First publ. in: Liebigs Annalen der Chemie 1993, 3, pp. 321-323

Notizen / Notes

Asymmetric Synthesis via Heterocyclic Intermediates, L[1]

Trichloroacetimidates, II[2]

Asymmetric Synthesis of α-Amino Acid Benzyl Esters via the Bisbenzyl Bislactim Ether of cyclo(-L-Val-Gly-)

Ulrich Groth*, Carsten Schmeck and Ulrich Schöllkopf*

Institut für Organische Chemie der Universität Göttingen,
Tammannstraße 2, W-3400 Göttingen, Germany

Key Words: Peptides / Amino acids / Trichloroacetimidates / Bislactim ether method

The diketopiperazine cyclo(-L-Val-Gly-) (**1**) can be *O*-alkylated under mild acidic reaction conditions with the alkyl trichloroacetimidates **2** to the corresponding bisalkyl bislactim ethers. Alkylation of the bisbenzyl bislactim ether anion of cyclo(-L-Val-Gly-) **4c** with benzyl bromide and subsequent hydrolysis with aqueous trifluoroacetic acid afforded D-phenylalanine benzyl ester (**8**) with an enantiomeric excess of >95%.

The bislactim ether method is well established in the asymmetric synthesis of proteinogenic and nonproteinogenic amino acids[3]. The key intermediate of this method is the bismethyl bislactim ether of cyclo(-L-Val-Gly-) (**4a**), which has to be prepared from trimethyloxonium tetrafluoroborate and cyclo(-L-Val-Gly-) in dichloromethane[4]. This reaction is cumbersome since trimethyloxonium tetrafluoroborate, **1** as well as the primary product — the bistetrafluoroborate of the bismethyl bislactim ether of **1** — are insoluble in dichloromethane. Moreover, the quality and consistency of trimethyloxonium tetrafluoroborate and cyclo(-L-Val-Gly-) depend on their preparation. Therefore, the obtainable yields of the bismethyl bislactim ether of **1** vary, depending on the quality of the starting materials and the scale of the preparation.

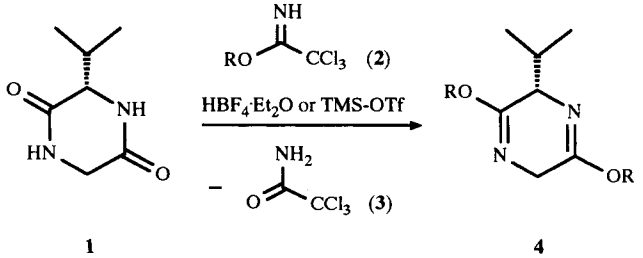
Trichloroacetimidates seem to be suitable for the *O*-alkylation of **1**, since benzyl trichloroacetimidate (**2c**) has been successfully employed for the benzylation of base- and acid-sensitive primary, secondary and tertiary alcohols[2], carbohydrates[5,6], lactams[7] and β-hydroxy esters[8]. Trichloroacetimidates were first prepared and thoroughly investigated by Cramer and his group in the late fifties[9].

Methyl trichloroacetimidate (**2a**), ethyl trichloroacetamidate (**2b**) and benzyl trichloroacetimidate (**2c**) have been prepared on a 300-g scale by a base-catalyzed addition of methanol, ethanol or benzyl alcohol to trichloroacetonitrile according to Cramer's protocol[9a]. Treatment of cyclo(-L-Val-Gly-) (**1**) with four equivalents of ethyl trichloroacetimidate (**2b**) and four equivalents of tetrafluoroboric acid—diethyl ether ($HBF_4 \cdot OEt_2$) furnishes the bisethyl bislactim ether of cyclo(-L-Val-Gly-) (**4b**) in 82% yield besides trichloroacetamide (**3**), which can be easily separated by distillation or — when the reactions have been carried out on a smaller scale — by column filtration.

According to this procedure the bismethyl bislactim ether of cyclo(-L-Val-Gly-) (**4a**) should be obtainable by treatment of **1** with four equivalents of methyl trichloroacetimidate (**2a**) and four equivalents of tetrafluoroboric acid—dimethyl ether ($HBF_4 \cdot OMe_2$).

