213. High Asymmetric Induction in *Lewis* Acid-Promoted Intramolecular Ene-Type Reactions: A Diastereo- and Enantioselective Synthesis of (+)-α-Allokainic Acid

Preliminary Communication

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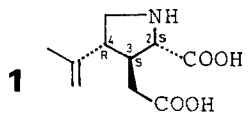
Summary

The monocyclic amino diacid (+)-α-allokainic acid **1** has been prepared enantioselectively from the ester of *cis*-β-chloroacrylic acid and (−)-8-phenylmenthol by a series of four synthetic operations in over 15% yield. The crucial step is the intramolecular 'ene-type' reaction of the (*Z*)-diene **4** which on treatment with a mild *Lewis* acid undergoes a highly accelerated, dia- and enantiostereoselective cyclization to give the pyrrolidines **6** and **7** in a ratio of 95:5 *(Scheme 3)*. Subsequent ester hydrolysis regenerates the auxiliary chiral alcohol. Similar cyclization of the (*E*)-diene **5** furnished a 15:85 mixture of **6** and **7** showing an efficient reversal of the optical induction by variation of the enoate geometry.

(+)-α-Allokainic acid, isolated from *Digenea simplex* AG., has been assigned structure **1** on the basis of chemical, chiroptic and X-ray evidence [1]. In the preceding communication we have described stereospecific routes to the (*Z*)- and (*E*)-dienes **2** (R = Et) and their efficient diastereoselective cyclization to the *trans*-

Scheme 1



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substituted pyrrolidine **3** (R = Et) in the presence of diethylaluminum chloride [2] *(Scheme 2)*. In view of the simple and stereoselective conversion (±)-**3** (R = Et) → (±)-**1** [3] we turned our attention to the possibility of carrying out the crucial ene reaction in an enantioselective manner. This perspective seemed to be of general interest in synthesis since very little is known about asymmetric induction in ene reactions[1]). First the esters derived from (−)-menthol, (*Z*)-**2** (R = menthyl)[2]) and

[1]) We only know about one study allowing recyclization of the chirality directing group which deals with the *Lewis*-acid catalyzed addition of menthylglyoxalate to 1-pentene; the corresponding adducts were obtained in only modest optical yields in spite of wide variations of temperature, solvent and catalyst [4].

[2]) IR., ^{1}H-NMR. ($CDCl_3$) and MS. are in full agreement with the assigned structure.

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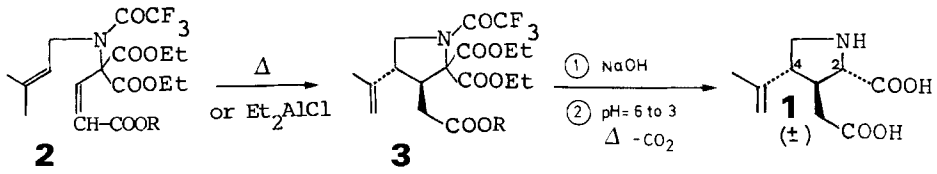
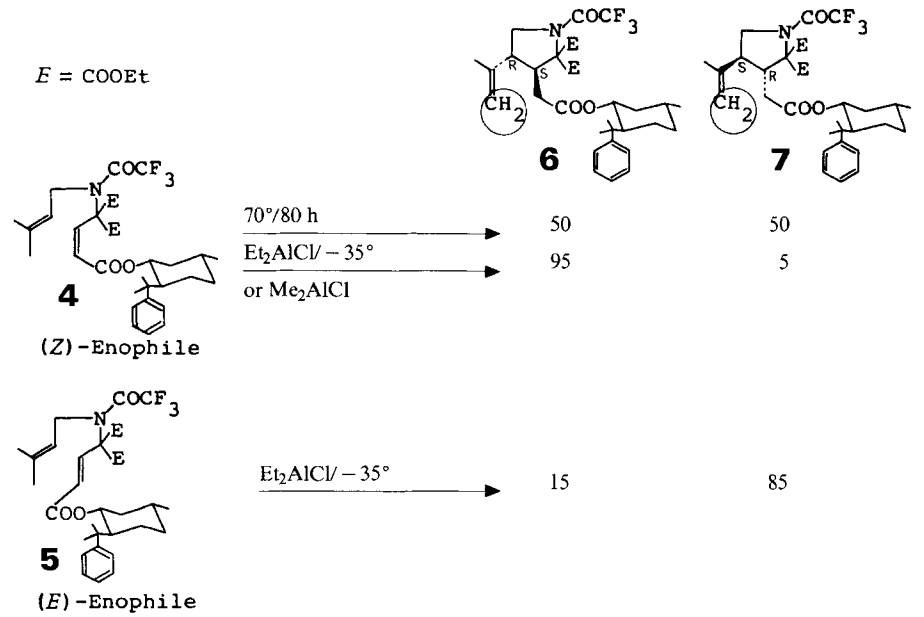
Scheme 2



