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Enantioselective Hetero-Diels-Alder Reaction with Glyoxylate Catalyzed by Chiral Titanium Complex: Asymmetric Synthesis of the Lactone Portion of Mevinolin and Compactin[1]

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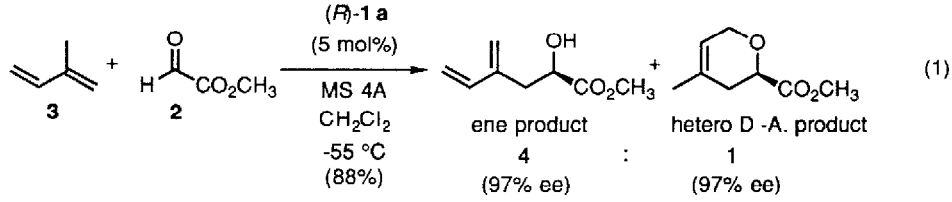
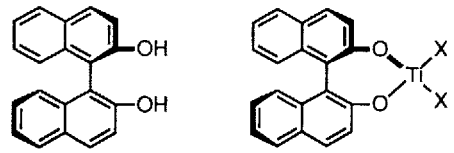
Abstract: Asymmetric Diels-Alder reaction with methyl glyoxylate catalyzed by the chiral titanium complex **1** provides the dihydropyran carboxylate in high enantiomeric purity, which can be converted to the lactone portion of mevinolin or compactin.

The development of asymmetric catalysis, particularly for carbon-carbon bond formations, is one of the most challenging and formidable endeavors in organic synthesis.[2] Recently we have reported the enantioselective carbonyl-ene reaction[3] with methyl glyoxylate (**2**) catalyzed by the chiral titanium complex of type (*R*)-**1** prepared *in situ* from $(i\text{-PrO})_2TiX_2$ and optically pure binaphthol (BINOL) in the presence of molecular sieves (MS 4A) [2e,4] In the course of studies on the asymmetric catalytic glyoxylate-ene reaction, we have found that the use of isoprene (**3**) as an ene provides not only the carbonyl-ene product but also the Diels-Alder product with extremely high enantioselectivity (eq 1). Herein we report the enantioselective hetero-Diels-Alder reaction[5] of prochiral glyoxylate **2** with methoxydienes catalyzed by the chiral titanium complex **1**.



(1)



(*R*)-BINOL (*R*)-**1** **a** (X = Cl) **b** (X = Br)

Table 1 summarizes the representative results with 1-methoxy-1,3-butadiene (**4**) as an activated diene. The chiral titanium complex **1a** was found to be an efficient asymmetric catalyst for the Diels-Alder reaction, which proceeded smoothly to give the *cis*-adduct **5a**[6] with high enantioselectivity (entry 1). No epimerization was observed at C-2 stereogenic center after

prolonged reaction (entry 2). The absolute configuration at C-6 was determined to be *R* in both **5a** and **5b** after conversion of the isomeric mixture to **5b** with $ZnCl_2$ followed by reduction to the (2*R*, 6*R*)-*trans*-alcohol **6**: $[\alpha]_D^{20}$ -119.9° (c 1 07, benzene); lit.[7] (2*S*, 6*S*)-**6**: $[\alpha]_D^{20}$ +127.7° (c 4 3, benzene). The sense of asymmetric induction is exactly the same as observed for the glyoxylate-ene reaction[2e,4]; (*R*)-**1** provides 6*R*-**5**. The dibromo catalyst **1b** affords a higher *cis*-selectivity but slightly lower enantiomeric excess, particularly in the *trans*-adduct **5b** (entry 3). An enhanced (96% ee) enantioselectivity was observed along with the increased (87%) *cis*-selectivity, when the reaction was carried out at lower temperature (entry 4)

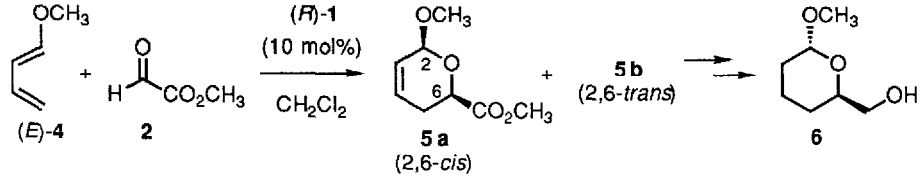
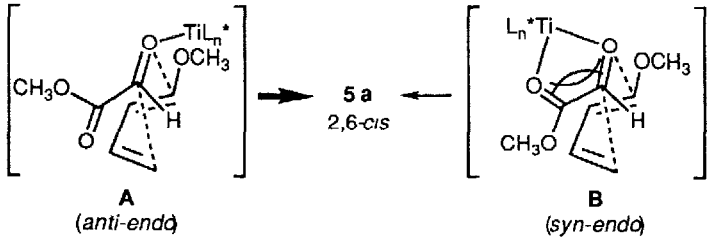


