Synthesis of *rac*-2′-(trimethylsilyl)isovaline: A novel silicon-containing α,α-dialkylated α-amino acid

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A B S T R A C T

An efficient, convenient, and reliable multi-step synthesis of *rac*-2′-(trimethylsilyl)isovaline (*rac*-**3**) that uses inexpensive reagents in all steps has been developed, starting from diethyl malonate (overall yield 28%). Compound *rac*-**3** is the first α-ethylated α,α-dialkylated silicon-containing α-amino acid.

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1. Introduction

Introduction of nonproteinogenic amino acids into peptides severely changes their conformational freedom and stabilizes secondary structures. In the ongoing search for new nonproteinogenic amino acids, silicon chemistry has been demonstrated to offer many opportunities for the design of novel silicon-containing amino acids (for recent studies, see ref. [1]). Most of the compounds known today are α-monoalkylated α-amino acids (such as **1**) [1d], whereas α,α-dialkylated derivatives (such as **2**) [1e] have not been as thourougly investigated (Chart 1). Due to the well known fact that carbon-based α-ethylated α,α-dialkylated α-amino acids induce fully planar C_5-conformations when present in peptides, while the corresponding α-methylated derivatives induce 3_{10}-helical structures [2], analogous silicon-containing α-ethylated α,α-disubstituted α-amino acids are interesting building blocks for the synthesis of tailor-made peptides with conformations that are controlled by these amino acids. In addition, such nonproteinogenic silicon-containing amino acids are challenging precursors for the synthesis of new nonpeptidic drugs.

We have now succeeded in synthesizing the first silicon-containing α-ethylated α,α-disubstituted α-amino acid, racemic 2′-(trimethylsilyl)isovaline (*rac*-**3**). To the best of our knowledge, the corresponding carbon analogue (Si/C exchange) of this compound has not yet been reported in the literature. In contrast, both enantiomers of the carbon analogue of **1** are well known and are commercially available. The racemic carbon analogue of **2** has also been reported [3].

2. Results and discussion

Compound *rac*-**3** was synthesized according to Scheme 1, starting from diethyl malonate. Thus, reaction of diethyl malonate with sodium ethoxide in ethanol, followed by treatment with (chloromethyl)trimethylsilane, afforded diethyl [(trimethylsilyl)methyl]malonate (**4**, 87% yield). Deprotonation of **4** with sodium ethoxide in ethanol and subsequent reaction with iodoethane furnished diethyl ethyl[(trimethylsilyl)methyl]malonate (**5**, 95% yield). Compound **5** was then treated with an ethanolic solution of potassium hydroxide. Reprotonation with concentrated hydrochloric acid yielded *rac*-2-(ethoxycarbonyl)-2-[(trimethylsilyl)methyl]butanoic acid (*rac*-**6**, 77% yield). Compound *rac*-**6** was then reacted with thionyl chloride, to yield ethyl *rac*-2-(chlorocarbonyl)-2-[(trimethylsilyl)methyl]butanoate (*rac*-**7**). Reaction of *rac*-**7** with sodium azide [4], heating of the resulting carboxylic acid azide
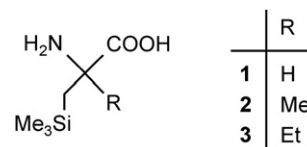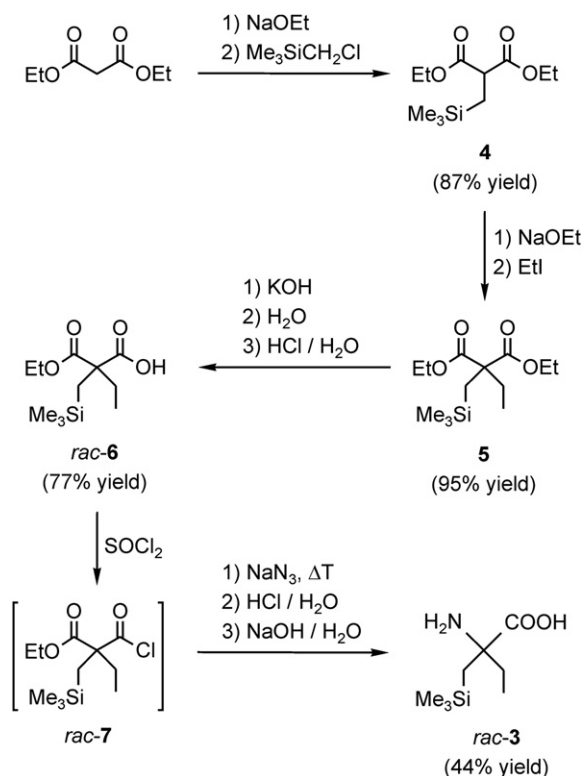

