

Synthesis of a novel crown ether derived from *chiro*-inositol and its catalytic activity on the asymmetric Michael addition

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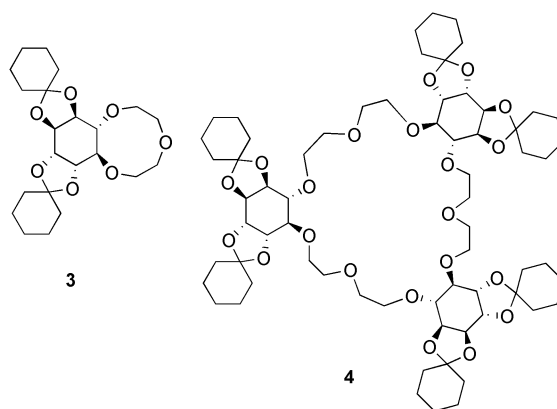
A novel 18-membered chiral crown ether was prepared in four steps starting from *L*-quebrachitol, a *chiro*-inositol, and its catalytic activity in the Michael addition reaction of glycine imine with several Michael acceptors was studied.

Development of a novel method for the preparation of amino acid derivatives has recently attracted the attention of synthetic organic chemists.¹ The base-catalyzed Michael addition reaction of glycine imine with α,β -unsaturated carbonyl compounds provides a useful method for the preparation of α -amino acid derivatives. Although chiral guanidine base catalysts² and quaternary ammonium salt catalysts³ exhibit high enantioselectivity,⁴ excellent enantioselectivity has not been observed in the chiral crown-ether catalyzed Michael reaction of glycine imines with α,β -unsaturated carbonyl compounds.^{5,6}

L-Quebrachitol is an optically active *chiro*-inositol obtained from the exudate of rubber trees and thus is naturally abundant. It has been used as a chiral pool for the enantioselective synthesis of natural products.^{7,8} We previously synthesized chiral alcohols starting from *L*-quebrachitol and applied them as chiral auxiliaries in a diastereoselective asymmetric reaction.⁹ However, to the best of our knowledge, the application of *L*-quebrachitol to an enantioselective asymmetric reaction has not been reported. Because *chiro*-inositol has C_2 -symmetry, we expected that the chiral diol derived from *L*-quebrachitol would work efficiently as a chiral diol unit in the crown ether. We have prepared a novel chiral crown ether from *L*-quebrachitol and applied it to the enantioselective Michael addition reaction.

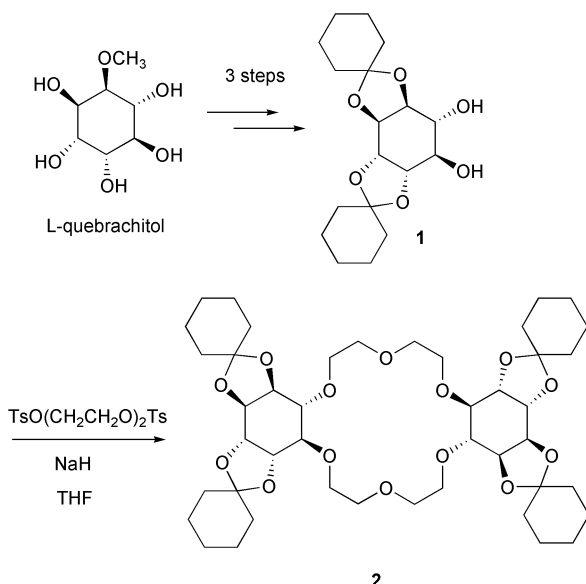
The requisite crown ether was synthesized in four steps starting from *L*-quebrachitol. A diol **1**¹⁰ was treated with diethyleneglycol di-*O*-tosylate in the presence of NaH in DMF at 120 °C for 14 h to give 18-membered crown ether **2** in 34% yield (Scheme 1) along with 4% of 9-membered crown ether **3** and 44% of 27-membered crown ether **4**. It was found that the

reaction in THF under reflux conditions improved the yield of **2** to 67%. The structures of the crown ethers were unambiguously determined by FAB mass spectroscopy.^{11,12}



