*Molbank* **2009**, M596

OPEN ACCESS

*molbank*

**ISSN 1422-8599**

www.mdpi.com/journal/molbank

*Short Note*

# Synthesis of *rac*-tert-butyl 3-(benzyloxycarbonylamino)-2-(4-bromophenyl)-tetrahydrofuran-3-carboxylate

**Andreas Grauer and Burkhard König***

Institute of Organic Chemistry, University of Regensburg, D-93040 Regensburg, Germany

* Author to whom correspondence should be addressed.
E-mail: Burkhard.koenig@chemie.uni-regensburg.de

*Received: 21 February 2009 / Accepted: 12 March 2009 / Published: 23 March 2009*

**Abstract:** A new $C^{\alpha}$-tetrasubstituted α-amino acid *rac*-tert-butyl 3-(benzyloxycarbonylamino)-2-(4-bromophenyl)-tetrahydrofuran-3-carboxylate was synthesized and characterized by NMR, MS, elemental analysis and X-ray.

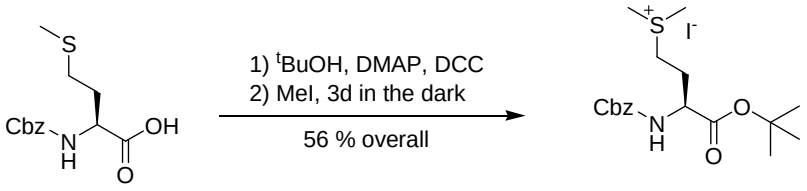
**Keywords:** amino acid synthesis, $C^{\alpha}$-tetrasubstituted α-amino acids, unnatural amino acids

## Introduction

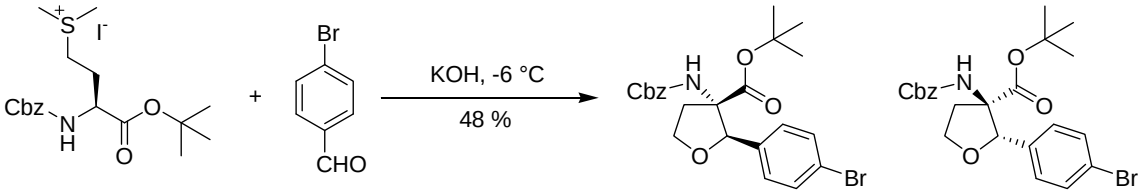
$C^{\alpha}$-Tetrasubstituted *α*-amino acids are important molecules for the synthesis of peptidemimetics with stabilized secondary structure, because of their ability to rigidify the peptide backbone [1–7]. Recently we developed a tetrahydrofuran based $C^{\alpha}$-tetrasubstituted α-amino acid which is Boc-protected at the *N*-terminus and $^{t}$butyl protected at the *C*-terminus [8]. Unfortunately, these two protecting groups are not entirely orthogonal: Cleavage of the Boc-group with HCl saturated diethyl ether is possible in the presence of the $^{t}$butyl-ester, but the ester group cannot be saponified without cleaving the Boc-group. Therefore we decided to synthesize a tetrahydrofuran amino acid with orthogonal protecting groups. We use the Cbz-group for amine protection and the $^{t}$butyl-group for the protection of the carboxylic acid, because both moieties are stable to the strongly basic conditions which are used during the synthesis of the tetrahydrofuran amino acid.

## Synthesis

The synthesis starts from methionine (**1**) which was protected at the *N*-terminus using benzyl carbonochloridate. Subsequently, the $^{t}$butyl-ester was introduced using a Steglich-type esterification reaction. After methylation resulting in the sulfonium salt **2**, the cyclisation reaction was performed using *4*-bromobenzaldehyde **3**. *rac*-tert-Butyl 3-(benzyloxycarbonylamino)-2-(4-bromophenyl)-tetrahydrofuran-3-carboxylate (*rac*-**4**) was formed in a highly diastereoselective manner as a racemic mixture of the *trans*-products in a yield of 48 %.