When **1** is allowed to react with methyl trichloroacetimidate (**2a**) and tetrafluoroboric acid—diethyl ether ($HBF_4 \cdot OEt_2$), a mixture of the bismethyl bislactim ether **4a**, the bisethyl bislactim ether **4b** and both regioisomeric ethyl methyl bislactim ethers of cyclo(-L-Val-Gly-) is obtained. This result is in agreement with the proposed mechanism for the *O*-alkylation of **1** with methyl trichloroacetimidate in the presence of $HBF_4 \cdot OEt_2$ (Scheme 2).

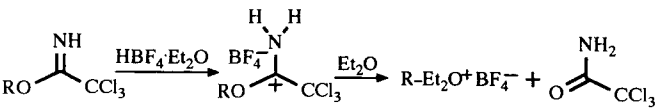
Scheme 1



1 **4**

2, 4	R	Yield of 4 (%)
a	Me	
b	Et	82
c	Bn	61

Scheme 2



2a,b **5** **6** **3**

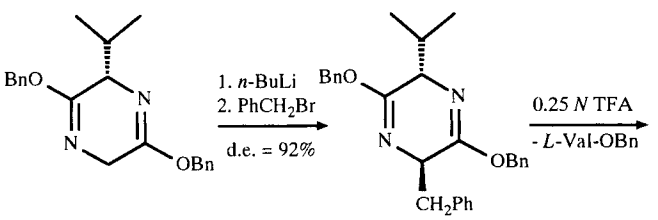
R = Me, Et

In the first step tetrafluoroboric acid – diethyl ether ($HBF_4 \cdot OEt_2$) reacts with the methyl acetimidate to the tetrafluoroboronate **5** and diethyl ether. In the second step the diethyl ether attacks the methoxy group to yield trichloroacetamide (**3**) and the "mixed" diethylmethyloxonium tetrafluoroborate **6**. This oxonium salt transmits either a methyl or an ethyl group to the amido oxygen of **1** to give a mixture of bislactim ether isomers.

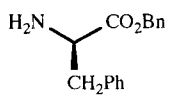
Upon treatment of **1** with 2.5 equivalents of benzyl trichloroacetimidate (**2c**) and 0.2 equivalents of trimethylsilyl trifluoromethanesulfonate (TMS-OTf), 62% of the bisbenzyl bislactim ether of cyclo(-L-Val-Gly-) (**4c**) is obtained. The yields of **4c** should be increased by using equimolar amounts of TMS-OTf for this reaction. On the other hand, the amount of *N*-benzylacetamide resulting from an acid-induced rearrangement of benzyl trichloroacetimidate[9b] might increase as well. Moreover, the use of other Lewis acids might increase the yield of this bisbenzyl bislactim ether **4c**, since Lewis acids other than TMS-OTf have not been applied to this reaction until now.

Since the bislactim ethers **4** and trichloroacetamide (**3**) can be easily separated on a larger scale by filtration or distillation and since trichloroacetamide (**3**) can be recycled into the trichloroacetimidates **2** through simple dehydratisation[10], the use of alkyl trichloroacetimidates can be recommended for the preparation of bislactim ethers – particularly on a larger scale.

Scheme 3



4c **7**



8

The bisbenzyl bislactim ether of cyclo(-L-Val-Gly-) **4c** can be lithiated and alkylated in the same way as the classical bismethyl bislactim ether **4a**[4].

In an exemplary experiment **4c** is lithiated with *n*-butyllithium and treated subsequently with benzyl bromide to yield in 73% the (2*R*,5*S*)-2-benzyl-5-isopropyldihydropyrazine **7** with a diastereomeric excess of 92%. After chromatographical purification **7** is isolated diastereomerically pure. Upon acidic hydrolysis of **7** with 0.25 N trifluoroacetic acid (TFA)[11] D-phenylalanine benzyl ester (**8**) is obtained in 53% yield besides benzyl L-valinate, the chiral auxiliary of this synthesis.

The use of the bisbenzyl bislactim ether of cyclo(-L-Val-Gly-) (**4c**) in the asymmetric synthesis of α-amino acid benzyl esters offers several advantages:

1. C-terminal benzyl-protected amino acids or oligopeptides are well-established building blocks in peptide synthesis.
2. In contrast to α-amino acid methyl esters α-amino acid benzyl esters do not cyclize or polymerize quickly and can be stored at room temperature.
3. The benzyl ester group can be easily removed by hydrogenolysis. Therefore, amino acids, which are sensitive to bases or acids, can be prepared by using the bisbenzyl bislactim ether of cyclo(-L-Val-Gly-) (**4c**).

