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SHORT COMMUNICATION

A convenient route to optically pure α-alkyl-β-(*sec*-amino)alanines

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Abstract The cyclization of *N*-Boc-α-alkylserines to corresponding β-lactones under Mitsunobu reaction conditions and the ring opening with heterocyclic amines (pyrrolidine, piperidine, morpholine and thiomorpholine) produced *N*-Boc-α-alkyl-β-(*sec*-amino)alanines. The removal of the Boc group gives di-hydrochlorides of non-protein amino acids.

Keywords α-Alkyl-β-(*sec*-amino)alanines · *N*-Boc-α-alkylserines β-lactones · α,α-Disubstituted glycines · Mitsunobu reaction

Introduction

α,α-Disubstituted glycines are excellent tools for the designing of peptidomimetics with potential therapeutic properties. Their incorporation into biologically active peptide chains restricts flexibility and enhances biological activity and resistance to enzymatic hydrolyses (Cativiela et al. 2007). Moreover, α,α-disubstituted glycines are often found in nature, either in the free form or as constituents of biologically active natural products (for example, see: Burges and Leach 1973; Seebech et al. 1987). The biological significance and synthetic utility of symmetrically and asymmetrically α,α-disubstituted glycines continue to stimulate the development of new routes to these compounds (Soloshonok and Sorochinsky 2010; Soloshonok et al. 2001; Soloshonok 2002; Ohfune and Shinada 2005; Fustero et al. 2011). In our laboratory, we have focused on the synthesis of α-alkylserines and their incorporation into bioactive peptide analogues (for example, see: Metzger et al. 1987; Olma et al. 1998, 2001, 2003; Łempicka et al. 1999; Olma and Tourwe 2000; Zabłotna et al. 2006). *N*-Boc-α-alkylserines can be easily cyclized under Mitsunobu reaction conditions to *N*-protected β-lactones (Olma and Kudaj 2005; Fukujama and Xu 1993; Smith and Goodman 2003; Olma 2004), which are excellent starting materials for further derivatization in medicinal chemistry. We recently reported the synthesis of α-alkyl-β-azido-and α-alkyl-β-aminoalanines as well as α-halogenomethyl-α-alkylglycines (Kudaj and Olma 2007, 2008) via ring opening of 3-amino-3-alkyl-2-oxetanones. Enantiomerically pure *N*-Boc-α-alkylserines are easily available using a procedure developed in our laboratory, involving the synthesis of racemic α-hydroxymethyl analogues of various amino acids (Kamiński et al. 1973) and their resolution by fractional crystallization of appropriate diastereoisomeric salts. The absolute configuration of some α-alkylserines was determined by chemical correlation with relevant α-methyl amino-acids or by X-ray analysis (Olma 1996; Wieczorek et al. 1991). α-Alkylserines could also be obtained via the diastereoselective alkylation of pyramidalized bicyclic serine enolates [(bicyclic *N,O*-acetals derived from serine, (Jimenez-Oses et al. 2007)] or in an asymmetric version of the Strecker synthesis (Ohfune and Shinada 2005).

Herein, we present the use of *N*-Boc-α-alkylserine β-lactones for the preparation of α-alkyl-β-(*sec*-amino) alanines. Naturally occurring heterocyclic β-alkylamino-L-alanines (non-proteinogenic amino acids) were found in

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nature as free acids and as constituents of biologically active peptides (Ikegami and Murakoshi 1994).

Scheme 1 outlines our method of synthesis of (*R*)-α-alkyl-*β*-(*sec*-amino) alanines. Heterocyclic amines, such as pyrrolidine, piperidine, morpholine and thiomorpholine were used as nitrogen nucleophiles.