Table 1. Asymmetric hetero D.-A. reaction of **2** with **4** catalyzed by chiral titanium complex (**1**).[a]

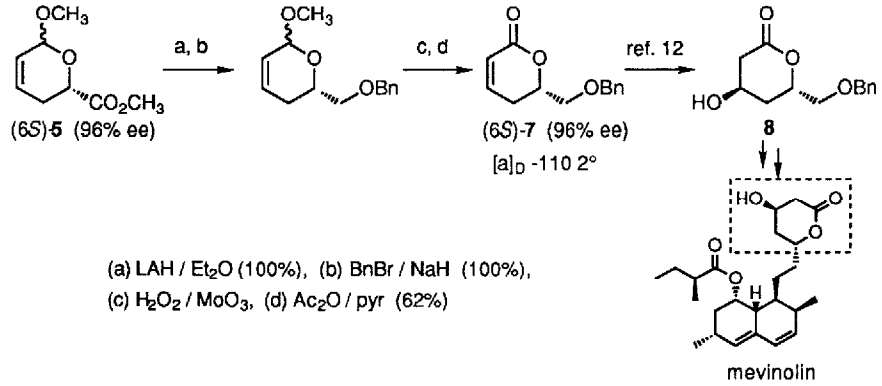
entry	catalyst	condition	yield (%)	**5a**[b] (% ee)[c]	:	**5b**[b] (% ee)[c]
1	**1a**	-30 °C, 10 min	56	78 (94% ee)	:	22 (>90% ee)
2	**1a**	-30 °C, 48 h	77	78 (94% ee)	:	22 (>90% ee)
3	**1b**	-30 °C, 1 h	88	84 (92% ee)	:	16 (50% ee)
4	**1a**	-55 °C, 1 h	72	87 (96% ee)	:	13 (>90% ee)

[a] All reactions were carried out using 1 0 mmol of **2** and 0 1 mmol of 1. [b] The 2,6-*cis/trans* ratio was determined by ^1H NMR analysis (see: ref. 6). [c] Determined by LIS-NMR analysis using (+)-Eu(DPPM)$_3$ as a chiral shift reagent.

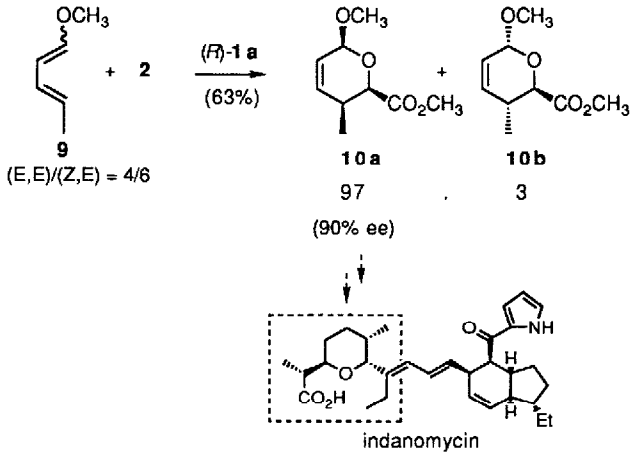
The observed *cis*-selectivity provides a mechanistic insight into the state of complexation between glyoxylate **2** and the chiral titanium catalyst **1**. Of the two transition states leading to the *cis*-product **5a**, the *syn-endo* transition state **B** should be less favorable because of the steric repulsion in the sterically demanding titanium complex. Thus, the titanium catalyst **1** should be complexed in an *anti* fashion and then the D.-A. reaction proceeds through an *endo*-orientation **A**.



The D.-A. adduct thus obtained by the use of (*S*)-**1a** can readily be converted not only to monosaccharides[8] but also to the lactone portion **8** of mevinolin or compactin[9-11] in a short step. Reduction and benzylation of ester **5** followed by oxidation catalyzed by MoO_3 and decomposition of the resulting peroxide gave the α,β-unsaturated lactone **7** in 62% overall yield along with 96% ee: $[\alpha]_D^{23}$ -110.2° (c 0 69, $CHCl_3$); lit.[12] $[\alpha]_D^{24}$ -115.1° (c 1.0, $CHCl_3$). The stereoselective introduction of hydroxy group into **7** has already been reported.[12,13] Thus, the present catalytic process is practically useful for the asymmetric synthesis of the lactone **8**.



In connection with the asymmetric synthesis of the left-wing of ionophere antibiotic indanomycin,[14] the D.-A. reaction with 1-methoxy-1,3-pentadiene (**9**) was also examined. The reaction of **2** with excess of **9** (2.5 eq) was found to proceed with high level of stereocontrol over up to three stereogenic centers to give the *cis*-adduct **10a**.



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