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Stereoselective Iodocyclization of (*S*)-Allylalanine Derivatives: γ-Lactone vs Cyclic Carbamate Formation

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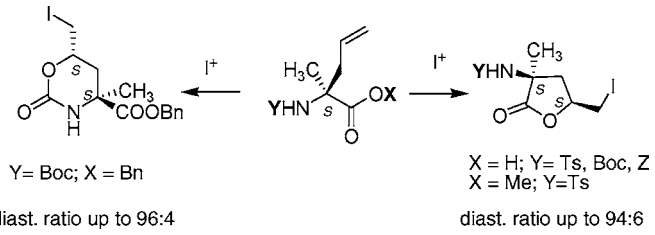
ABSTRACT



An efficient procedure for highly chemo- and stereoselective cyclization of (*S*)-allylalanine derivatives is reported (diastereomeric ratios up to 96:4) where the reaction course can be completely controlled by switching from γ-lactones to cyclic carbamates simply with the proper choice of the amino acid protecting groups. Both processes are stereoconvergent and afford the (*S,S*)-products in high yields, short reaction times, and mild reaction conditions.

Nonproteinogenic α,α-disubstituted amino acids are becoming very appealing building blocks for the synthesis of natural and artificial compounds endowed with biological activity and for applications in the field of de novo design of proteins and enzyme mimetics.[1] This is due, inter alia, to two peculiar features of these molecules: their stability to racemization and the limited conformational freedom they impart to a peptide sequence.

Our recent interest in the use of conformationally controlled peptides for the preparation of catalysts or molecular devices[2] drove us to explore methods for the selective functionalization of Cα tetrasubstituted amino acids to broaden the repertoire of available building blocks and to obtain potentially interesting chiral ligands. (*S*)-α-Allylalanine (**1**), characterized by the presence of an easily derivatizable allylic double bond on the side chain, constitutes an appealing starting compound. Enantiopure (*S*)-**1** used in the present work has been obtained via an economically attractive and generally applicable chemoenzymatic approach developed by DSM Research.[3] However, other stereoselective syntheses of **1** have been reported.[4]

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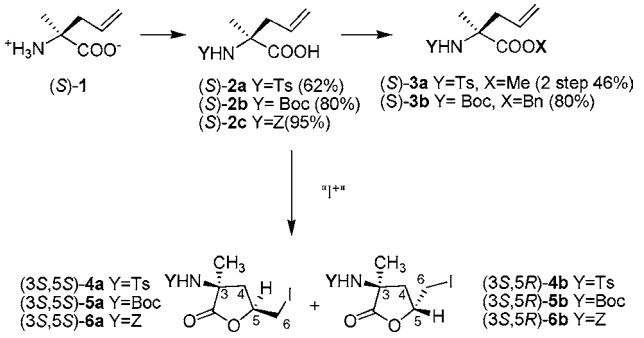
Among the different functionalizations of carbon−carbon double bonds, iodine-based electrophilic addition provides an efficient entry to heterocyclic intermediates, especially employing bifunctional substrates. Since the first example reported by Bougault in 1904,[5] this useful process has been widely used in asymmetric synthesis.[6] The investigation of the scope of the reaction includes the effect of the nucleophiles and the iodinating agents on stereoselections. The most common and reactive nucleophiles employed in these transformations were carboxylic acids and their derivatives, such as esters and amides. The iodocyclization of 4-pentenoic acids, structural analogues of **1**, generates preferentially γ-iodolactones. The generally accepted mechanism involves a favored *exo-trig* intramolecular nucleophilic attack to the double bond activated by an electrophilic iodinating reagent as an iodonium ion or, more likely, in the presence of an intramolecular nucleophile, an iodine−π complex.[7] Concerning the new stereocenter generation, good degrees of stereoselectivity have been reached with 4-pentenoic acids under substrate control.[8] On the contrary, despite the valuable synthetic potential, examples of efficient stereoselective halolactonizations with reagent control are quite rare.[9]

Here, we report that iodolacyclization of N- and C-protected derivatives of (*S*)-**1** affords efficiently and in high yields two different cyclic products, γ-lactones or tetrahydro-1,3-oxazine-2-ones, and in both cases, a new stereocenter forms with high stereoselectivity (up to 96:4) even in the presence of a remote homoallylic stereocenter. Furthermore, the chemoselective γ-lactones or cyclic carbamate formation can be totally controlled by choosing the appropriate protecting groups on the amino acid. Both reactions are stereoconvergent, affording the new stereocenter with the same (*S*)-absolute configuration.

