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An efficient synthesis of optically active 3-amino-3-alkyl-2-oxetanones

Aleksandra Olma* and Adam Kudaj

Institute of Organic Chemistry, Technical University, 90-924 Łódź, Żeromskiego 116, Poland

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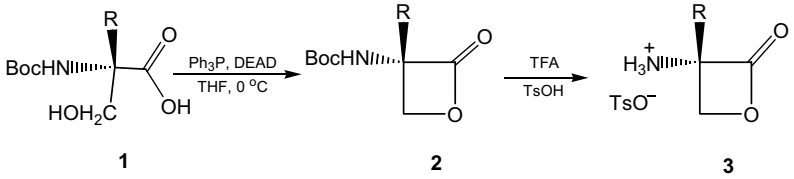
Abstract—An efficient two-step synthesis of *p*-toluenesulfonic acid salts of optically active 3-amino-3-alkyl-2-oxetanones is reported that involves cyclization of *N*-Boc-α-alkylserines under Mitsunobu reaction conditions followed by deprotection of the amino group with trifluoroacetic acid in the presence of anhydrous *p*-toluenesulfonic acid.

1. Introduction

The discovery of a significant number of natural β-lactones (2-oxetanones) with very interesting biological activities has attracted much attention towards the preparation of the β-lactone moiety and its use as a synthetic intermediate.[1] *N*-Protected-α-amino-β-lactones are useful and versatile intermediates for the synthesis of β-substituted α-amino acids via ring opening by various nucleophiles.[2,3] The *p*-toluenesulfonic acid salt of (*S*)-3-amino-2-oxetenone obtained from *N*-protected serine β-lactone reacts with a variety of nucleophiles to afford unprotected, optically pure α-amino acids.[4] *N*-Boc-α-methylserine-β-lactone has been used for the synthesis of *N*- and *S*-protected α-methylcysteine.[5]

Recently, we described a transformation of various Boc-α-hydroxymethylamino acids (α-alkylserines) into Boc-α-mercaptomethyl-α-amino acids (α-alkylcysteines) via *N*-protected β-lactones as intermediates.[6] *N*-Benzyloxycarbonyl-L-serine-β-lactone represents a new class of cysteine proteinase inhibitors[7] and therefore our current interest is focused on the synthesis of optically active α-substituted-β-lactones. In this letter, we report an efficient two-step synthesis of *p*-toluenesulfonic acid salts of optically active 3-alkyl-2-oxetanones from optically active *N*-Boc-α-alkylserines. The starting optically active intermediates were easily available via a procedure developed in our laboratory involving the synthesis of racemic α-hydroxymethyl analogues of various amino acids[8] and their resolution by fractional crystallization of appropriate diastereoisomeric salts. The absolute configurations of some α-hydroxymethylamino acids were determined by chemical correlation with relevant α-methylamino acids or by X-ray analysis.[9]

Scheme 1 outlines our approach for the preparation of α-substituted-β-lactones, which involves transformation



1 2 3

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

Scheme 1. Synthesis of *p*-toluenesulfonic acid salts of (*S*)- and (*R*)-3-amino-3-alkyl-2-oxetanones **3**.

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* Corresponding author. Tel.: +48 426313155; fax: +48 426365530; e-mail: olmaola@p.lodz.pl

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Table 1. *N*-Boc- (**2**) and *p*-toluenesulfonic salts of 3-amino-3-alkyl-2-oxetanones (**3**)

R	**2** (yield %)	**3** (yield %)
CH_3	98	80
$CH(CH_3)_2$	92	82
$CH_2CH(CH_3)_2$	95	74
$CH_2C_6H_5$	94	77

of *N*-Boc-α-alkylserines into β-lactones under Mitsunobu reaction conditions and deprotection of the amino function with trifluoroacetic acid in the presence of anhydrous *p*-toluenesulfonic acid.