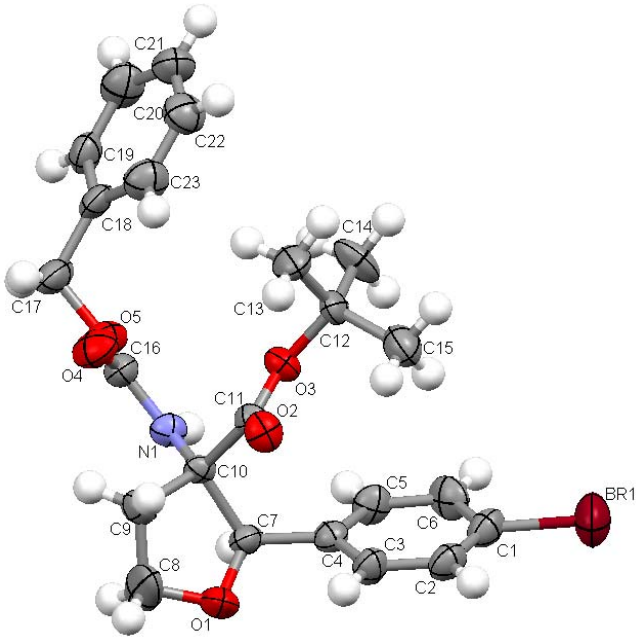



**1** **2**



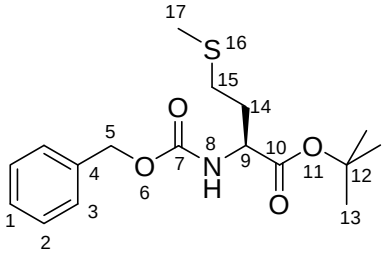

**2** **3** **4**

The connectivity and relative configuration of tert-butyl 3-(benzyloxycarbonylamino)-2-(4-bromophenyl)-tetrahydrofuran-3-carboxylate (**4**) was confirmed by an X-ray structure analysis. Suitable crystals were obtained by recrystallization from MeOH.



*tert-Butyl 2-(benzyloxycarbonylamino)-4-(methylthio)butanoate*

2-(Benzyloxycarbonylamino)-4-(methylthio)butanoic acid (**1**, 3.00 g, 10.6 mmol) was dissolved under a nitrogen atmosphere in 50 ml of dry DCM and cooled to 0 °C in an ice bath. To this solution DMAP (108 mg, 0.88 mmol) and $^{t}$butanol (1.21 ml, 12.7 mmol) were added. Under vigorous stirring dicyclohexyl carbonate (2.84 g, 13.8 mmol) was slowly added in portions. The mixture was stirred at 0 °C for 2 hours, allowed to warm to room temperature and stirred for additional 12 hours. Precipitated urea was filtered off and washed twice with 25 ml of DCM. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc:PE 30:70, $R_f$ = 0.48) to give the product as colorless oil (1.84 g, 6.02 mmol, 57 %).



MS (CI, $NH_3$): *m/z* (%) = 284.0 (7) [$MH^+$ - $C_4H_8$], 301.1 (52) [$MNH_4^+$ - $C_4H_8$], 340.1 (15) [$MH^+$], 357.1 (100) [$MNH_4^+$].

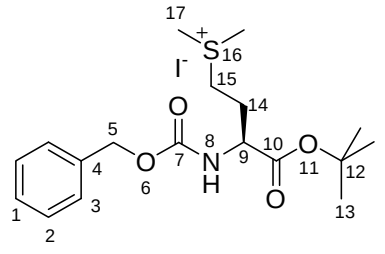
IR (NEAT) [$cm^{-1}$]: $\tilde{\nu}$ = 2979, 2917, 1708, 1523, 1455, 1368, 1224, 1149, 1046, 965, 845, 738, 696.

$^1$H-NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 13), 1.82-2.20 (m, 5 H, 14 + 17), 2.41-2.61 (m , 2 H, 15), 4.25-4.44 (m, 1 H, 9), 5.11 (s, 2 H, 5), 5.39 (d, $^3J_{H,H}$ = 7.4, 1 H, 8), 7.28-7.43 (m, 5 H, H-Ar).

$^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 15.5 (+, 1 C, 17), 28.0 (+, 3 C, 13), 29.9 (-, 1 C, 15), 32.5 (+, 1 C, 14), 53.8 (+, 1 C, 9), 67.0 (+, 1 C, 5), 82.4 ($C_{quat}$, 1 C, 12), 128.1 (+, 2 C, 3), 128.2 (+, 1 C, 1) , 128.5 (+, 2 C, 2), 136.3 ($C_{quat}$, 1 C, 4), 155.9 ($C_{quat}$, 1 C, 7), 171.0 ($C_{quat}$, 1 C, 10).

*(3-(Benzyloxycarbonylamino)-4-tert-butoxy-4-oxobutyl)dimethylsulfonium iodide* (**2**)

tert-Butyl 2-(benzyloxycarbonylamino)-4-(methylthio)butanoate (3.00 g, 10.6 mmol) was dissolved in 32 ml of methyl iodide (3 ml/mmol) and stirred for three days at room temperature in the dark. The solution was cooled to 0 °C in an ice bath and 32 ml of heptane (3 ml/mmol) were added to precipitate the product. The mixture was kept at 0 °C in the dark for four hours to complete the precipitation. The hygroscopic and light sensitive product was obtained after filtration and washing with ice-cold heptane as a colorless solid (1.39 g, 2.89 mmol, 98%) in analytically pure form.



MP 35-37 °C.

MS (ES, DCM/MeOH + 10 mmol/l $NH_4OAc$): *m/z* (%) = 354.1 (100) [$M^+$].

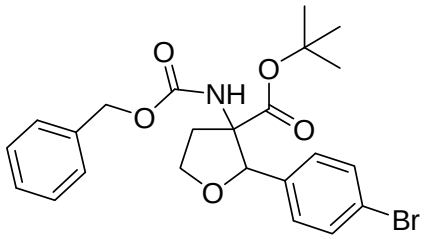
IR (NEAT) [$cm^{-1}$]: $\tilde{\nu}$ = 2980, 2928, 1707, 1518, 1238, 1151, 1047, 740, 698.