Chart 1.

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Scheme 1.

(Curtius rearrangement), and addition of hydrochloric acid to the resultant isocyanate gave rac-2′-(trimethylsilyl)isovaline hydro-chloride (rac-**3**·HCl). Treatment of rac-**3**·HCl with an aqueous solution of sodium hydroxide finally afforded rac-**3** (44% yield). Compound rac-**3** was obtained with an overall yield of 28%, starting from diethyl malonate.

Compound rac-**3** was isolated as a colorless crystalline solid, whereas **4**, **5**, rac-**6**, and rac-**7** were obtained as colorless liquids. The identities of rac-**3**, **4**, **5**, and rac-**6** were established by elemental analyses (C, H, N) and multinuclear NMR studies (^{1}H, ^{13}C, ^{15}N, ^{29}Si).

Attempts to prepare the two enantiomers (R)-**3** and (S)-**3** analogously to the synthesis of (R)-**2** and (S)-**2**, utilizing an enantioselective enzymatic conversion as the key step [**5** → (R)-**6**], failed. In contrast to diethyl methyl[(trimethylsilyl)methyl]malonate [1e], the corresponding ethyl analogue (Me/Et exchange) could not be converted with porcine liver esterase (no reaction observed) when
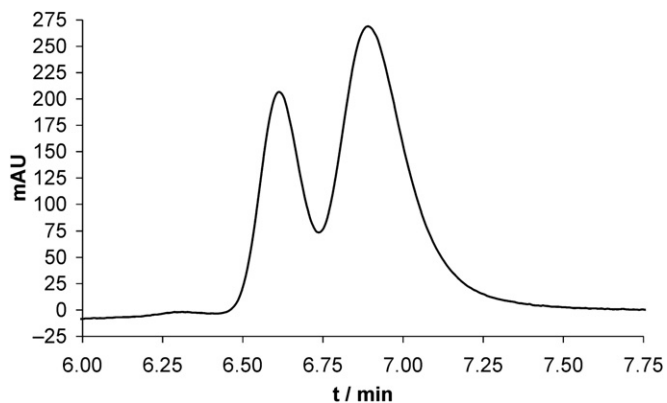
Fig. 1. Analytical HPLC chromatogram of the partial resolution of rac-**3** by using a chiral stationary phase. For details, see section 4.6.

using the protocol described in ref. [1e]. However, in principle the two enantiomers of **3** should be available by chromatographic resolution of rac-**3** using a chiral stationary phase. This method has also been used for the preparation of (R)-**1** and (S)-**1** on a preparative scale [5]. Preliminary studies on an analytical scale have already shown that rac-**3** can also be resolved chromatographically on a chiral macrocyclic glycopeptide phase (Fig. 1). This method needs to be further optimized and then to be applied to the preparative scale.

3. Conclusions

We have succeeded in synthesizing the first α-ethylated α,α-dialkylated silicon-containing α-amino acid, rac-2′-(trimethylsilyl)-isovaline (rac-**3**). Compound rac-**3** was prepared in a multi-step synthesis on a multi-gram scale, starting from diethyl malonate. The synthesis with an overall yield of 28% is efficient, convenient, and reliable and uses inexpensive reagents in all steps. A further scale-up of the synthesis of rac-**3** and the development of a preparative chromatographic resolution method for the preparation of (R)-**3** and (S)-**3** should be possible. The potential of this α-ethylated α,α-dialkylated silicon-containing α-amino acid as a precursor and building block for the synthesis of novel peptidic and nonpeptidic drugs needs to be evaluated in future studies (for reviews on silicon-containing drugs, see ref. [6]).

