

Enantioselective Halocyclization Reaction using a Chiral Titanium Complex

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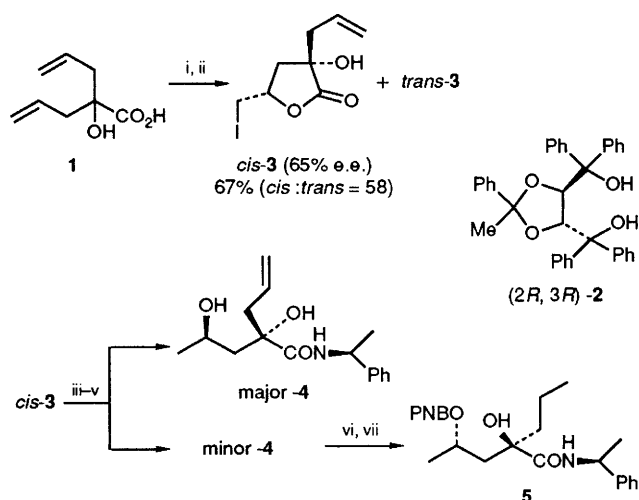
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Enantioselective halocyclizations of diallyl-2-hydroxyacetic acid **1** and 2-hydroxymethylpent-4-en-1-ol **6** have been developed using a chiral titanium complex.

Halocyclizations play an important role in the synthesis of heterocyclic intermediates and the functionalization of a double bond. A high degree of diastereoselectivity in halocyclization can be attained depending on reaction conditions and the structure of the substrate.¹ However, to date

enantioselective halocyclization has not been conducted except with substrates having chiral auxiliaries as in the case of asymmetric iodolactonization with two identical alkenic groups on chiral pyrrolidides² and asymmetric bromoetherification of pent-4-enylglycosides.³ Recently, we reported the



Scheme 1 Reagents and conditions: i, **2**, $\text{Ti}(\text{OPr})_4$, pyridine, I_2 , CH_2Cl_2 , $-78-0^\circ\text{C}$; ii, *p*-TsOH, benzene, reflux; iii, Bu^n_3SnH , azoisobutyronitrile, benzene, reflux; iv, (*S*)-PhCH(NH₂)Me, Me_3Al , benzene, reflux; v, separation by medium pressure liquid chromatography (MPLC); vi, H_2 , Pd-C, MeOH; vii, *p*-NO₂C₆H₄CH₂Cl, pyridine, CH_2Cl_2 ; (PNBO = *p*-nitrobenzoyl)

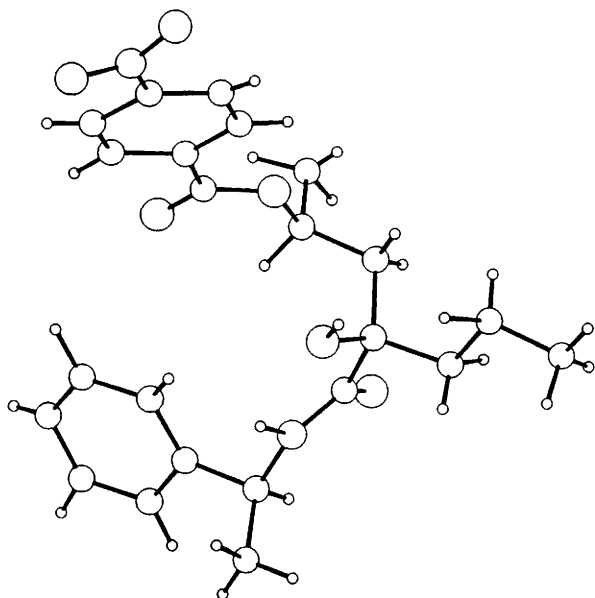
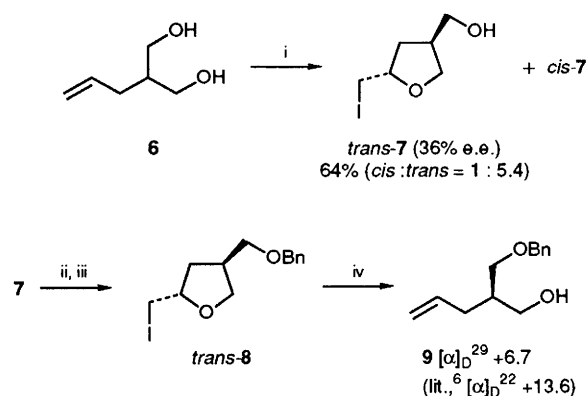


Fig. 1 Perspective view of the molecular structure of **5**

remarkable changes in stereoselectivity in the halocyclization of pent-4-enoic acids and pent-4-en-1-ol having a polar substituent at C-2, which was achieved by the addition of $\text{Ti}(\text{OPr})_4$.⁴ It was suggested that bidentate bonding of the substrate with Ti^{IV} regulates the stereoselectivity in that reaction. We anticipated that enantioselective halocyclization may be possibly carried out if such a Ti^{IV} complex possesses an additional chiral ligand. In this paper, we report the enantioselective iodocyclization by distinguishing between two identical functional groups of prochiral (σ -symmetric) substrates, diallyl(hydroxy)acetic acid **1** and 2-hydroxymethylpent-4-en-1-ol **6**[†] using chiral titanium complex.

