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ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS THROUGH α-IODINATION OF CHIRAL UNSATURATED CARBOXAMIDES AND STEREOSELECTIVE IODOLACTONIZATION

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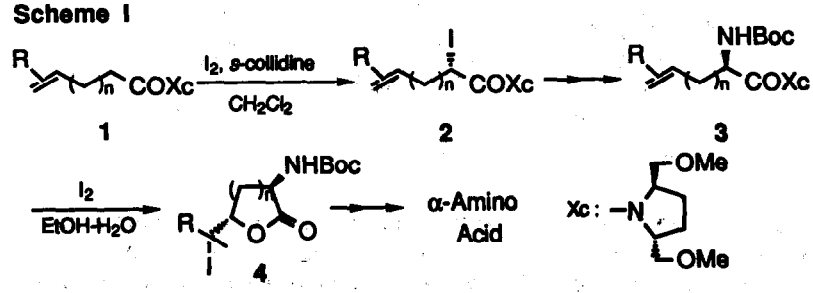
Abstract: *The α-iodination reaction of chiral enamides 1 possessing (2R,5R)-2,5-bis(methoxymethyl)pyrrolidine as a chiral auxiliary proceeded with high diastereoselectivity in the presence of I_2 and s-collidine. The chiral iodides 2 thus obtained were converted to the α-BocNH-amides 3 without epimerization. The subsequent iodolactonization afforded trans-lactones 4 with a relatively high selectivity.*

Asymmetric α-halogenation reactions using chiral ester or imido enolates provide useful intermediates for the preparation of a wide variety of organic compounds including α-hydroxy and α-amino acids.[1] Recently, we reported that the α-iodination reaction of unsaturated carboxamides was efficiently performed by treating them with I_2 and *s*-collidine.[2] The reaction mechanism of the present reaction involving the reversible activating process via an intermediate of iodolactonization of the parent amide was also suggested. In this paper, we report the asymmetric α-iodination of enamides 1 possessing (2*R*, 5*R*)-bis(methoxymethyl)pyrrolidine,[3] which proceeds with high diastereoselectivity under mild conditions. Futhermore, the conversion of the iodides 2 to the amino acids through *trans*-selective iodolactonization of α-BocNH amides 3 is also described.

Scheme I

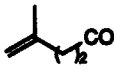
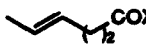


The α-iodination reaction using 4-pentenamides of various chiral amines was initially conducted to optimize the diastereoselectivity. We found that the α-iodination of the 4-pentenamide **1a** of (2*R*, 5*R*)-bis(methoxymethyl)pyrrolidine proceeds with high stereoselectivity (2*S* : 2*R* = 95 : 5) in the presence of I_2 and *s*-collidine in CH_2Cl_2 (Table I, entry 1). Under the same conditions, non-diastereoselective iodination was observed

in the cases of the 4-pentenamide of (*S*)-phenethylamine, (*S*)-leucinol or (*S*)-prolinol. It should be noted that the selectivity of **2a** was strongly affected by the solvent used [THF (2*S* : 2*R* = 7.5 : 1), EtOH (3.1 : 1), DMF (2.3 :1)].

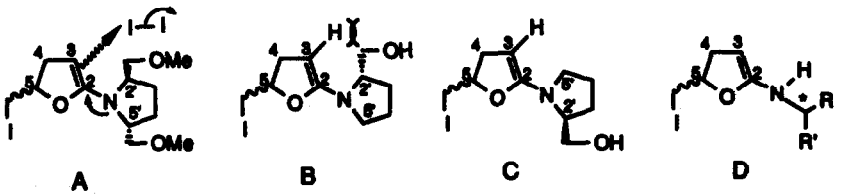
The preliminary results of the asymmetric iodination of various enamides **1** are summarized in Table I. The reaction of 4-methyl-4-pentenamide **1b** gave the α-iodination product **2b** as a single isomer in good yield (entry 2). (4*E*)-Hexenamide **1c** also gave a good yield of the iodide **2c**, although the selectivity was slightly lower than those of other compounds (entry 3). The present reaction is also applicable to the 5-hexenamide derivative **1d** to provide the iodide **2d** in a highly stereoselective manner (entry 4). The stereochemistries of the major products are the (2*S*)-configuration in all cases (*vide infra*). The efficacy of the C_2-symmetrical chiral auxiliary to achieve a high asymmetric induction can be rationally explained by considering the structure A of the intermediate in the reaction pathway (Fig. I). Thus, iodine approaches from the less hindered site to minimize the steric repulsion with the armed substituents at C2' on the pyrrolidine ring. On the other hand, in the case of C_1-symmetrical chiral auxiliary, among the two possible conformers B and C, C may be more favorable than B to avoid steric repulsion as shown in Fig I. Since the chiral center (C2') of the chiral auxiliary in C should be so far from the reaction center (C3) that no chiral induction occurs in α-iodination. Similar consideration may lead to the conformer D in the case of chiral primary amines. As shown here, a highly diastereoselective α-iodination of **1** can be carried out under mild conditions by simple procedures.

Table I. Asymmetric α-Iodination[a]

Entry	Substrate[b]		Yield (%)[c] of 2		Ratio[d]	Config.[e]
1		**1a**	84	**2a**	95 : 5	(*S*)
2		**1b**	87	**2b**	> 98: 2[f]	(*S*)
3		**1c**	89	**2c**	89 : 11	(*S*)
4		**1d**	67	**2d**	97 : 3	(*S*)

[a] α-Iodination: amide (1 mmol), I_2 and *s*-collidine (1.5 mmol), CH_2Cl_2 (8 ml), room temperature,15h. [b] Xc = (2*R*,5*R*)-2,5-bis(methoxymethyl)pyrrolidyl. [c] Isolated yield. [d] Determined by 400MHz ^{1}H-NMR. [e] Determined after conversion to the corresponding amino acid derivatives(see text). [f] Minor isomer could not be detected by 400 MHz ^{1}H-NMR.

