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Diastereoselective Iodocarbocyclization Reaction of 8-Phenylmenthyl Allylmalonate: An Efficient Preparation of a Synthetic Intermediate of Cyclopropane Amino Acids

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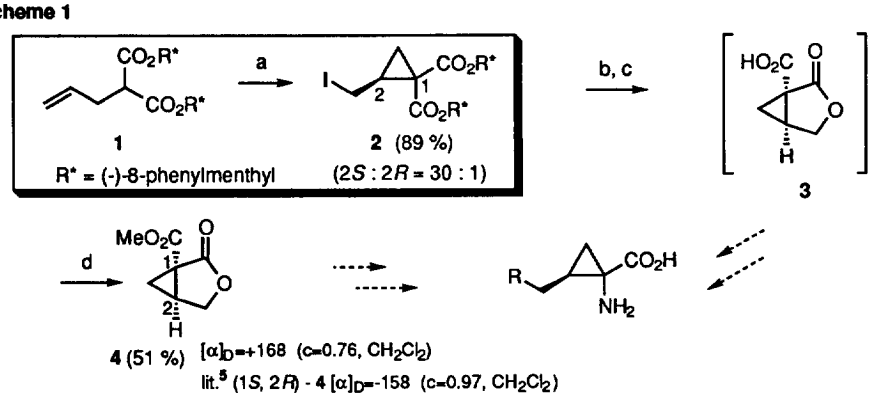
Abstract: The iodocarbocyclization of allylmalonate using (-)-8-phenylmenthol as a chiral auxiliary proceeded with high diastereoselectivity to give the iodomethylcyclopropane dicarboxylic ester in good yield.

Recently we have reported that the "iodocarbocyclization reaction" of 4-alkenyl or 4-alkynylmalonate derivatives proceeds in good yields in the presence of $Ti(OR)_4$ and I_2 to give cyclopentane derivatives in regio- and stereocontrolled manner.[1] Furthermore, we also found that the enantioselective iodocarbocyclization of 4-alkenylmalonate derivatives proceeds with moderate to high enantiomeric excess (up to 85 % ee) by treating these with I_2 and CuO in the presence of a chiral titanium alkoxide.[1d] Unfortunately, the reaction of allylmalonate using the same chiral titanium alkoxide proceeded without chiral induction to give a racemic iodomethylcyclopropane. The optically active cyclopropane derivative obtained in the present reaction should be useful as a synthetic intermediate of cyclopropane amino acids having the potential value in medicinal chemistry.[2] On the basis of consideration of transition state model, for the chiral synthesis of cyclopropane derivative, the use of a chiral auxiliary in the ester moiety may be more effective than that of chiral titanium complex.[3] In this paper, we report the result of diastereoselective iodocarbocyclization of allylmalonate derived from 8-phenylmenthol as a chiral auxiliary and transformation of the product to a synthetic intermediate of cyclopropane amino acids.

Scheme 1



a $Ti(O\text{-}t\text{-}Bu)_4$ (1 eq), I_2 (4 eq), pyridine (2eq), CH_3CN,0 °C, 20h b AgOTf (2.2 eq), *n*-Bu_2SnO (2.2 eq), DMF, r.t., 1h c 7N KOH, 70 °C, 15h d $TMSCHN_2$

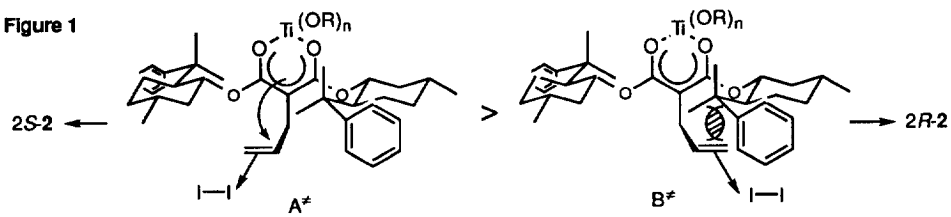
Although we have reported that the iodocarbocyclization reactions of dimethyl allyl- and prenylmalonate in the presence of I_2 and $Ti(OR)_4$ in CH_2Cl_2 gave the cyclopropane derivatives in low yields (41 % and 38 %, respectively),[1b] these reactions proceeded smoothly by addition of CuO to give the corresponding iodocarbocyclization products in good yields (96 % and 78 %, respectively). Diastereoselective

iodocarbocyclization was further examined using allylmalonates derived from the chiral alcohols under the conditions with CuO. The reaction of allylmalonate **1** with (-)-8-phenylmenthol as a chiral auxiliary proceeded with moderate diastereoselectivity (60 % de in CH_3CN, 44 % de in CH_2Cl_2), while with (-)-menthol ester, no diastereoselectivity was observed. The remarkable increase in diastereoselectivity in the reaction of **1** was possible through the use of pyridine[4] as an additive instead of CuO. In this case, iodomethylcyclopropane **2** with the 2*S* configuration was obtained in a diastereomer ratio of 30 : 1 (Scheme 1).

The stereochemistry of **2** was determined from its specific rotation value after conversion to the known bicyclic lactone **4** (Scheme 1). Lactones **3** and **4**[2d,5] are synthetic intermediates of 2,3-methanologs of protein amino acid. The present method should provide a more direct means for the synthesis of the amino acid analogs.[2]

The diastereoselectivity may be explained based on the transition structure model for the cyclopropanation of the Na enolate of 4-bromo-2-butenylmalonic acid 8-phenylmenthyl ester proposed by Quinkert *et al.*[6,7] That is, of two possible transition structures, $A^{\neq}$ should be more favourable than $B^{\neq}$, owing to steric repulsion between the dimethylphenylmethyl group and olefin part in $B^{\neq}$, to give cyclopropane derivative with 2*S* configuration (Figure 1).

Figure 1



In conclusion, this study thus demonstrates an efficient means for preparing a synthetic intermediate of cyclopropane amino acid through highly diastereoselective iodocarbocyclization.

References and Note

1 (a) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, 33, 2167-2170. (b) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, 58, 3106-3112. (c) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tearahedron Lett.* **1994**, 35, 1059-1062. (d) Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett, in press.*

2 Examples of the synthesis of cyclopropane amino acids: (a) Stammer, C. H. *Tetrahedron* **1990**, 46, 2231-2254. (b) Kodama, H.; Shimoshige, Y. *J. Synth. Org. Chem., Jpn.* **1994**, 52, 180-191. (c) Burgess, K.; Ho, K. K. *J. Org. Chem.* **1992**, 57, 5931-5936. (d) Pirrug, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv. Chim. Acta.* **1989**, 1301-1310.

3 In the transition state of the reaction of allylmalonate, the olefin moiety may be situated more closely to the ester moiety than Ti complex. See Figure 1.

4 Effective trapping of HI generated during the reaction may be indispensable to a high yield and diastereoselectivity of the relatively unstable iodomethylcyclopropane **2**, presumably under kinetic conditions.

5 Fliche, C.; Braun, J.; Goffic, F. *Syn Commun.* **1991**, 21, 1429-1432.

6 (a) Quinkert, G.; Stark, H. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 637-655. (b) Quinkert, G.; Schwartz, U.; Stark, H; Weber, W. D.; Baier, H.; Adam, F.; Dürner, G. *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 1029-1030.

7 Examples of the synthesis of optically active cyclopropanes: Salaün, J. *Chem. Rev.* **1989**, 89, 1247-1270 and references cited therein.

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