

## Section Chemical Research of the NSCS

### A Selection of Papers Presented at the Fall Meeting of the New Swiss Chemical Society (NSCS) in Basel, November 21, 1996

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### Synthesis of Non-proteinogenic Amino-Acid Methyl Esters with Acid-Sensitive Side Chains from a Chiral Glycine Derivative<sup>a)</sup>

Matthias Hoffmann [1] and Dieter Seebach\*

**Abstract.** A superior chiral glycine derivative **1** (*tert*-butyl 2-(*tert*-butyl)-4-methoxy-2,5-dihydro-1,3-imidazole-1-carboxylate, BDI) for the synthesis of acid-sensitive and highly hindered  $\alpha$ -amino-acid methyl esters is readily available by resolution methods. The heterocycle **1** is alkylated once and twice in the 5-position with very high diastereoselectivity, and the resulting products (**2**, **3**) are hydrolyzed under very mild conditions to give methyl esters of the corresponding amino acids (**6–10**).

The synthesis of non-proteinogenic amino acids has been a major research area of our group for many years. Our contribution to this field has recently been reviewed [2]. We reported on the preparation of the new chiral glycine building block **1** in 1993 [3]. The advantage of **1**, over previously studied glycine derivatives [2], for amino-acid synthesis is that its products of alkylation and hydroxyalkylation (in the 5-position) are hydrolyzed to amino-acid methyl esters under very mild conditions. We have now im-

proved the preparation of **1** in an enantiomerically pure form and applied it for the preparation of highly hindered and of acid-sensitive non-proteinogenic amino-acid esters.

The heterocycle *rac*-**1** can be prepared in four steps from glycinamide hydrochloride as reported previously [3]. Our preferred approach for the preparation of the dihydroimidazole **1** in an enantiomerically pure form is outlined in *Scheme 1*. Resolution of the racemic 2-(*tert*-butyl)-tetrahydro-1,3-imidazol-4-one can be

achieved via two consecutive crystallizations of diastereoisomeric salts (the enantiomer of **1** is likewise accessible by using the corresponding chiral acids).

Besides this route, we have also used preparative chromatographic resolution of **1** and *ent*-**1** by high-performance liquid chromatography on a chiral stationary phase [4][5].

With the dihydroimidazole **1** available, we have investigated its use for the synthesis of amino-acid esters. Alkylation of **1** via its Li derivative gave the products **2** in a diastereomerically pure form (*Scheme 2* and *Table 1*) – we have no indication for the formation of the other diastereoisomer. The monoalkylation is so clean that it is possible to carry out a second alkylation *in situ*, which leads to the products **3**, once again in high yields and with the formation of only one diastereoisomer (*Table 2*). We have demonstrated [1][3] by chemical correlation with known amino acids and by NMR spectroscopy of products of type **2** and **3** that the alkylations proceed *trans* to the *tert*-butyl

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<sup>a)</sup> These results were presented as a poster at the autumn meeting of the New Swiss Chemical Society (NSCS) in Basel, Switzerland, on November 21 1996.