Iodocyclizations have been carried out using two different iodinating systems: I_2 in THF/water 1:1 (method A) and *N*-iodo succinimide (NIS) (method B).[10] In the second case, the reactions have been carried out also in the presence of amines or Lewis acids. Because all attempts to perform the halocyclization on the unprotected amino acid **1** were unsuccessful,[11] N-protected derivatives were used. Protecting groups considered were *para*-toluenesulfonyl (Ts, **2a**), *tert*-butyloxycarbonyl (Boc, **2b**), and benzyloxycarbonyl (Z, **2c**). The carboxylic function was also orthogonally protected as a methyl ester (**3a**) or a benzylic ester (**3b**) (Scheme 1).

Scheme 1. Synthesis of (*S*)-Allylalanine Derivatives **2a**−**c** and **3a**,**b** and Iodolactonization of **2a**−**c**



A thorough investigation with tosylamide **2a** as a model substrate was carried out (Scheme 1, Table 1).

Reactions were monitored following the disappearance of the reagent (double bond proton resonances) and product formation. Both methods gave complete conversion of **2a** into the corresponding γ-lactones **4** that could be isolated in good chemical yields by radial chromatography (Table 1, entries 1 and 2).

The absolute stereochemistry of the two diastereomeric products **4a** and **4b** was assigned by NOESY experiments on the two isolated lactones (see Supporting Information). Diagnostic cross-peaks for the assignment of the two diastereoisomers turned out to be the ones between C(5)H and C(3)CH_3 protons (only present in the major diastereoisomer **4a**) and between C(6)H_2I and C(3)CH_3 (only present in **4b**). Therefore, the cyclization affords preferentially the *syn*-lactone (3*S*,5*S*)-**4a** over the *anti*-one (3*S*,5*R*)-**4b**. Interestingly, lactones **4a** and **4b** have rather different ^{1}H NMR

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(10) Preliminary experiments carried out with ICl in CH_2Cl_2 afforded comparable reactivity as far as reaction rates and stereoselectivity but with significantly lower chemical yields (59%).

(11) When the unprotected substrate (*S*)-**1** was used, complex reaction mixtures were obtained where complete substrate disappearance and no significant amount of iodocyclization products were detected. Reactions between iodine and and amines have been reported to afford N-iodination, formation of molecular complexes, and in some cases, unusual oxidation processes, and therefore N-protection is required. See: Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182−1203 and refs therein.

Table 1. Iodolactonization of (*S*)-**2a**

no.	conditions[a]	temp (°C)	time (h)	convn (%)[b]	yield (%)[c]	**4a/4b**[b]
1	A	rt	0.5	100	84	70:30
2	B, $CHCl_3$	rt	0.5	100	87	73:27
3	B, CH_2Cl_2	−20	0.5	100	81	72:28
4	B, $CHCl_3$[d]	rt	72	100	61	80:20
5	B, Ti(O*i*Pr)$_4$, CH_2Cl_2	rt	0.5	100	98	80:20
6	B, Ti(O*i*Pr)$_4$, CH_2Cl_2	−20	18	94	90	87:13
7	B, Ti(O*i*Pr)$_4$, (*R*)-BINOL, CH_2Cl_2	−20	18	73	66	90:10
8	B, Ti(O*i*Pr)$_4$, (*S*)-BINOL, CH_2Cl_2	−20	20	84	80	78:22

[a] Reaction conditions. A: [**2a**]$_0$ = 0.04 M, I_2 (3 equiv), THF/H_2O 1:1. B: [**2a**]$_0$ = 0.1 M, NIS (1.2 equiv). [b] Determined by ^{1}H NMR of the reaction crude. [c] Determined on isolated material after chromatography. [d] The reaction was carried out in the presence of (±)-1-phenylethylamine (2 equiv).

spectra, in particular, for C(6)H_2 and C(4)H_2 proton signals in the 1.50−3.50 ppm region.[12]

The efficiency of I_2 and NIS as an I^+ source appears to be comparable as far as reactivity, stereoselectivity, and chemical yields are concerned (Table 1). Typically, after 30 min, complete conversion of the starting material was observed. Due to the more feasible reaction conditions using NIS, method B was explored more in detail, testing the effect of different parameters such as solvent, temperature, and the presence of a base or a Lewis acid (Table 1, entries 3−8). The reaction in CH_2Cl_2 at −20 °C gave complete conversion of the reagent and comparable diastereomeric ratios in the same reaction times (Table 1, entry 3). The presence of (±)-1-phenylethylamine, which should favor deprotonation of the acid and speed up the reaction, gave the products with higher dr's (**4a**/**4b** = 80:20), although at a slower rate (Table 1, entry 4). Disappointingly, no significant differences were found using enantiopure (*R*)- and (*S*)-1-phenylethylamine.[9b,f] The use of Ti(O-*i*Pr)$_4$ (1 equiv), a NIS activator as an I^+ donor,[13] gave a higher dr (**4a**/**4b** = 80:20) (Table 1, entry 5) which could be increased up to 87:13 working at lower temperatures (Table 1, entry 6). However, at this temperature, the reaction did not go to completion. With the aim to increase the stereoselectivity under double stereoselection conditions, we tested the use of enantiopure Ti complexes prepared in situ from Ti(O-*i*Pr)$_4$ and (*R*)- or (*S*)-1,1′-bi(2-naphtol) (BINOL).[14] This time a different response was observed with the two enantiomeric catalysts, and (*R*)-BINOL gave the matched pair with an increased **4a**/**4b** ratio of 90:10. (Table 1, entry 7).

