Enantioselective Halocyclization Reaction using a Chiral Titanium Complex

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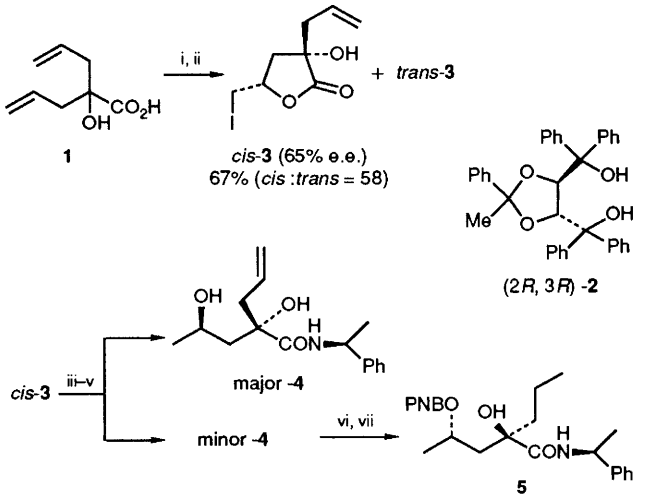
Enantioselective halocyclizations of diallyl-2-hydroxyacetic acid **1** and 2-hydroxymethylpent-4-en-1-ol **6** have been developed using a chiral titanium complex.

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 pyrrolidides[2] and asymmetric bromoetherification of pent-4-enylglycosides.[3] Recently, we reported the



Scheme 1 *Reagents and conditions*: i, **2**, $Ti(OPr^i)_4$, pyridine, I_2, CH_2Cl_2, −78–0 °C; ii, *p*-TsOH, benzene, reflux; iii, Bu^n_3SnH, azoisobutyronitrile, benzene, reflux; iv, (*S*)-$PhCH(NH_2)Me$, Me_3Al, benzene, reflux; v, separation by medium pressure liquid chromatography (MPLC); vi, H_2, Pd-C, MeOH; vii, *p*-$NO_2C_6H_4CH_2Cl$, pyridine, CH_2Cl_2; (PNBO = *p*-nitrobenzoyl)

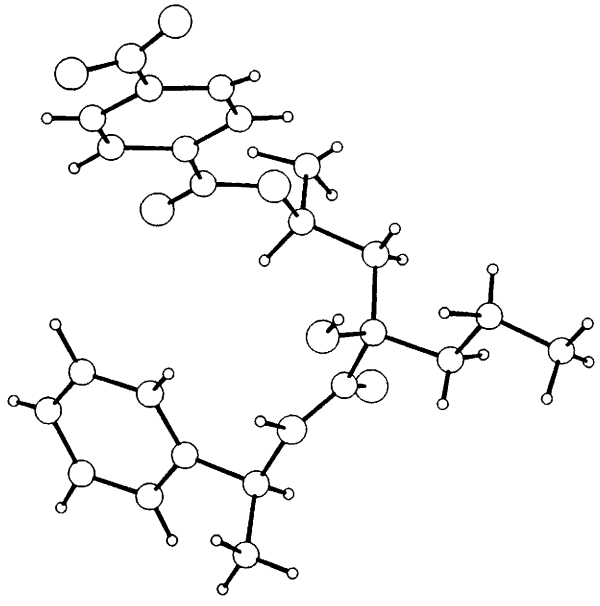
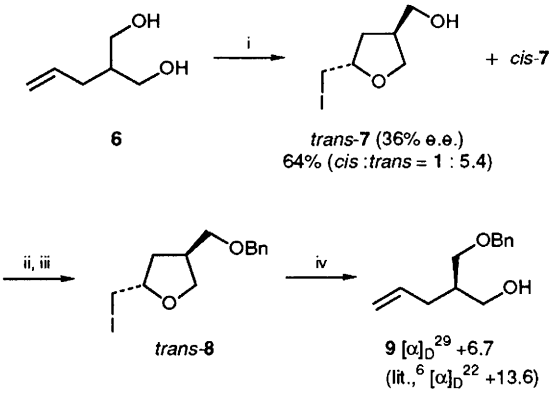


Fig. 1 Perspective view of the molecular structure of **5**

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 $Ti(OPr^i)_4$.[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 $Ti(OPr^i)_4$, **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

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



Scheme 2 *Reagents and conditions*: i, L-(+)-DIPT, $Ti(OPr^i)_4$, pyridine, I_2, CH_2Cl_2, −78 °C–room temp.; ii, NaH, $PhCH_2Br$, 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 °C).

On the other hand, the iodoetherification of the chiral titanium complex prepared *in situ* from $Ti(OPr^i)_4$, **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 ^{19}F 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 $Ti(OPr^i)_4$ (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 °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**: $C_{23}H_{28}N_2O_6$, M = 428.48, monoclinic, space group $P2_1$, 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 Crystallogrpahic Data Centre. See Notice to Authors, Issue No. 1.

stereoselectivity of the iodoetherification of **6**, reaction of **6** with I_2 in CH_2Cl_2 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 C_2-symmetric diol as a chiral ligand.

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