(*E*)-**2** (R = menthyl)[2]) were prepared by analogy to the preparation of the (*Z*)- and (*E*)-dienes **2** (R = Et)[3]) [2]. Disappointingly, thermal and Et_2AlCl-mediated cyclizations of the (*Z*)- and (*E*)-dienes **2** (R = menthyl) led to little if any ($\leq 18\%$ e.e.) optical induction at the newly formed centers of **3** as shown by NMR. evidence. Then, in view of the known asymmetric *Diels-Alder* additions of 8-phenylmenthyl acrylates [6] we envisaged 'ene-type' cyclizations of the dienes **4** and **5**. (−)-8-Phenylmenthol [6], prepared from natural (+)-pulegone, was esterified[3]) with *cis*- and *trans*-*β*-chloroacrylic acid. In analogy to previous work [2] the resulting (*Z*)-ester was converted to the (*Z*)-diene **4**[2]) ($[\alpha]_D^{23°} = +9.1°$ ($c = 1.4$, $CHCl_3$) in 40% overall yield. Similarly, the (*E*)-*β*-chloroacrylic ester was transformed into the (*E*)-diene **5**[2]) (60% overall yield). Heating the (*Z*)-diene **4** at 70° for 80 h gave a 1:1 mixture[2]) of the diastereoisomers **6** and **7** *(Scheme 3)*[4]), readily assessed by 360 MHz. – ^{1}H-NMR. evidence which shows the two singlets of the olefinic protons

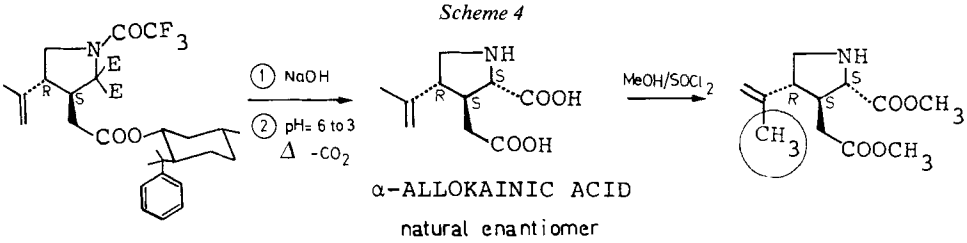
Scheme 3



[3]) The starting esters were obtained by treatment of the corresponding alcohol with *cis*- and *trans*-*β*-chloroacrylic acid and dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine [5].

[4]) On thermolysis of **4** the *trans*-products **6** + **7** were obtained together with the corresponding *cis*-isomer pair in a ratio of 4:1.