The same set of reactions with both methods was carried out also on derivatives (*S*)-**2b** and (*S*)-**2c** (Table 2).

(12) The *syn* diastereomer **4a** shows an ABX system for the distereotopic C(6)H_2I protons at 3.26 and 3.41 ppm, respectively, whereas in *anti*-**4b** the same systems can be found at 3.30 and 3.37 ppm, respectively. Also, the endocyclic C(4)H_2 appears as an ABX system at 2.42 and 2.71 ppm in **4a**, whereas in *anti*-**4b** it is at 1.96 and 3.12 ppm, respectively.

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Table 2. Iodolactonization of (*S*)-**2b** and (*S*)-**2c**

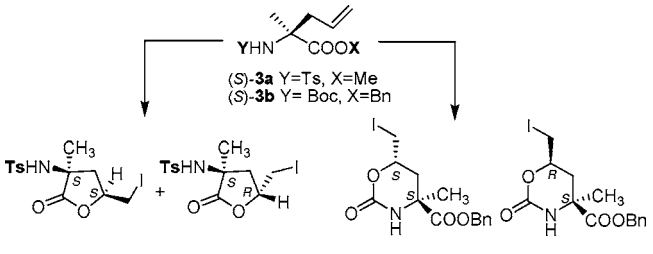
substrate	conditions[a]	temp (°C)	time (h)	convn (%)[b]	yield (%)[c]	**a/b**[d]
2b	A	rt	1	100	41	89:11
	B, $CHCl_3$	rt	1	100	82	86:14
	B, Ti(O*i*Pr)$_4$, CH_2Cl_2	−20	20	95	58	93:7
2c	A	rt	3	100	45	94:6
	B, $CHCl_3$	rt	2	100	92	87:13
	B, Ti(O*i*Pr)$_4$, CH_2Cl_2	−20	19	86	52	93:7

[a] Reaction conditions. A: [substrate]$_0$ = 0.04 M, I_2 (3 equiv), THF/H_2O 1:1. B: [substrate]$_0$ = 0.1 M, NIS (1.2 equiv). [b] Determined by ^{1}H NMR of the reaction crude. [c] Determined on isolated material after chromatography. [d] Determined by GC−MS of the reaction crude.

Substrates **2b** and **2c** gave the corresponding γ-lactones **5a**,**b** and **6a**,**b** with even higher selectivities in favor of the *syn*-lactones. In this case, the stereochemistry of the products could be assigned by comparison of the ^{1}H NMR spectra with those of the Ts analogues **4a** and **4b**. Both series of derivatives show very similar ^{1}H NMR patterns for methylenes C(6)H_2I and C(4)H_2. Both (*S*)-**2b** and (*S*)-**2c** gave the highest dr with NIS in the presence of Ti(O-*i*Pr)$_4$ (93:7). I_2 in THF/H_2O with (*S*)-**2c** gave high selectivities as well (**6a**/**6b** = 94:6).[15]

The iodocyclization was also tested with two ester derivatives, (*S*)-**3a** and (*S*)-**3b**, to verify if increased stereoselection could be achieved. Interestingly, both substrates were converted quantitatively but via two different reaction pathways: (*S*)-**3a** gave the two γ-iodolactones **4a** and **4b** but without any increase of stereoselectivity and with a significant decrease of the reaction rates. This last aspect is consistent with the diminished nucleophilic character of the ester C═O function compared to that of the carboxylic acid (Table 3, entries 1 and 2). On the other hand, carbamate

Table 3. Iodolactonization of (*S*)-**3a** and (*S*)-**3b**



4a **4b** **7a** **7b**

no.	substrate	condition[a]	time (h)	convn (%)[b]	yield (%)[c]	**4a/4b**[b]	**7a/7b**[d]
1	(*S*)-**3a**	A	2	100	84	70:30	–
2		B	72	100	68	56:44	–
3	(*S*)-**3b**	A	2	100	90	–	96:4
4		B	72	100	65	–	77:23

[a] Reaction conditions. A: [substrate]$_0$ = 0.04 M, I_2 (3 equiv), THF/H_2O 1:1, rt. B: [substrate]$_0$ = 0.1 M, NIS (1.2 equiv) $CHCl_3$, rt. [b] Determined by ^{1}H NMR of the reaction crude. [c] Determined on isolated material after chromatography. [d] Determined by GC−MS of the reaction crude.