4. Experimental

4.1. General procedures

All syntheses in organic solvents were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. Melting points were determined with a Mettler Toledo DSC 823e apparatus. The ^{1}H, ^{13}C, ^{15}N, and ^{29}Si spectra were recorded at 23 °C on a Bruker Avance 500 NMR spectrometer (^{1}H, 500.1 MHz; ^{13}C, 125.8 MHz; ^{15}N, 50.7 MHz; ^{29}Si, 99.4 MHz). DMSO-d_6, C$_6$D$_6$, or D$_2$O were used as the solvent. Chemical shifts (δ, ppm) were determined relative to internal DMSO-d_5 (^{1}H, δ 2.49; DMSO-d_6), internal C$_6$HD$_5$ (^{1}H, δ 7.28; C$_6$D$_6$), internal DHO (^{1}H, δ 4.70; D$_2$O), internal DMSO-d_6 (^{13}C, δ 39.5; DMSO-d_6), internal C$_6$D$_6$ (^{13}C, δ 128.0; C$_6$D$_6$), external TMS (^{13}C, δ 0; D$_2$O/^{29}Si, δ 0; DMSO-d_6, C$_6$D$_6$, or D$_2$O), or external H$_2$NC(O)H (^{15}N, 90% in DMSO-d_6, δ −268.0; D$_2$O). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H COSY, ^{13}C,^{1}H, and ^{15}N,^{1}H correlation experiments, and the spin systems were analyzed by using the WIN-DAISY software package (version 4.05, Bruker) [7]. Assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C,^{1}H correlation experiments. The ^{15}N NMR data were obtained via ^{15}N,^{1}H correlation experiments. Coupling constants are given as their absolute values. The elemental analyses were performed via using a VarioMicro apparatus (Elementar Analysensysteme GmbH).

4.2. Preparation of rac-2′-(trimethylsilyl)isovaline (rac-2-amino-2-[(trimethylsilyl)methyl]butanoic acid, rac-**3**)

A solution of thionyl chloride (5.79 g, 48.7 mmol) in dichloromethane (30 mL) was added dropwise within 15 min to a stirred solution of rac-**6** (10.0 g, 40.6 mmol) in a mixture of dichloromethane (60 mL) and N,N-dimethylformamide (90 μL) at 0 °C. The resulting mixture was allowed to warm to 20 °C and was then stirred at this temperature for 16 h. The solvent and the excess thionyl chloride were removed under reduced pressure (20 °C, 0.02 mbar) to give the intermediate ethyl rac-2-(chlorocarbonyl)-2-[(trimethylsilyl)methyl]butanoate (rac-**7**) as a colorless liquid [^{1}H NMR (500.1 MHz, C$_6$D$_6$): δ 0.08 (9 H, s, SiCH$_3$), 0.84 (δ_X), 1.48 (δ_M),