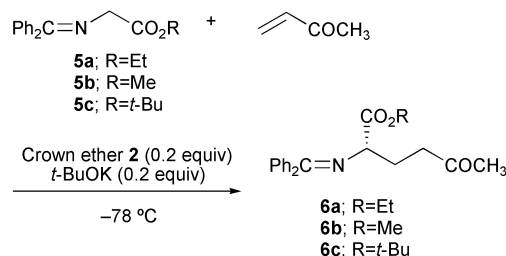
At the outset, glycine imine **5a** (1.5 equiv.) was treated with methyl vinyl ketone in the presence of the crown ether **2** (0.2 equiv) and *t*-BuOK (0.2 equiv.) to give an adduct **6a**. The results of the screening of the solvents are shown in Table 1. Although toluene gave excellent enantioselectivity, the yield was modest. CH_2Cl_2 turned out to be the most effective solvent and **6a** was obtained in 74% yield and in 91% ee at $-78\text{ }^\circ\text{C}$ for 1 h (Table 1, entry 3). The enantiomeric excess of **6a** was determined by HPLC analysis with a chiral stationary phase column (Daicel CHIRALCELL OD-H).

Study of the ester substituents revealed that the ethyl ester **5a** gave the best results. For instance, the methyl ester **5b** and *tert*-butyl ester **5c** exhibited 80% ee and 69% ee respectively,



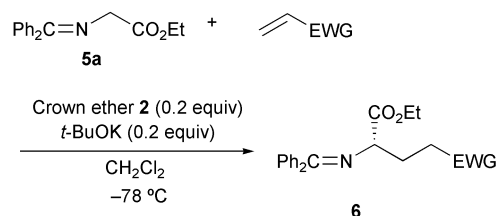
Scheme 1

Table 1 Effect of solvent on the enantioselectivity^a



Entry	Solvent	Time	Yield of 6a (%)	ee of 6a (%)
1	Toluene	1 h	32	92
2	CH_3CN^b	1 h	96	78
3	CH_2Cl_2	1 h	74	91
4	Et_2O	1 h	50	82
5	THF	1 h	45	87

^a Methyl vinyl ketone and **5a** (1.5 equiv.) were treated with **2** (0.2 equiv.) and *t*-BuOK (0.2 equiv.) at $-78\text{ }^\circ\text{C}$. ^b The reaction was carried out at $-40\text{ }^\circ\text{C}$.

Table 2 Results of the Michael reaction^a

Entry	EWG	Time	Yield (%)	ee ^b (%)
1	COCH ₃	15 min	80	90
2	COEt	15 min	65	96
3	CO ₂ Me	1 d	77	80
4	CO ₂ Et	1 d	76	87
5	CO ₂ ^{<i>t</i>} -Bu	3 h	80	82
6	CN	1 d	70	46

^a 1.5 equiv. of electrophile based on **5a** was employed. ^b Enantiomeric excess was determined by HPLC analysis with a chiral stationary phase column (Daicel CHIRALCELL OD-H).

whereas the ethyl ester **5a** gave 91% ee. The absolute configuration of **6c** was determined to be *S* by comparison of the optical rotation of the adduct **6c** with the literature data.^{5,13} By analogy the absolute stereochemistries of **6a** and **6b** were assigned to be *S*.

Next, Michael reactions of **5a** with other electrophiles (1.5 equiv.) were examined in CH₂Cl₂ at -78 °C and the results are shown in Table 2. When ethyl vinyl ketone was employed, the corresponding adduct **6** was obtained in 96% ee (entry 2). Michael reaction with acrylates also proceeded smoothly to afford diesters in high yields with high enantioselectivities (entries 3–5).

In summary, we have developed an enantioselective Michael addition of glycine imine employing a novel crown ether derived from L-quebrachitol.

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- 6c** (74% ee); $[\alpha]_{\text{D}}^{21} -52.1$ (c 1.0, CHCl₃), lit.⁵ $[\alpha]_{\text{D}}^{23} -47.9$ (c 1.15, CHCl₃) (72% ee, *S* isomer).