The cyclization of *N*-Boc-(*R*)-α-alkylserines **1** was carried out in anhydrous ethyl acetate under conventional Mitsunobu conditions. Corresponding α-alkylserine *β*-lactones **2** were obtained in 86–91% yield—slightly lower than that in modified Mitsunobu conditions (Olma and Kudaj 2005), however, the procedure described here is significantly simplified. Modified Mitsunobu conditions are a method of choice for the synthesis of serine and threonine *β*-lactones (for example, see: Lee et al. 1985; Adam et al. 1984; Ramer et al. 1986; Pansare et al. 2002; Lall et al. 2002; Schneider et al. 2006). The ring opening of *N*-protected serine *β*-lactones with nitrogen nucleophiles can give a mixture of amide (acyl-oxygen cleavage) and *N*-protected *β*-aminoalanines (alkyl-oxygen cleavage). The reaction is very sensitive not only to nitrogen nucleophiles, but also to the solvent and reaction conditions. The use of trialkylsilyl derivatives of ammonia as well as primary, secondary and heterocyclic amines allows the synthesis of *β*-aminoalanine derivatives (Ratemi and Vederas 1994). The treatment of *N*-Boc-α-alkylserine *β*-lactones with free amines (pyrrolidine, piperidine, morpholine or thiomorpholine) gives suitable, enantiomerically pure *N*-protected α-alkyl-*β*-(*sec*-amino) alanines. The results are presented in Table 1. We did not observe the formation of amides arising from acyl-oxygen cleavage in different solvents (acetonitrile, dimethylformamide or methylene chloride). The removal of the Boc group gives dihydrochlorides of non-protein amino acids **7**–**10** (Table 1).

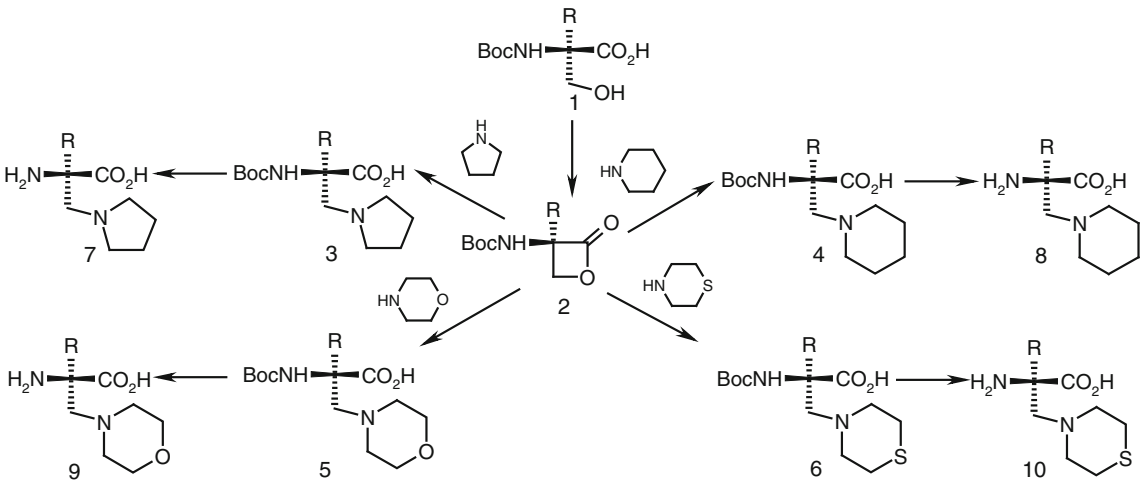
We also applied selected heteroaromatic amines (pyrazole and imidazole) as nucleophiles. The ring opening of *N*-Boc- α-alkylserine *β*-lactones with pyrazole as nucleophile failed, however, the use of imidazole followed by treatment with diazomethane provided *N*-Boc-α-alkyl-*β*-imidazol-1-yl-alanine methyl ester with low yields (30–40%).

General procedure for the preparation *N*-Boc-(*R*)-α-alkyL-serine *β*-lactones (2)

To a solution of *N*-Boc-(*R*)-α-hydroxymethylamino acids **1** (3 mmol) and triphenylphosphine (943 mg, 3.6 mmol) in 3 ml of dry ethyl acetate, a solution of DEAD (563 µl, 3.6 mmol) in 3 ml of dry ethyl acetate was dropped at −10°C for 20 min. The mixture was stirred at 0°C for 1.5 h and at room temperature for 2 h; then, 6 ml of *n*-hexane was added and the mixture was left in a refrigerator overnight. The solid (most of the triphenylphosphine oxide and *N,N*-diethoxycarbonyl hydrazine) was filtered off and washed with a small amount of ethyl acetate–*n*-hexane (1:1). The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel 60 (230–400 mesh) using ethyl acetate–n-hexane (1:2) as eluent. Pure *N*-Boc-(*R*)-α-alkyl-serine *β*-lactones 2 were obtained in 86–91% yield.

