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New asymmetric transformation of optically active allene-1,3-dicarboxylate and its application to the formal asymmetric synthesis of (−)-epibatidine

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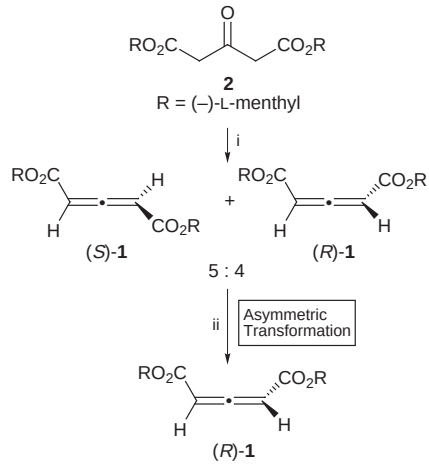
A new efficient synthesis of di-(−)-L-menthyl (*R*)-allene-1,3-dicarboxylate [(*R*)-1] involving asymmetric transformation through *epimerization–crystallization* with the assistance of a catalytic amount of Et_3N was developed; the highly *endo*-selective asymmetric Diels–Alder reaction of (*R*)-1 with *N*-Boc-pyrrole for the asymmetric synthesis of 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one [(−)-6], a synthetic intermediate of (−)-epibatidine, is described.

Allene-1,3-dicarboxylates are useful for [4 + 2] cycloaddition as dienophiles.[1] Kanematsu and his colleagues have reported the highly diastereoselective Diels–Alder reaction of cyclopentadiene with optically active dimenthyl allene-1,3-dicarboxylate **1**, which was prepared by optical resolution using crystallization from a diastereomeric mixture of di-(−)-L-menthyl allene-1,3-dicarboxylates.[2] Naruse and his colleagues recently reported the enantiomeric enrichment of allene-1,3-dicarboxylates by a chiral organoeuropium reagent.[3] For the synthesis of optically active allene, the former method using optical resolution provides a low yield (< 25%), and the latter method has major drawbacks, *i.e*. the need for an equimolar amount of expensive $Eu(hfc)_3$, and the partial decomposition of the substrate due to the long reaction times needed. Therefore, a more efficient method for the preparation of optically active allene-1,3-dicarboxylate is required. Although several crystallization-induced asymmetric transformations by racemization have been reported,[4] the asymmetric transformation of dissymmetric compounds such as allenes has not been examined. We report here a new efficient synthesis of optically active allene-1,3-dicarboxylate by asymmetric transformation through *epimerization–crystallization* with the assistance of a catalytic amount of Et_3N, and its application to the formal total synthesis of (−)-epibatidine using the Diels–Alder reaction as a key step.

Since allene-1,3-dicarboxylate is an excellent Michael acceptor,[5] the epimerization of optically active allene-1,3-dicarboxylate, which was prepared from di-L- or -D-menthyl acetone-1,3-dicarboxylate by a new method[6] using 2-chloro-1,3-dimethylimidazolinium chloride (DMC), as shown in Scheme 1, was examined in the presence of a catalytic amount of Et_3N.

Thus, an optically pure di-(−)-L-menthyl (*R*)-allene-1,3-dicarboxylate [(*R*)-**1**][2] was treated with Et_3N (0.1 equiv.) in an NMR tube to give a diastereomeric mixture of **1** (*R*:*S* = 4:5) within 30 min. This experiment shows that these diastereomers are in equilibrium in the presence of a catalytic amount of Et_3N, as shown in Scheme 2. This result suggests that crystallization-induced asymmetric transformation of **1** would be possible, since the *R* diastereomer formed good crystals.[2a]

To crystallize the *R* diastereomer, a pentane solution of a diastereomeric mixture (*R*:*S* = 4:5) of di-(−)-L-menthyl allene-1,3-dicarboxylate **1** and 0.01 equiv. of Et_3N was kept below −20 °C for 2 days. After removal of the mother liquid, the precipitated crystals were washed with cooled pentane. This crystallization procedure of the mother liquid was repeated twice. Colorless crystalline (*R*)-**1** was obtained in 90% yield (> 98% de). Similarly, the enantiomer (*S*)-**1** was also obtained

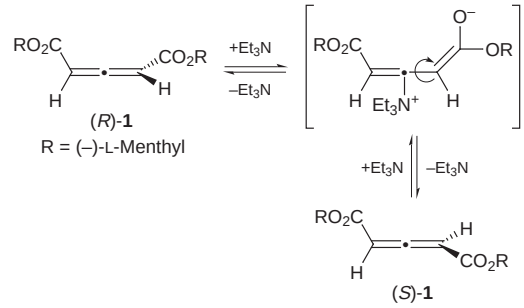


Scheme 1 *Reagents and conditions*: i, DMC, Et_3N, CH_2Cl_2, room temp., 86%; ii, Et_3N (0.01 equiv.), pentane, crystallization (×3), 90%.