Attempts to use commercially available diisopropyl azodicarboxylate (DIAD) were inefficient and only *N*-Boc-α-methylserine-β-lactone could be obtained in reasonable yield (60%) under these conditions. Instead, the application of diethyl azodicarboxylate (DEAD) for sterically hindered α-hydroxymethylamino acids such as β-branched **1b** (Val analog) or γ-branched **1c** or **1d** (Leu or Phe analogs) provided β-lactones in excellent yields (Table 1).

Under these conditions, Boc-α-hydroxymethylamino acids undergo the cyclization reaction to *N*-Boc-α-alkylserine-β-lactones in 92–98% yield. Although the efficiency of the Mitsunobu reaction does not depend on the alkyl groups of azodicarboxylate and diethyl or diisopropyl azodicarboxylate can be used interchangeably,[10] for the synthesis of *N*-Boc-α-alkylserine-β-lactones, diethyl azodicarboxylate was the reagent of choice. DEAD is easily accessible in a two-step sequence as described by Rabjohn.[11] In every case, pure *N*-protected β-lactones were obtained in good yields after flash chromatography. Removal of the Boc group was carried out using TFA in the presence of anhydrous *p*-toluenesulfonic acid. All products were characterized by ^1H NMR, IR and HR-MS (FAB).

α-Alkyl-serine-β-lactones show promise as useful intermediates in the synthesis of dipeptides containing α-mercaptomethyl-α-amino acids at the C-terminal position as depicted in Scheme 2.

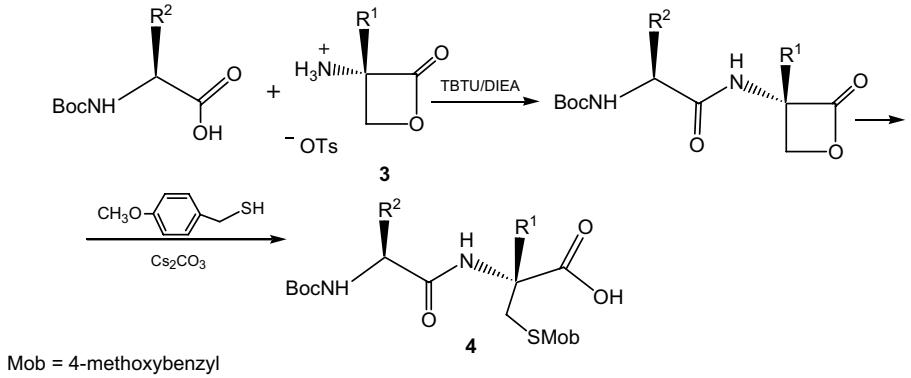
Incorporation of unnatural α,α-disubstituted amino acids into peptides is of interest in the synthesis of peptidomimetics. Conventional peptide synthetic methods are often unsuccessful. In our hands, attempts to couple the amino group of α-mercaptomethyl-α-amino acids residues with most known reagents, failed. The approach depicted in Scheme 2 via the less hindered β-lactone intermediates shows great promise in solving the so-called 'difficult' coupling problem. Thus, the coupling with 3-amino-3-alkyl-2-oxetanone proceeded smoothly and the dipeptides (Boc-Asp(Bzl)-MmVal(Mob)-OH and Boc-Asp(Bzl)-MmLeu(Mob)-OH) were obtained in good yields (Scheme 2).[12] Experiments are underway to explore the further potential of this approach and to evaluate the versatility of β-lactones as intermediates.

2. General procedure for preparation of *N*-Boc-α-alkylserine-β-lactones 2

To a solution of triphenylphosphine (525 mg, 2 mmol) in dry THF, DEAD (313 μl, 2 mmol) was added at 0 °C. The mixture was stirred for 20 min at 0 °C and then a solution of the Boc-α-hydroxymethylamino acid (2 mmol) in dry THF (1 ml) was added. Stirring was continued for 1 h at 0 °C and then for 16 h at room temperature. The THF 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 (1:1) as eluent to give the *N*-Boc-α-alkylserine-β-lactones **2** in 92–98% yields. The products could be used without further purification in the next step.