Fig. I

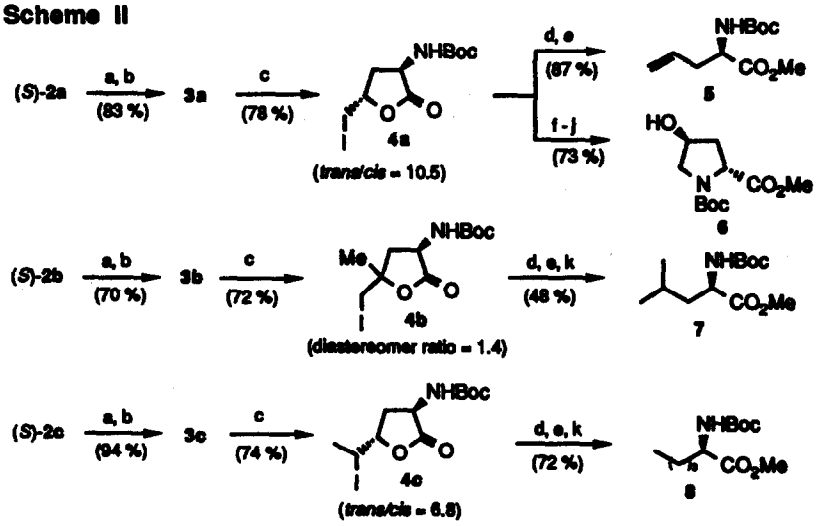


The successful conversion of the diastereomerically pure iodides **2** to various amino acids in homochiral forms as shown in Scheme II also provides a basis for determing the absolute configuration of each product. It should be also noted that these procedures involve the iodolactonization reaction of **3** not only to functionalize the

double bond stereoselectively (in the cases of 4a, 4c), but also to remove the chiral auxiliary, since direct acidic hydrolysis of this kind of amide usually requires high temperature and long reaction time. After separation of the minor isomer of 2 by MPLC, the major isomers 2a-c were converted in good yield to the α-BocNH derivatives 3a-c without epimerization.[4] The conversion of the amide part to a carboxylic acid was achieved by iodolactonization of 3 and subsequent zinc reduction without damage to the Boc group. The carboxylic acids were converted to the *N*-Boc methyl ester forms of allylglycine 5, leucine 7 and norleucine 8 and the absolute configurations of 2a-c were determined by comparison of the $[\alpha]_D$ values of 5, 7 and 8 with those of literature data.[5] The reaction of (*S*)-2d with NaN_3 followed by hydrogenation in the presence of Boc_2O gave *N*-Boc norleucine pyrrolidide, which was identical with the compound obtained by the hydrogenation of 3c.

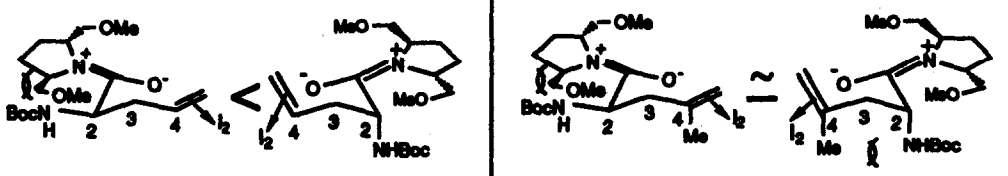
Iodolactonization of 3a and 3c preferentially gave *trans*-4a and 4c, respectively, which is in remarkable contrast to the *cis* selectivity of the corresponding 2-amino-4-pentenoic acid.[6,7] The *trans*-selectivity of 3a and 3c may be explained by considering the transition-structure model:[7a] That is, in the chair type model, axial orientation of the NHBoc group may be favorable to avoid steric repulsion between the amide part and equatorial NHBoc group (Fig. II, TS-I).[7a] However, an additional 4-methyl group as in the case of 3b may cause a 1,3-diaxial type repulsion between the NHBoc group and C4-Me resulting in low selectivity during lactonization (Fig. II, TS-II).

Scheme II



Reagents and conditions: (a) NaN_3, DMF (b) $SnCl_2$, dioxane/H_2O then Boc_2O, Na_2CO_3 (c) I_2, EtOH/H_2O, r.t (3a 41h, 3b15h, 3c 33h) (d) Zn, THF (e) CH_2N_2, Et_2O (f) Separation by MPLC (g) CF_3CO_2H, CH_2Cl_2 (h) 0.5N NaOHaq (i) $SOCl_2$, MeOH (j) Boc_2O, Et_3N, CH_2Cl_2 (k) H_2, 5%Pd-C, MeOH

Fig. II



Recently, we reported the iodolactonization of 2-*N*-sulfonylamino-4-pentenoic acid with NIS to give the iodolactone with increased 1,3-*cis*-selectivity with the addition of $Ti(O\textit{i}\text{-}Pr)_4$.[8] Thus, the stereodivergent synthesis of 3-amino-5-substituted γ-butyrolactone can be carried out by halolactonization of the carboxylic acid and dialkyl amide, respectively.[9] After separation of the *cis*-isomer[9] of **4a** by MPLC, the *trans*-lactone **4a** was converted in good yield according to the procedure of Ohfune et al. to 4-hydroxy proline **6** of the unnatural type.[10]

In summary, the asymmetric α-iodination reaction of chiral enamides which proceeds with high diastereoselectivity under mild conditions was achieved. The iodides were easily derivatized to various amino acids through iodolactonization as a key step.

Acknowledgement. The authors are grateful to the Daiso Company for providing (*R*)-glycidol.

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