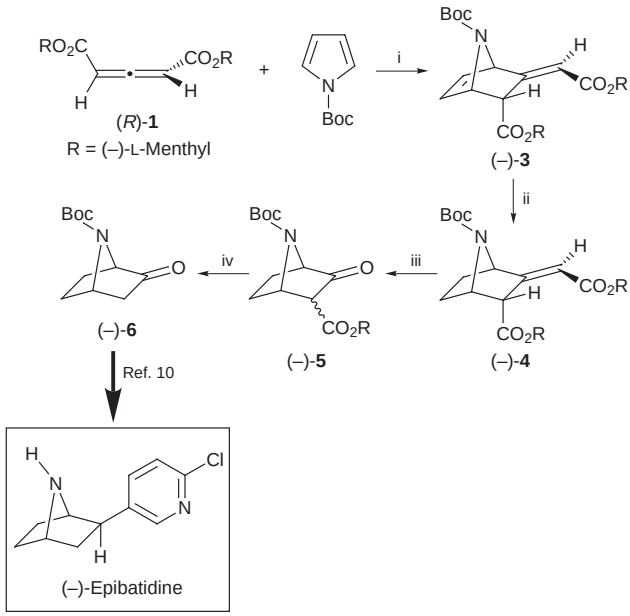
by the above asymmetric transformation using (+)-D-menthol as a chiral auxiliary.

Next, we applied di-(−)-L-menthyl (*R*)-allene-1,3-dicarboxylate (*R*)-**1** to an asymmetric synthesis of (−)-epibatidine, which was isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*, and possesses a unique 7-azabicyclo-[2.2.1]heptane skeleton and a potent non-opioid analgesic effect.[7] There have been only a few reports[8] on the asymmetric synthesis of (−)-epibatidine, although there have been many reports on its total synthesis.[9,10] We planned the asymmetric synthesis of a synthetic intermediate for (−)-epibatidine using the Diels–Alder reaction of **1** according to Kanematsu *et al*.,[2a] as shown in Scheme 3.

The Diels–Alder reaction of (±)-dimethyl allene-1,3-dicarboxylate with *N*-Boc-pyrrole (10 equiv.) gave almost equimolar amounts of the *endo* and *exo* adducts, both at a low temperature with the assistance of a Lewis acid [$AlCl_3$ (1.2 equiv.), CH_2Cl_2, −78 °C, 12 h, 73%], and at a high temperature[9d] [toluene, 90 °C, 12 h, 89%]. On the other hand, we found that the same reaction of di-L-(−)-menthyl allene-1,3-dicarboxylate (*R*)-**1** with *N*-Boc-pyrrole and $AlCl_3$ in CH_2Cl_2 at −78 °C for 13 h gave the endo adduct (−)-**3** as a sole product in 86% yield. The absolute stereochemistry of the *endo*



Scheme 2



Scheme 3 *Reagents and conditions*: i, $AlCl_3$, CH_2Cl_2, −78 °C, 13 h, 86%; ii, 10% Pd/C, H_2, EtOAc, room temp., 99%; iii, O_3, PPh_3, CH_2Cl_2, −78 °C, 52%; iv, 10% HCl, heat, then Boc_2O, Et_3N, CH_2Cl_2, room temp., 55%.

adduct (−)-**3** was elucidated by an X-ray crystallographic analysis.

The observed significant difference in *endo*/*exo* selectivity between the dimethyl ester and the di-L-(−)-menthyl ester could be explained on the basis of steric repulsion between the *N*-Boc group of the diene and the methyl or menthyl group in the dienophile **1**, based on an X-ray crystallographic analysis.[2a]

The *endo* adduct (−)-**3** was subsequently converted into a synthetic intermediate (−)-**6**[10] for (−)-epibatidine. Thus, regioselective hydrogenation of non-conjugated olefin on (−)-**3** with 10% Pd/C gave the dihydro derivative (−)-**4** quantitatively. After ozonolysis of the remaining double bond, the obtained β-keto ester **5** was subjected to hydrolysis, decarboxylation, and *N*-*tert*-butoxycarbonylation (reprotection of the deprotected secondary amine) to give (−)-**6** in moderate yield; its specific rotation {$[\alpha]_D^{17}$ −74.5 (*c* 1.02, $CHCl_3$), lit.[10a] $[\alpha]_D^{26}$ −75.1 (*c* 1.56, $CHCl_3$)} and spectroscopic data were identical to those in the literature.[10] This transformation constitutes a formal asymmetric synthesis of (−)-epibatidine.

In conclusion, we have developed the first asymmetric transformation of dissymmetric allene-1,3-dicarboxylate through *epimerization* based on addition–elimination with a tertiary amine, and a quite efficient synthesis of (−)-**6** from di-(−)-L-menthyl acetone-1,3-dicarboxylate.

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