Scheme 4



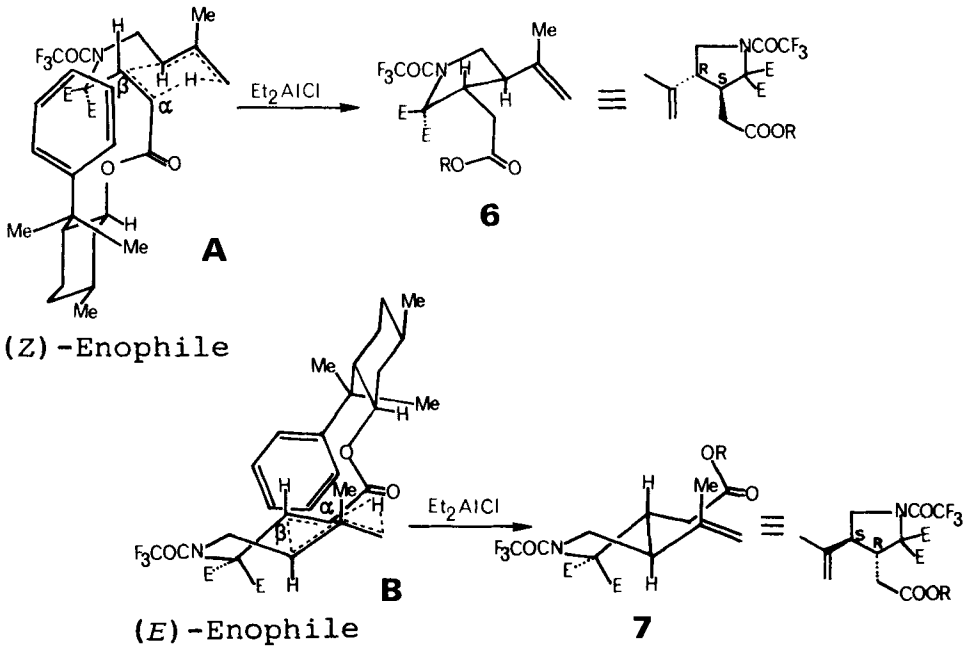
at 4.83/4.90 ppm for **6** and at 4.96/5.02 ppm for its isomer **7**. On the other hand, we were delighted to find that treatment of the (*Z*)-phenylmenthyl ester **4** with 3 mol-equiv. of Et_2AlCl or Me_2AlCl in dry CH_2Cl_2 at $-35°$ for 18 h furnished the isomers **6** and **7** in a ratio of 95 : 5 (60% chemical yield). This assignment is based on the conversion of this mixture to (+)-*α*-allokainic acid (**1**), carried out in the following manner *(Scheme 4)*. Saponification (2 N NaOH/EtOH 1:1, 100°, 20 h) furnished on extraction the unchanged starting (−)-8-phenylmenthol. Successive decarboxylation of the non-isolated malonic acid at pH = 6 to 3, precipitation of the copper salt of **1** ($Cu(OAc)_2$, 100°, 30 min) and its decomposition with H_2S in water gave the enantiomerically pure (+)-*α*-allokainic acid (**1**) in 73% yield from **6**. The synthetic and natural amino acids **1** were shown to be identical and enantiomerically pure by their conversion to the dimethylester **8** ($MeOH/SOCl_2$) [7] and subsequent comparison of the chromatographic properties, IR. and ^{1}H-NMR. spectra particularly using a chiral shift reagent[5]). The strikingly high asymmetric induction in the Et_2AlCl-promoted 'ene-type' reaction **4**→**6** agrees nicely with a transition state geometry resembling **A** *(Scheme 5)*. Invoking antiplanar conjugated $C_\alpha = C_\beta$/C=O bonds and a synplanar arrangement of the alkoxy H-atom and the carbonyl O-atom in **4**[6]) the phenyl group is smoothly positioned over the enophile double bond. In support of this conformation, the phenylmenthyl ester **4** shows in the ^{1}H-NMR. spectrum the signal of H–C_α shifted up-field by 1.01 and 1.04 ppm from its position in the (*Z*)-esters **2** (R = Et) and **2** (R = menthyl). Association of the acrylate unit with the *Lewis* acid may lead to a charge-transfer complex which could account for the slower cyclization of **4** in comparison with the (*Z*)-ethyl- and menthyl esters **2**. The *si*-face of the enophile-C_β being blocked by interaction with the phenyl group, attack of the ene is therefore directed to the C_β-*re*-face in agreement with experiment. Similar stereochemical analysis of the *Lewis*-acid induced cyclization of the (*E*)-phenylmenthyl ester **5** (conformation **B**) predicts shielding of the enophile-*re*-face by the phenyl group and, consequently, ene-attack from the *si*-face. Indeed, treatment of **5** with Et_2AlCl (3 mol-equiv., CH_2Cl_2, $-35°$, 18 h) gave the *trans*-isomers **6** and **7** in a ratio of 15 : 85[7]) in perfect agreement with our

[5]) The ^{1}H-NMR. spectrum of racemic **8** after addition of tris(3-trifluoroacetyl-d-camphorato)-europium(III) shows the signals of the olefinic protons, one carbomethoxy- and the olefinic methyl group corresponding to the two antipodes well separated. Under these conditions (controlled by admixture of racemic **8**) both samples of **8** either derived from **6** or of natural origin displayed only the signals of the antipode which appear at lower field.

[6]) Such a conformation is assumed to be the preferred one in acrylates derived from secondary alcohols [8]. See also the rationalization proposed for asymmetric *Diels-Alder* reactions (s. [9]).

[7]) The corresponding *cis*-products were not formed according to ^{1}H-NMR. evidence.

Scheme 5



prediction. In summary, the cyclizations **4**→**6** and **5**→**7** are the first examples of 'ene-type' reactions proceeding with high asymmetric induction, allowing recyclization of the chirality directing group. This together with the possibility to manipulate the absolute sense of induction by variation of the enoate geometry may prove of further value in synthesis. Further exploration of these findings and the implied reaction mechanism are presently under study in our laboratory.

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