1.60 (δ_N), 2.13 (δ_A), and 2.28 (δ_B) (7 H, ABMNX$_3$ system, $^2J_{AB} = 14.5$ Hz, $^2J_{MN} = 15.2$ Hz, $^3J_{AX} = 7.5$ Hz, $^3J_{BX} = 7.6$ Hz, $^4J_{BN} = 0.8$ Hz, SiCH$_M$H$_N$CCH$_A$H$_B$C(H$_X$)$_3$), 1.01 (δ_X), 3.98 (δ_A), and 4.08 (δ_B) (5 H, ABX$_3$ system, $^2J_{AB} = 10.8$ Hz, $^3J_{AX} = {}^3J_{BX} = 7.1$ Hz, OCH$_A$H$_B$C (H$_X$)$_3$). ^{13}C NMR (125.8 MHz, C$_6$D$_6$): δ 0.0 (SiCH$_3$), 9.0 (CCH$_2$CH$_3$), 14.1 (OCH$_2$CH$_3$), 21.9 (SiCH$_2$C), 29.1 (CCH$_2$CH$_3$), 62.4 (OCH$_2$CH$_3$), 67.6 (CCH$_2$CH$_3$), 170.3 (C(O)OCH$_2$CH$_3$), 174.9 (C(O)Cl). ^{29}Si NMR (99.4 MHz, C$_6$D$_6$): δ −0.4]. The intermediate rac-**7** (crude product, not further purified) was dissolved in acetone (40 mL), and the resulting solution was added dropwise within 15 min to a stirred suspension of sodium azide (2.91 g, 44.8 mmol) in acetone (50 mL) at 0 °C. The mixture was allowed to warm to 20 °C and was then stirred at this temperature for 4 h. The resulting precipitate was separated by suction filtration, washed with acetone (3 × 10 mL), and discarded. The filtrate (including the wash solutions) was then heated under reflux for 16 h, the mixture was allowed to cool to 20 °C, and the solvent was removed under reduced pressure [4]. Subsequently, hydrochloric acid (6 M, 300 mL) was added to the residue in a single portion at 20 °C, and the resulting mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure, and the solid residue was dissolved in water (150 mL). The resulting aqueous solution was extracted with diethyl ether (3 × 50 mL), and the aqueous phase was freeze-dried to afford a colorless powder [rac-**3**·HCl; the NMR data of the product (solvent, D$_2$O) were identical with those obtained for rac-**3**], which was dissolved in a mixture of methanol (112 mL) and an aqueous sodium hydroxide solution (1 M, 33.0 mL; 33.0 mmol of NaOH) [8]. The solution was kept undisturbed at 20 °C for one day, and the resultant precipitate was separated by filtration and washed with diethyl ether (2 × 30 mL) to afford rac-**3** in 44% yield as a colorless crystalline solid (3.36 g, 17.7 mmol). Mp.: 264 °C (dec.). Anal. Calc. (C$_8$H$_{19}$NO$_2$Si): C, 50.75; H, 10.12; N, 7.40; M, 189.33. Found: C, 50.6; H, 10.0; N, 7.5%. ^{1}H NMR (500.1 MHz, D$_2$O): δ 0.00 (9 H, s, SiCH$_3$), 0.88 (δ_X), 1.80 (δ_A), and 2.00 (δ_B) (5 H, ABX$_3$ system, $^2J_{AB} = 14.9$ Hz, $^3J_{AX} = 7.5$ Hz, $^3J_{BX} = 7.6$ Hz, CCH$_A$H$_B$C(H$_X$)$_3$), 1.23 (δ_A) and 1.28 (δ_B) (2 H, AB system, $^2J_{AB} = 14.8$ Hz, SiCH$_A$H$_B$C), NH$_3$ not detected (H/D exchange). ^{13}C NMR (125.8 MHz, D$_2$O): δ 0.0 (SiCH$_3$), 8.7 (CCH$_2$CH$_3$), 26.9 (SiCH$_2$C), 32.0 (CCH$_2$CH$_3$), 65.1 (CCH$_2$CH$_3$), 175.9 (C(O)OH). ^{15}N NMR (30.4 MHz, D$_2$O): δ −330.3. ^{29}Si NMR (99.4 MHz, D$_2$O): δ −1.3.

4.3. Preparation of diethyl [(trimethylsilyl)methyl]malonate (**4**)

This compound was prepared according to refs. [1d] and [1e].

4.4. Preparation of diethyl ethyl[(trimethylsilyl)methyl]malonate (**5**)

Compound **4** (211.1 g, 857 mmol) was added dropwise within 30 min to a stirred freshly prepared solution of sodium ethoxide in ethanol [prepared from sodium (21.7 g, 944 mmol) and ethanol (400 mL)] under reflux conditions. The resulting mixture was heated under reflux for 2 h, iodoethane (146.9 g, 942 mmol) was then added dropwise under reflux conditions within 1 h, and the resultant mixture was then heated under reflux for 24 h. Subsequently, the mixture was allowed to cool to 20 °C and was then neutralized with a few drops of concentrated hydrochloric acid. The solvent and the excess iodoethane were removed under reduced pressure, water (400 mL) was added to the residue, the aqueous phase was extracted with diethyl ether (3 × 100 mL), and the combined organic solutions were washed with an aqueous sodium thiosulfate solution (1 M, 3 × 75 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by distillation in vacuo (Vigreux column) to afford **5** in 95% yield as a colorless liquid