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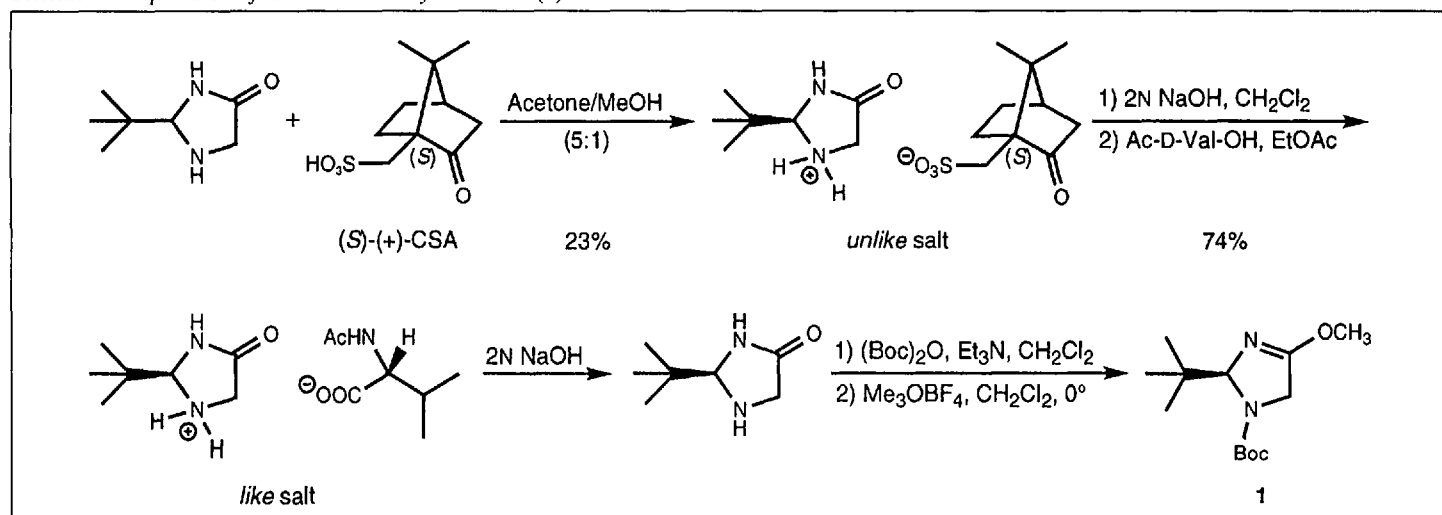
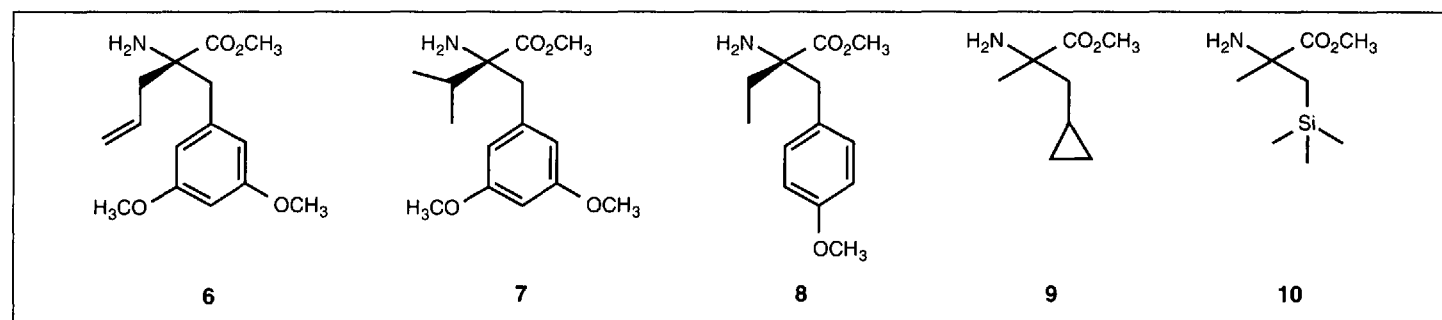
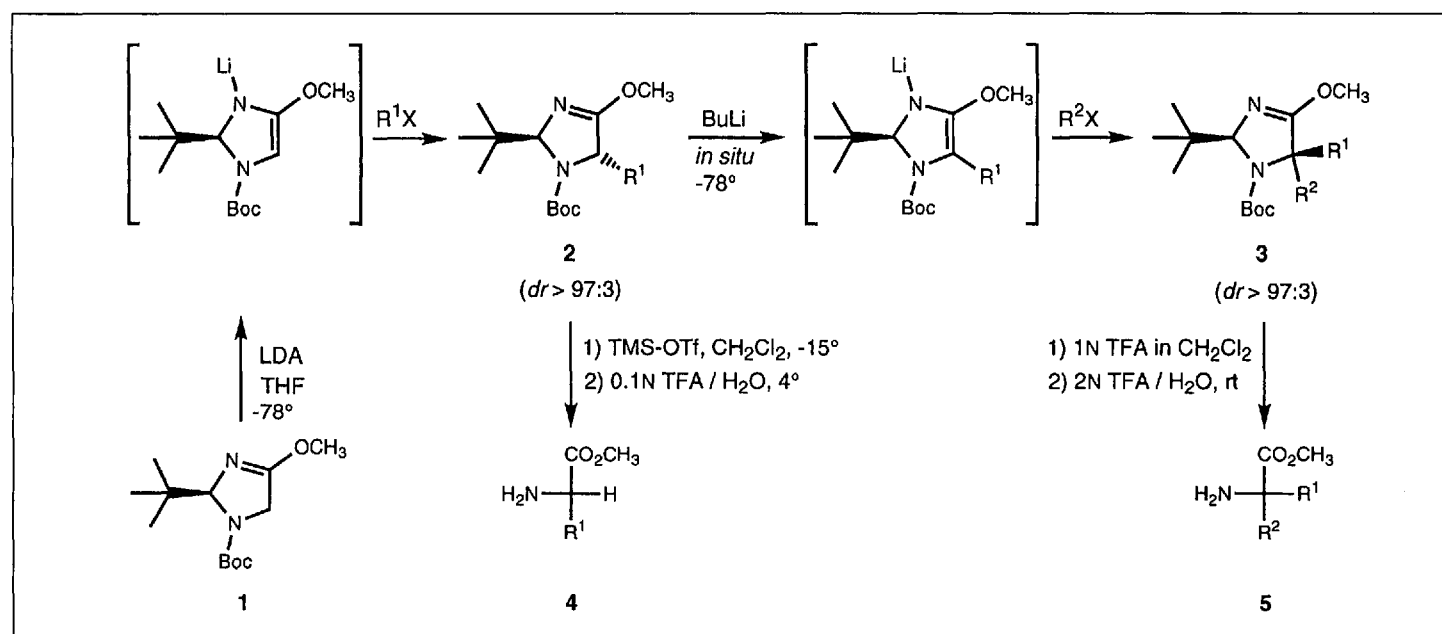
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Scheme 1. Preparation of Enantiomerically Pure BDI (1)

