 7, and 12). Expecting predominant formation of *anti*-**2d** through Cram's chelation model by α-chelation between magnesium-alkoxy moiety and carbonyl oxygen, excess Grignard reagent was used in the reaction with **1d**, however, it resulted in *syn* preference (entry 17). Isopropylation by isopropyllithium or cerium reagent caused better *syn*-selectivity in the reaction with **1a** and **1b** than methylation (entries 5, 6, and 11), however, it was reverse in the case of **1c** (entries 12 and 15). In the case of methylation of **1c** with methyllithium, ether was much superior to THF in respect to both yield and selectivity (entries 12 and 13).

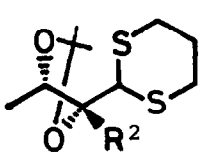
The *syn* preference in the addition to **1** can be rationalized by the following model **A** or **B**, in which the addition to ketone is assumed to proceed from the less encumbered side of the axial C_2 hydrogen in the dithiane.[3] When the alkoxy group is incapable of chelation (*e.g.* t-butyldimethylsiloxy), five-membered chelation with the carbonyl oxygen and the sulfur in the dithiane ring in **A** makes the ether oxygen and the another non-coordinated sulfur the "Large" substituents in Felkin-Anh model to give *syn* product. In model **B**, chelation with the ether oxygen and the sulfur in the dithiane forms a stable six-membered chelate with equatorial methyl group and the attack to ketone from the side of the two axial hydrogens provides also *syn* products. These two models can explain *syn* preference whether the protecting group R^1 is capable or incapable of chelation. It might be also possible to form two five- and six-membered chelate rings as combination of **A** and **B**.



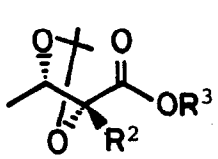
A



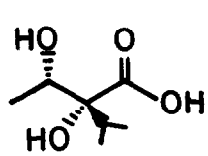
B



5 R^2 = Me
6 R^2 = ^{i}Pr



7 R^2 = Me, R^3 = Et
8 R^2 = ^{i}Pr, R^3 = H



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The above *syn* selective addition was applied to the enantioselective synthesis of (2R,3S)-(-)-trachelanthic acid (9), the necic acid of indicine N-oxide which shows marked antitumor effects.[15,16] Desilylation of pure *syn*-(1R,2S)-3a, prepared by the reaction of (S)-1a with isopropyllithium (entry 5 in Table 1), with hydrofluoric acid and protection with dimethoxypropane gave acetonide 6 in 96% yield. Hydrolysis of dithiane[17] and oxidation with pyridinium dichromate gave the corresponding acid 8 in 77% yield; $[\alpha]_D^{23}$ +36.0° (c 1.15, EtOH), lit.[15] $[\alpha]_D^{25}$ +36.0° (c 0.31, EtOH); mp 52 ~ 54 °C, lit.[15] mp 55 ~ 56 °C. On treatment with trifluoroacetic acid, acid 8 quantitatively gave (2R,3S)-(-)-trachelanthic acid (9); $[\alpha]_D^{23}$ -4.3° (c 1.94, EtOH), lit.[15] $[\alpha]_D^{25}$ -4.8° (c 1.85, EtOH); mp 89 ~ 90 °C, lit.[15] mp 89.5 ~ 90 °C.

Thus, the addition of organometallics to chiral 2-alkoxy-1-(1,3-dithian-2-yl)-1-alkanones provides diastereospecifically *syn*-1,2-diol derivatives with a chiral quaternary carbon, which are able to be converted to chiral polyol type natural products utilizing 1,3-dithiane group.[8,14,18]

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