(224.2 g, 817 mmol). Bp.: 120 °C/12 mbar. Anal. Calc. (C$_{13}$H$_{26}$O$_4$Si): C, 56.90; H, 9.55; M, 274.43. Found: C, 56.6; H, 9.6%. ^{1}H NMR (500.1 MHz, C$_6$D$_6$): δ 0.19 (9 H, s, SiCH$_3$), 1.02 (3 H, t, $^3J_{HH} = 7.5$ Hz, CCH$_2$CH$_3$), 1.06 (δ_X), 4.07 (δ_A), and 4.13 (δ_B) (10 H, ABX$_3$ system, $^2J_{AB} = 10.8$ Hz, $^3J_{AX} = 7.0$ Hz, $^3J_{BX} = 7.2$ Hz, OCH$_A$CH$_B$C(H$_X$)$_3$), 1.60 (2 H, s, SiCH$_2$C), 2.25 (2 H, q, $^3J_{HH} = 7.5$ Hz, CCH$_2$CH$_3$). ^{13}C NMR (125.8 MHz, C$_6$D$_6$): δ −0.1 (SiCH$_3$), 9.2 (CCH$_2$CH$_3$), 14.0 (OCH$_2$CH$_3$), 21.6 (SiCH$_2$C), 29.5 (CCH$_2$CH$_3$), 56.5 (CCH$_2$CH$_3$), 60.8 (OCH$_2$CH$_3$), 172.4 (C(O)OCH$_2$CH$_3$). ^{29}Si NMR (99.4 MHz, C$_6$D$_6$): δ −0.3.

4.5. Preparation of rac-2-(ethoxycarbonyl)-2-[(trimethylsilyl)-methyl]butanoic acid (rac-**6**)

Potassium hydroxide (6.44 g, 115 mmol) was added in a single portion at 20 °C to a stirred solution of **5** (27.4 g, 99.8 mmol) in ethanol (100 mL). The mixture was heated under reflux for 16 h and was then allowed to cool to 20 °C. The solvent was removed under reduced pressure and water (400 mL) was added. The aqueous phase was extracted continuously with diethyl ether (700 mL) over a period of 6 h using a perforator, and the extract was discarded. The remaining aqueous solution was acidified with concentrated hydrochloric acid (10 mL) and was then extracted continuously with diethyl ether (700 mL) over a period of 9 h using a perforator. The organic phase was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (160 °C, 0.02 mbar) to afford rac-**6** in 77% yield as a colorless liquid (18.9 g, 76.7 mmol). Anal. Calc. (C$_{11}$H$_{22}$O$_4$Si): C, 53.63; H, 9.00; M, 246.38. Found: C, 53.6; H, 9.1%. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ −0.03 (9 H, s, SiCH$_3$), 0.76 (3 H, t, $^3J_{HH} = 7.5$ Hz, CCH$_2$CH$_3$), 1.13 (δ_A) and 1.15 (δ_B) (2 H, AB system, $^2J_{AB} = 15.0$ Hz, SiCH$_A$H$_B$C), 1.15 (δ_X), 4.04 (δ_A), and 4.09 (δ_B) (5 H, ABX$_3$ system, $^2J_{AB} = 10.9$ Hz, $^3J_{AX} = {}^3J_{BX} = 7.1$ Hz, OCH$_A$H$_B$C(H$_X$)$_3$), 1.79 (2 H, q, $^3J_{HH} = 7.5$ Hz, CCH$_2$CH$_3$), 12.7 (1 H, br. s, C(O)OH). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ −0.3 (SiCH$_3$), 8.7 (CCH$_2$CH$_3$), 13.9 (OCH$_2$CH$_3$), 20.5 (SiCH$_2$C), 28.2 (CCH$_2$CH$_3$), 55.5 (CCH$_2$CH$_3$), 60.5 (OCH$_2$CH$_3$), 172.3 (C(O)OCH$_2$CH$_3$), 173.4 (C(O)OH). ^{29}Si NMR (99.4 MHz, DMSO-d_6): δ −0.4.