Financial support by the *Stiftung Volkswagenwerk* and the *Fonds der Chemischen Industrie* is gratefully acknowledged. Special thanks are due to Dr. *H.-P. Albrecht*, BASF pharmaceutical research, for his kind assistance. We thank the *BASF AG* and the *Degussa AG* for providing valuable starting materials.

Experimental

Infrared (IR) spectra were recorded with a Perkin-Elmer 298 spectrometer. NMR spectra were measured with a Varian XL 200 or a VXR 200 spectrometer for ^1H and ^{13}C NMR. Chemical shifts are given in δ values by using tetramethylsilane as an internal standard for ^1H- and ^{13}C NMR spectroscopy. Mass spectra were recorded with Varian MAT 731 or 311 A spectrometers. Optical rotations were measured on a Perkin-Elmer Mod. 141 polarimeter. TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (30–60 μm) from Baker was used for flash chromatography. Combustion analyses were carried out by the microanalytical laboratory of the University of Göttingen. All reactions were carried out under nitrogen or argon except those involving hydrolysis. All reagents were purified and dried if necessary before use. cyclo(-L-Val-Gly-) was obtained from Degussa AG (Germany). The 54% solution of $HBF_4 \cdot Et_2O$ in diethyl ether was purchased from Merck-Schuchardt (Germany).

(2S)-3,6-Diethoxy-2,5-dihydro-2-isopropylpyrazine (**4b**): To a suspension of 0.78 g (5 mmol) of **1** in 100 ml of dichloromethane 3.81 g (20 mmol) of ethyl trichloroacetimidate (**2b**) was added. Then 20 mmol of $HBF_4 \cdot Et_2O$ (2.7 ml of a 54% solution in diethyl ether) was added with stirring at 0°C, and stirring was continued at room temp. for 7 d. Subsequently 100 ml of 2.5 N NaOH was added at 0°C, and stirring was continued at room temp. for 30 min. The aqueous layer was extracted twice with 100 ml of dichloromethane, the combined organic layers were reextracted with 100 ml of H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (0°C/15 Torr) and the residue purified by bulb-to-bulb distillation to afford 0.87 g (82%) of **4b** as a colorless oil. In order to obtain correct analytical data, a sample was further purified by chromatography (silica gel; diethyl ether/petroleum ether, 1:5); R_f = 0.31, b.p. 94–96°C/14 Torr, $[\alpha]_D^{20}$ = +86.0 (*c* = 1.0, EtOH). – IR (neat): $\tilde{\nu}$ = 1695 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.79 and 1.06 [2 d, *J* = 7.5 Hz; 6H, $CH(CH_3)_2$], 1.29 and 1.31 (2 t, *J* = 7.0 Hz; 6H, OCH_2CH_3), 2.25 [dsept, *J* = 7.5 and 3.0 Hz; 1H, $CH(CH_3)_2$], 3.83–4.01 (m; 3H, 2-H and 5-CH_2), 4.05–4.30 (m; 4H, OCH_2CH_3).

$C_{11}H_{20}N_2O_2$ (212.3) Calcd. C 62.24 H 9.50
Found C 62.02 H 9.34

(2S)-3,6-Dibenzyloxy-2,5-dihydro-2-isopropylpyrazine (**4c**): To a suspension of 1.56 g (10 mmol) of **1** in 200 ml of dichloromethane 6.31 g (25 mmol) of benzyl trichloroacetimidate (**2c**) was added under argon. Then 0.37 ml (2 mmol) of trimethylsilyl trifluoromethanesulfonate (TMS-OTf) was added with stirring at 0°C, and stirring was continued at room temp. for 6 d. Subsequently 100 ml of 2.5 N NaOH was added at 0°C, and stirring was continued at room temp. for 30 min. The aqueous layer was extracted twice with 100 ml of dichloromethane, the combined organic layers were reextracted with of 100 ml H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (30°C/15 Torr) and the residue purified by chromatography (silica gel, 100 g; diethyl ether/petroleum ether, 1:10) to yield 2.05 g (61%) of **4c** as a colorless oil; R_f = 0.30. –