$^1$H-NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 13), 2.20-2.49 (m, 2 H, 14), 3.19 (s, 3 H, 17), 3.23 (s, 3 H, 17), 3.59-3.81 (m, 1 H, 15), 3.85-4.02 (m, 1 H, 15), 4.21-4.38 (m, 1 H, 9), 5.10 (s, 2 H, 5), 6.09 (d, $^3J_{H,H}$ = 7.1, 1 H, 8), 7.28-7.47 (m, 5 H, 1 -3).

$^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 25.7 (+, 1 C, 17), 26.0 (+, 1 C, 17), 28.0 (+, 3 C, 13), 31.9 (-, 1 C, 14), 40.5 (+, 1 C, 15), 53.2 (+, 1 C, 9), 67.2 (+, 1 C, 5), 83.5 ($C_{quat}$, 1 C, 12), 128.2 (+, 2 C, 3), 128.3 (+, 1 C, 1) , 128.6 (+, 2 C, 2), 136.3 ($C_{quat}$, 1 C, 4), 156.5 ($C_{quat}$, 1 C, 7), 169.9 ($C_{quat}$, 1 C, 10).

*rac-tert-Butyl 3-(benzyloxycarbonylamino)-2-(4-bromophenyl)-tetrahydrofuran-3-carboxylate* (*rac*-**4**)

In an oven dried Schlenk flask under nitrogen atmosphere (3-(benzyloxycarbonylamino)-4-tert-butoxy-4-oxobutyl)-dimethylsulfonium iodide (**2**, 4.68 g, 9.73 mmol, 1.2 eq.) was dissolved in dry acetonitrile (5 ml per 1 mmol sulfonium salt). The colorless solution was cooled to -6 °C and potassium hydroxide (546 mg, 9.73 mmol, 1.2 eq.) followed by *4*-bromobenzaldehyde (**4**, 1.50 g, 8.11 mmol, 1 eq.) were added. The mixture was stirred at -6 °C for 6 h. After complete consumption of the starting material (checked via TLC, 60:40 PE:diethyl ether, $R_f$ = 0.05) the reaction mixture was quenched with water (4 ml per mmol sulfonium salt) and extracted with diethyl ether (1 x 4 ml/mmol, 2 x 5 ml/mmol sulfonium salt). The combined organic layers were washed with brine solution and dried over $MgSO_4$. After removal of the solvent under reduced pressure the crude product was purified by flash chromatography [9] using a 80:20 mixture of PE:diethyl ether ($R_f$ = 0.15) to give a white crystalline solid in 48 % yield (1.85 g, 3.90 mmol).




MP 133-135 °C.

MS (ES, DCM/MeOH + 10 mmol/l $NH_4OAc$): *m/z* (%) = 476.2 (7) [$MH^+$], 495.2 (100) [$MNH_4^+$], 476.1 (100) [$M - H^+$], 536.2 (10) [$M + CH_3COO^-$].

IR (NEAT) [$cm^{-1}$]: $\tilde{\nu}$ = 3334, 2977, 2947, 2860, 1702, 1593, 1524, 1491, 1361, 1247, 1154, 1073, 1011, 986, 827, 790, 750, 697.

$^1$H-NMR (300 MHz, $CDCl_3$): δ = 1.11(s, 9 H, $^t$Bu), 2.54-2.81 (m, 2 H, $CH_2$), 4.22-4.37 (m, 2 H, O-$CH_2$), 5.08-5.21 (m, 3 H, $CH_2$–Cbz + CH), 6.00 (bs, 1 H, NH), 7.20 (d, $^3J_{H,H}$ = 7.9, 2 H, CH-Ar), 7.28-7.45 (m, 7 H, CH-Cbz, CH-Ar).

$^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 27.4 (+, 3 C, $CH_3$-$^t$Bu), 35.8 (-, 1 C, $CH_2$), 66.8 (-, 1 C, O-$CH_2$), 67.9 (-, 1 C, $CH_2$-Bzl), 69.5 ($C_{quat}$, 1 C, C-NH), 83.0 ($C_{quat}$, 1 C, C-$^t$Bu), 83.8 (+, 1 C, CH) , 121.7 ($C_{quat}$, 1 C, C-Br), 127.7 (+, 2 C, CH-Bzl), 128.2 (+, 2 C, CH-Bzl), 128.3 (+, 1 C, CH-Bzl), 128.6 (+, 2 C, CH-Ar), 131.0 (+, 2 C, CH-Ar), 136.2 ($C_{quat}$, 1 C, C-Ar), 136.5 ($C_{quat}$, 1 C, C-Ar), 154.6 ($C_{quat}$, 1 C, CO-Bzl), 169.9 ($C_{quat}$, 1 C, COO$^t$Bu).

Elemental analysis calcd. (%) for $C_{23}H_{26}BrNO_5$ (524.49): C 57.99, H 5.50, N 2.94; found: C 58.04, H 5.55, N 2.82.

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