Scheme 2. Alkylations of BDI to give Mono- and Geminally Disubstituted Derivatives 2 and 3, and Conditions for the Hydrolysis to  $\alpha$ -Amino-Acid Methyl Esters

group on the five-membered ring (see the Li-enamines in Scheme 2).

The mono- and disubstituted derivatives 2 and 3 were hydrolyzed to the corresponding amino-acid methyl esters 4 and 5 using mildly acidic conditions. A number of  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino-acid esters 6–10 has been synthesized by this method (these compounds have been dif-

ficult or impossible to make using our previous oxazolidinone and imidazolidinone building blocks [2] or other literature procedures).

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[1] Part of the projected Dissertation of M.H., ETH-Zürich.

[2] D. Seebach, A.R. Sting, M. Hoffmann, *An-*

*gew. Chem.* **1996**, *108*, 2880; *ibid. Int. Ed.* **1996**, *35*, 2708.

[3] S. Blank, Dissertation No. 10193, ETH-Zürich, Switzerland, 1993; S. Blank, D. Seebach, *Angew. Chem.* **1993**, *105*, 1780; *ibid. Int. Ed.* **1993**, *32*, 1765.

[4] D. Seebach, M. Hoffmann, E. Küsters, E. Schmid, *Chirality*, submitted.

[5] D. Seebach, A.R. Sting, M. Hoffmann, J.N. Kinkel, M. Schulte, E. Küsters, *J. Chromatogr. A*, in preparation.

Table 1. Electrophiles Used for the Alkylation of 1 and Yields of Products of Type 2 (after chromatography)




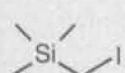
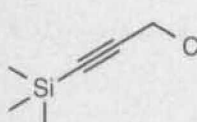

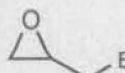
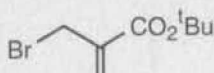

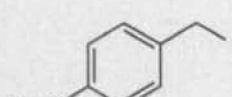
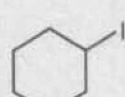
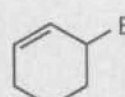
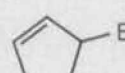
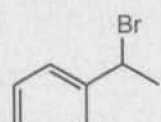

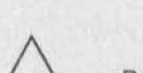
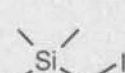
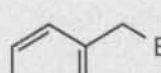
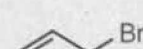
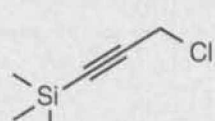
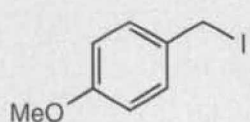

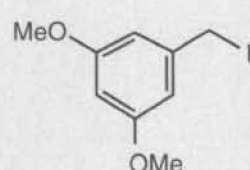

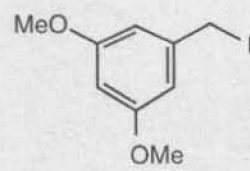

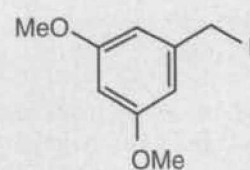
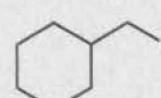
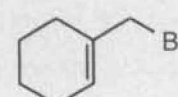

| R <sup>1</sup> X  | Yield of 2 [%] |
|---|----------------|
| CH <sub>3</sub> I   | 95             |
|    | 92             |
|    | 93             |
|    | 64             |
|    | 85             |
|    | 42             |
|  | 92             |
|  | 56             |
|  | 21             |
|  | 92             |
|  | 90             |
|  | 40             |
|  | 80             |
|  | 86             |
|  | 64             |

Table 2. Yields of Chromatographed Samples of the 5,5-Disubstituted Dihydroimidazoles 3 Obtained by in situ Double Alkylation

| R <sup>1</sup> X   | R <sup>2</sup> X  | Yield of 3 [%] |
|--|---|----------------|
| CH <sub>3</sub> I  |    | 79             |
| CH <sub>3</sub> I  |    | 82             |
| CH <sub>3</sub> I  |    | 80             |
| CH <sub>3</sub> I  |    | 91             |
|   |  | 53             |
|  |  | 70             |
|  |  | 52             |
|  |  | 57             |
|  |  | 53             |
|   |  | 80             |