IR (neat): $\tilde{\nu}$ = 1690 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.72 and 1.04 [2 d, J = 7.0 Hz; 6H, $CH(CH_3)_2$], 2.32 [dsept, J = 7.0 and 3.0 Hz; 1H, $CH(CH_3)_2$], 4.06–4.18 (m; 3H, 2-H and 5-CH_2), 5.08 and 5.18 (AB signal, J_{AB} = 11.5 Hz; 2H, $OCH_2C_6H_5$), 5.17 and 5.26 (AB signal, J_{AB} = 12.5 Hz; 2H, $OCH_2C_6H_5$), 7.12–7.50 (m; 10H, C_6H_5). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 16.75 and 19.11 [$CH(CH_3)_2$], 32.29 [$CH(CH_3)_2$], 46.72 (C-5), 61.09 (C-2), 66.79 and 66.91 (3- and 6-$OCH_2C_6H_5$), 127.66, 127.78, 127.95, 128.05, 128.37, 128.90, 136.92 and 137.03 (C_6H_5), 161.42 and 164.07 (C=N). – MS (70 eV): m/z (%) = 336 (28) [M^+], 91 (100) [$C_7H_7^+$].

$C_{21}H_{24}N_2O_2$ (336.4) Calcd. C 74.97 H 7.19
Found C 74.63 H 7.02

(2R,5S)-2-Benzyl-3,6-dibenzyloxy-2,5-dihydro-5-isopropylpyrazine (**7**): A solution of *n*-butyllithium in hexane (1.58 N, 1.9 ml, 3 mmol) was added at –70°C to a stirred solution of 0.81 g (2.4 mmol) of the bislactim ether **4c** in 30 ml of THF. After 30 min a solution of 0.51 g (3 mmol) of benzyl bromide in 5 ml of THF was added within 10 min. After stirring had been continued at –78°C for 12 h, 30 ml of a saturated NH_4Cl solution was added, and the solution was allowed to warm up to room temp. within 10 min. The layers were separated, the aqueous layer was reextracted twice with 30-ml portions of diethyl ether, and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo (30°C/15 Torr) and the residue purified by chromatography (silica gel, 70 g; diethyl ether/petroleum ether, 1:5) to yield 0.75 g (73%) of **7**; R_f = 0.44. Diastereomeric ratio: 23:1, determined by GC-MS of the crude product **7**; diastereomerically pure after chromatography. – IR (neat): $\tilde{\nu}$ = 1680 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.58 and 0.94 [2 d, J = 7.0 Hz; 6H, $CH(CH_3)_2$], 2.22 [dsept, J = 7.0 and 3.2 Hz; 1H, $CH(CH_3)_2$], 3.08 and 3.17 (AB part of ABX, J_{AB} = 12.5 Hz, J_{AX} = J_{BX} = 5 Hz; 2H, 2-$CH_2C_6H_5$), 3.31 (dd, ^3J = ^5J = 3.2 Hz; 1H, 5-H), 4.42 (X part of ABX, J_{AX} = J_{BX} = 5 Hz, ^5J = 3.2 Hz; 1H, 2-H), 5.07 and 5.19 (AB signal, J_{AB} = 12.5 Hz; 2H, $OCH_2C_6H_5$), 5.11 and 5.21 (AB signal, J_{AB} = 13.0 Hz; 2H, $OCH_2C_6H_5$), 6.90–7.51 (m; 15H, C_6H_5). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 16.29 and 19.14 [$CH(CH_3)_2$], 30.94 [$CH(CH_3)_2$], 39.91 (2-$CH_2C_6H_5$), 56.80 (C-2), 60.29 (C-5), 66.49 and 66.62 (3- and 6-$OCH_2C_6H_5$), 126.24, 127.68, 127.73, 127.79, 127.95, 128.11, 128.35, 128.47, 130.01, 137.16, 137.33 and 137.39 (C_6H_5), 161.65 and 163.27 (C=N). – MS (70 eV): m/z (%) = 426 (7) [M^+], 335 (8) [$M^+ - CH_2C_6H_5$], 91 (100) [$C_7H_7^+$].