General procedure for the preparation of *N*-Boc-(*R*)-α-alkyl-*β*-(*sec*-amino)alanines (3–6)

To a solution of *N*-Boc-(*R*)-α-alkylserine *β*-lactone **2** (1 mmol) in 2 ml of CH_2Cl_2, 3 mmol of amine (pyrrolidine,



Scheme 1 $R = CH_3$ (**a**), $CH(CH_3)_3$ (**b**), $CH_2CH(CH_3)_2$ (**c**), $CH_2C_6H_5$ (**d**)

Table 1 Preparation of *N*-Boc-(*R*)-α-alkyl-β-(sec-amino)alanines (**3–6**) and (*R*)-α-alkyl-β-(sec-amino)alanines x 2HCl (**7–10**)

No.			Yield (%)	Mp (°C)	$[\alpha]_D$ ($c = 1$, MeOH)	No.	Yield (%)	Mp (°C)	$[\alpha]_D$ ($c = 1$, H_2O)
3a	CH_3	Pyrrolidine	82	95–97	−11.9	**7a**	87	218–220	−6.0
3b	$CH(CH_3)_2$	Pyrrolidine	95	133–135	−12.6	**7b**	89	223–224	−14.3
3c	$CHCH_2(CH_3)_2$	Pyrrolidine	55	123–125	10.1	**7c**	98	218–220	2.8
3d	$CH_2C_6H_5$	Pyrrolidine	71	112–114	45.3	**7d**	92	208–210	−12.9
4a	CH_3	Piperidine	90	97–99	−11.3	**8a**	93	223–225	−8.1
4b	$CH(CH_3)_2$	Piperidine	95	161–162	−11.4	**8b**	97	218–220	−16.6
4c	$CHCH_2(CH_3)_2$	Piperidine	69	147–149	14.1	**8c**	99	230–232	−4.0
4d	$CH_2C_6H_5$	Piperidine	90	93–95	38.2	**8d**	84	240–241	−11.2
5a	CH_3	Morpholine	92	94–96	−13.1	**9a**	98	193–195	−9.8
5b	$CH(CH_3)_2$	Morpholine	95	138–140	−12.8	**9b**	92	224–225	−19.6
5c	$CHCH_2(CH_3)_2$	Morpholine	75	108–110	17.9	**9c**	91	217–219	−1.8
5d	$CH_2C_6H_5$	Morpholine	89	120–122	41.3	**9d**	94	228–230	−12.3
6a	CH_3	Thiomorpholine	94	90–92	−8.3	**10a**	98	265–267	−5.3
6b	$CH(CH_3)_2$	Thiomorpholine	89	173–175	4.7	**10b**	89	213–215	−12.6
6c	$CHCH_2(CH_3)_2$	Thiomorpholine	88	91–93	11.8	**10c**	90	296–299	−6.0
6d	$CH_2C_6H_5$	Thiomorpholine	99	100–102	39.2	**10d**	94	208–210	−9.4

piperidine, morpholine or thiomorpholine) was added. The mixture was stirred for 2–24 h (TLC) and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel 60 (230–400 mesh) using chloroform–methanol–acetic acid (90:10:2).

General procedure for the preparation of (*R*)-α-alkyl-β-(*sec*-amino)alanines × 2 HCl (7–10)

To a solution of *N*-Boc-(*R*)-α-alkyl-β-(*sec*-amino)alanines **3–6** (0.5 mmol) in 2 ml of ethyl acetate, 1 ml of 4 N HCl in ethyl acetate was added. The mixture was stirred for 2–4 h (TLC) and the product was filtered off.

In summary, lactones **2** are convenient precursors for the preparation of *N*-protected (*R*)-α-alkyl-β-(*sec*-amino) alanines **3–6**, building blocks to be incorporated in peptide chains. The new multifunctional α,α-disubstituted glycines **7–9** are useful tools for SAR studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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