(*S*)-**3b** gave in high yields and stereoselectivities (up to 96:4) two diastereomeric tetrahydro-1,3-oxazoline-2-one derivatives, **7a** and **7b** (Table 3, entries 3 and 4).

The different reaction pathways originate from a competitive intramolecular nucleophilic attachment to the activated double bond by the two C═O's present in the molecule: the carbamate and the carboxylic ester. Such competition was not observed with acids **2b** and **2c**, because of the much higher nucleophilicity of the carboxylate compared to the carbamate, and with derivative **3a**, because of the presence of a noncompetitive S═O in the N-protecting group. Analysis of the conformation of substrate **2** yielding the γ-lactones reveals the possible formation of an intramolecular hydrogen bond between the carboxylic acid and the carbamate C═O, both favoring the lactone formation and increasing the nucleophilicity of the carboxylic C═O (Figure 1).

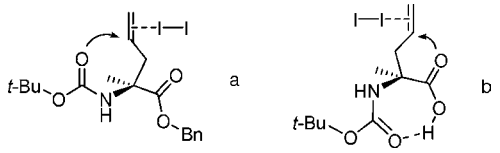


Figure 1. Competitive nucleophilic attacks for the synthesis of carbamate **7** from (*S*)-**3b** (path a) or of γ-lactone **5** from (*S*)-**2b** (path b).

To the best of our knowledge, this is the first example of a complete switch of reactivity between the formation of a γ-lactone and a cyclic carbamate, both occurring with high degrees of stereoselectivity.[16] Determination of the X-ray structure of the minor diastereoisomer **7b**[19] allowed us to assign the absolute configuration of the two diastereoisomers, (4*S*,6*S*)-**7a** and (4*S*,6*R*)-**7b** (Figure 2).

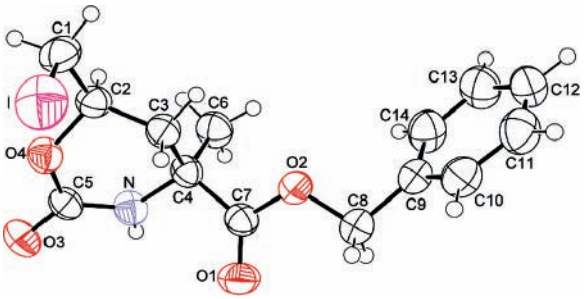


Figure 2. ORTEP view of (4*S*,6*R*)-**7b**. Ellipsoids are represented at 50% probability level.

Therefore, in this case also the preferential formation of a new stereocenter with *S* absolute configuration has been obtained. This is rather significant because both reaction pathways provide high stereocontrol in the formation of a new stereocenter with the same absolute configuration.

We may conclude that an efficient procedure for the highly stereoselective synthesis (dr's up to 96:4) of new, highly functionalized amino acids has been developed, where the chemoselective outcome of the reaction (formation of cyclic carbamates or γ-lactones) can be completely controlled by choosing the proper amino acid derivative. Mechanistic studies to understand the origin of the chemo- and stereoselection of the reaction are currently under investigation, along with the use of the enantiopure lactones and cyclic carbamates as building blocks for the synthesis of new chiral ligands, taking advantage of the presence of two functionalized arms on the same side of the cycle.

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Supporting Information Available: Experimental details and spectroscopic characterization for new compounds together with the crystallographic data are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Although the diastereomeric mixtures **4a**/**4b** and **6a**/**6b** are separable through radial chromatography, the isomers **5a**/**5b** remain unseparable.

(16) Examples of intramolecular cyclic carbamate formation with good stereoselectivities have been reported in the iodocyclization of a few acyclic homoallyl-β-amino esters (carbamates vs δ-lactones) (ref 17) and in one case on the bromocyclization of a bicyclic allyl α-amino ester where, for steric reasons, only the C═O carbamate could give the nucleophilic attack (ref 18).

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(19) Crystal Data for **7b**: $C_{14}H_{16}INO_4$, $M_W = 389.18$, $T = 293(2)$ K, $l = 0.71073$ Å, orthorhombic, space group $P2_12_12_1$, $a = 6.725$ Å, $b = 13.858$ Å, $c = 16.061$ Å, $V = 1496.7$ Å^3, $Z = 4$, $D_c = 1.727$ g/cm^3, $F(000) = 768$, crystal size $0.5 \times 0.5 \times 0.5$ mm^3, 24 277 reflections measured, 4577 independent reflections ($R_{int} = 0.0206$); the final w$R(F^2)$ was 0.1534 (all data) and final R was 0.0536 for 3704 unique data [$I > 2s(I)$]. The crystal structure of (4*S*,6*R*)-**7b** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 635632).