3. General procedure for preparation of *p*-toluenesulfonic acid salts of (*S*)-3-alkyl-2-oxetanones 3

To a cooled mixture of (1 mmol) of *N*-Boc-α-alkylserine-β-lactone and (181 mg, 1.05 mmol) of anhydrous *p*-toluenesulfonic acid under argon, anhydrous trifluoro-



Mob = 4-methoxybenzyl

4a $R^1 = CH(CH_3)_2$, $R^2 = CH_2COOCH_2C_6H_5$ (61%)

4b $R^1 = CH_2CH(CH_3)_2$, $R^2 = CH_2COOCH_2C_6H_5$ (70%)

Scheme 2. Synthesis of dipeptides via α-alkylserine-β-lactones.

acetic acid (2.6 ml) was added. The mixture was stirred for 2–4 h (TLC) and evaporated under vacuum. Anhydrous ether was added and the solid obtained was separated, washed with ether and dried under reduced pressure. Yield 74–82%.

3.1. (*S*)-3-Amino-3-methyl-2-oxetanone *p*-toluenesulfonic acid salt 3a

Yield 80%; colorless crystals, mp 186–188 °C (dec); $[\alpha]_D^{20}$ −15.6 (*c* 1, MeOH); IR (film) 1832 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$/TFA) δ: 1.93 (s, 3H); 2.42 (s, 3H); 4.45, 4.86 (AX system, 2H, $J = 6.88$ Hz); 7.28, 7.67 (AA'XX' system, 4H, $J = 8.11$ Hz); HR-MS (FAB) *m/z* 102.0559 (M+H), calcd for $C_4H_8NO_2$ 102.0555.

3.2. (*S*)-3-Amino-3-*iso*-propyl-2-oxetanone *p*-toluenesulfonic acid salt 3b

Yield 82%; colorless crystals, mp 187–189 °C (dec); $[\alpha]_D^{20}$ −35.5 (*c* 1, MeOH), IR (film) 1832 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$/TFA) δ: 1.11, 1.12 (2d, 6H, $J = 6.80$ Hz); 2.22, 2.42 (heptet, 1H, $J = 6.80$ Hz); 2.35 (s, 3H); 4.36, 4.68 (AX system, 2H, $J = 7.05$ Hz); 7.25, 7.67 (AA'XX' system, 4H, $J = 8.10$ Hz); HR-MS (FAB) *m/z* 130.0872 (M+H), calcd for $C_6H_{12}NO_2$ 130.0868.

3.3. (*S*)-3-Amino-3-*iso*-butyl-2-oxetanone *p*-toluenesulfonic acid salt 3c

Yield 74%; colorless crystals, mp 209–211 °C (dec); $[\alpha]_D^{20}$ −21.8 (*c* 1, MeOH); IR (film) 1832 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$/TFA) δ: 0.96, 1.02 (2d, 6H, $J = 6.23$ Hz); 1.80, 1.99 (m, 2H); 2.08, 2.14 (m, 1H); 2.41 (s, 3H); 4.49, 4.79 (AX system, 2H, $J = 7.15$ Hz); 7.28, 7.68 (AA'XX' system, 4H, $J = 8.32$ Hz); HR-MS (FAB) *m/z* 144.1019 (M+H), calcd for $C_7H_{14}NO_2$ 144.1024.

3.4. (*S*)-3-Amino-3-benzyl-2-oxetanone *p*-toluenesulfonic acid salt 3d

Yield 77%; colorless crystals, mp 212–214 °C (dec); $[\alpha]_D^{20}$ −44.2 (*c* 1, MeOH); IR (film) 1832 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$/TFA) δ: 2.39 (s, 3H); 3.28, 3.42 (AB system, 2H, $J = 14.2$ Hz); 4.40, 4.89 (AX system, 2H, $J = 11.5$ Hz); 7.12, 7.21 (m, 2H); 7.25, 7.68 (AA'XX' system, 4H, $J = 7.75$ Hz); 7.30, 7.39 (m, 3H); HR-MS (FAB) *m/z* 178.0872 (M+H), calcd for $C_{10}H_{12}NO_2$ 178.0686.

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