$C_{28}H_{30}N_2O_2$ (426.6) Calcd. C 78.84 H 7.09
Found C 78.67 H 7.16

D-Phenylalanine Benzyl Ester (**8**): A suspension of 0.73 g (1.7 mmol) of diastereomerically pure **7** in 27.2 ml of 0.25 N trifluoroacetic acid (6.8 mmol) was stirred at room temp. for 6 d. Then 30 ml of diethyl ether was added, and the mixture was brought to pH = 8–10 by the addition of conc. ammonia with stirring. The layers were separated, and the aqueous layer was extracted twice with 30-ml portions of diethyl ether. The combined ethereal layers were dried with $MgSO_4$, the solvent was evaporated in vacuo (20°C/10 Torr) and the residue – crude benzyl D-phenylalaninate (**8**) and benzyl L-valinate – was separated by bulb-to-bulb distillation to yield 0.23 g (53%) of **8**. Enantiomeric excess: >95%, determined by ^1H NMR spectroscopy with the chiral shift reagent $Eu(TFC)_3$[12]. B.p. 120–130°C/0.01 Torr, $[\alpha]_D^{20}$ = +21.8 (c = 0.9, 0.1 N HCl) ⟨ref.[13]: $[\alpha]_D^{25}$ = –22.5 (c = 1.01, 0.1 N HCl) for L-Phe-OBzl⟩. – IR (neat): $\tilde{\nu}$ = 3400–3200 (NH_2), 1725 cm^{-1} (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.54 (s; 2H, NH_2), 2.89 and 3.09 (AB part of ABX, J_{AB} = 13.5 Hz, J_{AX} = 7.8 Hz, J_{BX} = 5.4 Hz; 2H, $CH_2C_6H_5$), 3.78 (X part of ABX, J_{AX} = 7.8 Hz, J_{BX} = 5.4 Hz; 1H, 2-H), 5.14 (s; 2H, $OCH_2C_6H_5$), 7.13–7.32 (m; 10H, C_6H_5). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 40.87 ($CH_2C_6H_5$), 55.73 (C-2), 66.77 ($OCH_2C_6H_5$), 126.82, 126.92, 127.42, 128.49, 128.58, 129.29, 135.45 and 136.89 (C_6H_5), 174.75 (C=O).

$C_{16}H_{17}NO_2$ (255.3) Calcd. C 75.27 H 6.71
Found C 75.52 H 6.59

[1] For part XLIX see: K. Busch, U. Groth, W. Kühnle, U. Schöllkopf, *Tetrahedron* **1992**, *48*, 5607 [Tetrahedron Symposia-in-Print *"Organotitanium Reagents in Organic Synthesis"*].

[2] For part I see: P. Eckenberg, U. Groth, T. Huhn, N. Richter, C. Schmeck, *Tetrahedron* **1993**, in print.

[3] For a recent review on the asymmetric synthesis of amino acids by using the bislactim ether method, see: R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, **1989**, p. 1–33.

[4] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem.* **1981**, *93*, 793; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798.

[5] R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212.

[6] [6a] T. Iversen, D. R. Bundle, *J. Chem. Soc., Chem. Commun.* **1981**, 1240. – [6b] H. P. Wessel, T. Iversen, D. R. Bundle, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.

[7] J. Danklmaier, H. Hönig, *Liebigs Ann. Chem.* **1989**, 665.

[8] [8a] P. Barbier, F. Schneider, U. Widmer, *Helv. Chim. Acta* **1987**, *70*, 1412. – [8b] U. Widmer, *Synthesis* **1987**, 568. – [8c] P. Barbier, F. Schneider, *J. Org. Chem.* **1988**, *53*, 1218. – [8d] J. D. White, G. N. Reddy, G. O. Spessard, *J. Am. Chem. Soc.* **1988**, *110*, 1624.

[9] [9a] F. Cramer, K. Pawelzik, H. J. Baldauf, *Chem. Ber.* **1958**, *91*, 1049. – [9b] F. Cramer, N. Hennrich, *Chem. Ber.* **1961**, *94*, 976.

[10] J. v. Braun, W. Rudolf, *Ber. Dtsch. Chem. Ges.* **1943**, *67*, 1769.

[11] T. Beulshausen, U. Groth, U. Schöllkopf, *Liebigs Ann. Chem.* **1991**, 1207.

[12] $Eu(TFC)_3$ = Tris[3-(2,2,2-trifluoro-1-hydroxyethyliden)-d-camphorato]europium(III). – [12a] M. D. McGreary, D. W. Lewis, D. L. Wernick, G. M. Whitesides, *J. Am. Chem. Soc.* **1974**, *96*, 1038. – [12b] H. L. Goering, J. N. Eikenberry, G. S. Koemer, C. J. Lattimer, *J. Am. Chem. Soc.* **1974**, *96*, 1493.

[13] B. F. Erlanger, R. M. Hall, *J. Am. Chem. Soc.* **1954**, *76*, 5781.

[207/92]