4.6. Resolution of rac-**3** by analytical HPLC

The enantiomers of **3** were partially separated by analytical liquid chromatography (HPLC), starting from rac-**3** and using a chiral stationary phase. The experimental conditions were as follows: LC pump, SunChrom SunFlow 100; detector, SunChrom Spectra Flow 600 ($\lambda = 204.2$ nm); column thermostat, Spark Mistral; column temperature, 10 °C; column (25 cm, i.d. 4.60 mm), Chirobiotic R (macrocyclic glycopeptide phase (Ristotecin A) on spherical silica; particle size, 5 μm); mobile phase (purchased from LGC Promochem), water/acetonitrile [65:35 (v/v)], isocratic; flow, 0.5 mL min^{-1}; sample concentration, 10 mg mL^{-1} aqueous phosphoric acid solution (4 mL L^{-1}); injection volume, 5 μL.

References and notes

[1] (a) G. Reginato, A. Mordini, P. Meffre, A. Tenti, M. Valacchi, K. Cariou, Tetrahedr. Asymmetry 17 (2006) 922–926;
(b) F. Cavelier, D. Marchand, J. Martinez, Chem. Biodivers. 5 (2008) 1279–1287;
(c) D. Marchand, J. Martinez, F. Cavelier, Eur. J. Org. Chem. (2008) 3107–3112;
(d) S. Falgner, D. Schmidt, R. Bertermann, C. Burschka, R. Tacke, Organometallics 28 (2009) 2927–2930 and references therein;
(e) S. Falgner, C. Burschka, S. Wagner, A. Böhm, J.O. Daiss, R. Tacke, Organometallics 28 (2009) 6059–6066;
(f) M. Mortensen, R. Husmann, E. Veri, C. Bolm, Chem. Soc. Rev. 38 (2009) 1002–1010.
[2] (a) N. Imawaka, M. Tanaka, H. Suemune, Helv. Chim. Acta 83 (2000) 2823–2835;
(b) M. Oba, M. Tanaka, M. Kurihara, H. Suemune, Helv. Chim. Acta 85 (2002) 3197–3218;

(c) M. Tanaka, S. Nishimura, M. Oba, Y. Demizu, M. Kurihara, H. Suemune, Chem. Eur. J. 9 (2003) 3082–3090;
(d) M. Tanaka, Chem. Pharm. Bull. 55 (2007) 349–358.

[3] M. Procházka, Coll. Czechoslov. Chem. Commun. 42 (1977) 2394–2400.

[4] (a) Due to safety concerns with the use of sodium azide, the reaction step *rac*-**7** → *rac*-**3** was performed at 20 °C. Additionally, no acidic conditions were applied and, most importantly, neither the reaction mixture nor the product was concentrated during this step. (b) http://www.mrw. interscience.wiley.com/eros/articles/rs045/frame.html.

[5] M. Merget, K. Günther, M. Bernd, E. Günther, R. Tacke, J. Organomet. Chem. 628 (2001) 183–194.

[6] Recent reviews: (a) W. Bains, R. Tacke, Curr. Opin. Drug Discovery Dev. 6 (2003) 526–543;

(b) G.A. Showell, J.S. Mills, Drug Discovery Today 8 (2003) 551–556;
(c) J.S. Mills, G.A. Showell, Expert Opin. Invest. Drugs 13 (2004) 1149–1157;
(d) P.K. Pooni, G.A. Showell, Mini-Rev. Med. Chem. 6 (2006) 1169–1177;
(e) S. McN. Sieburth, C.-A. Chen, Eur. J. Org. Chem. (2006) 311–322;
(f) S. Gately, R. West, Drug Dev. Res. 68 (2007) 156–163;
(g) A.K. Franz, Curr. Opin. Drug Discovery Dev. 10 (2007) 654–671.

[7] (a) Program WIN-DAISY 4.05. Bruker-Franzen GmbH, Bremen, Germany, 1998;
(b) U. Weber, A. Germanus, H. Thiele, Fresenius J. Anal. Chem. 359 (1997) 46–49.

[8] The molar ratio takes into account the amount of *rac*-**3** · Hcl obtained in the previous step.