The iodolactonization of the chiral titanium complex prepared *in situ* from $\text{Ti}(\text{OPr})_4$, **1** and the chiral 1,4-diol **2**⁵ as a chiral ligand with I_2 in the presence of 1 mol equiv. of pyridine



Scheme 2 Reagents and conditions: i, L-(+)-DIPT, $\text{Ti}(\text{OPr})_4$, pyridine, I_2 , CH_2Cl_2 , -78°C –room temp.; ii, NaH, PhCH₂Br, tetrahydrofuran (THF); iii, separation by MPLC; iv, Mg, THF, reflux; (Bn = benzyl)

gave a mixture of iodolactone **3** and isopropyl 2-allyl-2,4-dihydroxy-5-iodopentanoate formed through ester exchange of **3**.[‡] Compound **3** was obtained in 67% yield after treating the reaction mixture with *p*-TsOH in benzene. The enantiomeric excess (e.e.) of the major *cis*-iodolactone **3** was 65% as confirmed by the ¹H NMR spectrum with Eu(hfc)₃.[§] The absolute stereochemistry of the major enantiomer of *cis*-**3** was determined to have the (3*S*,5*S*)-configuration by X-ray crystallographic analysis of the *p*-nitrobenzoate **5** derived from the minor enantiomer of *cis*-**3**, as shown in Scheme 1. The molecular structure of **5** is presented in Fig. 1.[¶] It is noted that the Ti^{IV} -mediated iodolactonization of **1** as described above provided the iodolactone **3** in high 1,3-*cis* selectivity (*cis/trans* = 58), while **3** was obtained in low selectivity (*cis/trans* = 1.4) by a standard procedure (I_2 , CH_2Cl_2 , $-78-0^\circ\text{C}$).

On the other hand, the iodoetherification of the chiral titanium complex prepared *in situ* from $\text{Ti}(\text{OPr})_4$, **6** and L-(+)-diisopropyl tartrate (DIPT) as a chiral ligand in the presence of 1 mol equiv. of pyridine gave the *trans*-tetrahydrofuran derivative **7** preferentially in 64% yield (*trans*:*cis* = 5.4). The 36% e.e. of the *trans* isomer of **7** was determined by ¹H and ¹⁹F NMR spectra of the corresponding α -methoxy- α -(trifluoromethyl)phenylacetic acid ester. The (2*S*,4*S*)-configuration of the major *trans*-**7** was confirmed by its conversion into the known compound **9** (Scheme 2).⁶ With regard to the

[‡] A typical experimental procedure is as follows: to a solution of $\text{Ti}(\text{OPr})_4$ (0.3 ml, 1 mmol) in CH_2Cl_2 (3 ml) was added a CH_2Cl_2 solution (2 ml) of **2** (528 mg, 1 mmol) at room temp. After stirring for 10 min, a CH_2Cl_2 solution (2 ml) of **1** (156 mg, 1 mmol) was added, and then stirred for 10 min. After evaporation under reduced pressure (this procedure was omitted when diisopropyl tartrate was used as a chiral ligand), CH_2Cl_2 (7 ml) and pyridine (0.08 ml, 1 mmol) were added to the residual slurry, followed by I_2 (381 mg, 1.5 mmol) at -78°C . The resultant reaction mixture was stirred for 15 h at $-78-0^\circ\text{C}$, after which products were purified by the usual work-up (extraction and column chromatography).

[§] The e.e. value was also confirmed by the ¹H NMR spectrum of a diastereoisomeric mixture of the amide **4** derived from *cis*-**3** (see Scheme 1). Eu(hfc)₃ = tris[heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III).

[¶] Crystal data for **5**: C₂₃H₂₈N₂O₆, *M* = 428.48, monoclinic, space group *P*2₁, *a* = 10.358(2), *b* = 10.859(2), *c* = 10.469(1) Å, *D*_c = 1.253 g cm⁻³, *Z* = 2, *F*(000) = 456, *R* = 0.049 for 1681 reflections. The absolute configuration was determined on the basis of the *S* configuration of α -methyl benzylamine. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

[†] **1** and **6** were easily prepared by treating diethyl oxalate with allylzinc bromide followed by alkaline hydrolysis, and LiAlH_4 reduction of allylmalonate, respectively.

stereoselectivity of the iodoetherification of **6**, reaction of **6** with I₂ in CH₂Cl₂ at -78-0°C gave a 1 : 1 mixture of *cis*-**7** and *trans*-**7** in 43% yield.

In these reactions, the yield of **3** and stereoselectivity of **7** decreased without pyridine. The iodolactonization of **1** using L-(+)-DIPT and iodoetherification of **6** using **2** as a chiral ligand gave (3*S*,5*S*)-*cis*-**3** in 30% e.e., and (2*S*,4*S*)-*trans*-**7** in 22% e.e., respectively.

In conclusion, the Ti^{IV}-mediated iodocyclization of σ -symmetric substrates **1** and **6** proceed with moderate enantioselectivity in the presence of a C₂-symmetric diol as a chiral ligand.

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