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Synthesis of the orthogonally protected amino alcohol Phaol and analogs

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The development of a multigram synthesis of the orthogonally protected amino acid-derived Phaol [2-{[(2*S*)-2-amino-3-phenylpropyl]amino}ethanol] is described. The goal of this work is to synthesize an orthogonally protected Phaol in a multigram scale up to 10 g (Cbz-Phaol), so it can be used in solution-based peptide synthesis of peptaibols. Two synthetic schemes were proposed and examined. Between the reduction-coupling and the coupling-reduction scheme, the latter gave the best results. A two-step synthesis affords easily purifiable products. Several analogs were synthesized using this methodology. All the molecules were orthogonally protected, so that they can be used in peptide synthesis. Deprotection posed no problems.

Supporting information may be found in the online version of this article

Keywords: amino alcohol; Phaol; septocylindrin; aibellin; synthesis

Introduction

Phaol, 2-{[(2*S*)-2-amino-3-phenylpropyl]amino}ethanol, is an amino alcohol present at the C-terminus of a number of peptaibols such as Aibellin [1] and Septocylindrin [2] (Figure 1), both naturally occurring peptides. In view of a total synthesis of these peptides, orthogonally protected Phaol is needed in large amounts.

The first report about Phaol and its synthesis was published in 1983 by Almquist *et al*. [3] where it was used as an intermediate for the synthesis of a tripeptide inhibitor of angiotensin-converting enzyme. In 1994, Kumazawa *et al*. [1] elucidated the structure of Aibellin, a 19-amino acid peptide antibiotic, with Phaol as terminal residue. He used an adapted version of the synthesis by Almquist. Both synthesize Phaol on small scale. In 2007, two new peptaibols, Septocylindrin A and Septocylindrin B, both with Phaol as terminal residue, were isolated from *Septocylindrum* sp. by Summers *et al*. [2]. They closely relate to Alamethicin, one of the most extensively studied among the peptaibols.

The goal of this work is to synthesize an orthogonally protected Phaol in a multigram scale, with easy purification, so that it can be used in solution-based peptide synthesis of peptaibols.

Experimental Procedures

The melting points were determined using a Reichert-Jung Thermovar or Electrothermal 9200 apparatus. The IR-spectra were recorded on a Bruker alpha-P spectrometer. NMR-spectra were recorded on a Bruker Avance 300 (300 MHz/75 MHz), Avance 400 (400 MHz/100 MHz) or Avance 600II$^+$ (600 MHz/150 MHz) spectrometer with tetramethylsilane as internal standard. For the ESI-MS spectra, a Thermo Electron LCQ Advantage with Agilent 1100 pump and injection system was used, methanol being the injection solvent. For purification, an MPLC Büchi Fraction collector C-660, Pump manager C-615, UV-photometer C-635, two Pump modules C-605 and Linseis D120S plotter were used. The flash silica gel used was Davisil® Chromatography Silica Medium, type LC 60A, 40–63 micron. For HPLC purifications, a Waters Delta 600 system, with a Waters 996 Photo Diode Array detector was used. For the polarimetry, a Propol automatic process polarimeter was used. Experimental detail for a representative synthetic route is given. All further experimental detail and characterization of all new compounds can be found in the supporting information.

General Procedure for the Coupling of Ethanolamine to *N*-protected Phenylalanine

N-protected phenylalanine is dissolved in dichloromethane. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl, 1.3 eq.) and HOBt (1.3 eq.) are added at 0 °C and the mixture is stirred for 20 min, after which ethanolamine (1.3 eq.) and NMM (1.3 eq.) are added at 0 °C. After stirring overnight, the mixture is washed with a 5% $KHSO_4$ solution, a 5% $NaHCO_3$ solution and with water. After drying over Na_2SO_4 and evaporation of the solvent, the residue is either crystallized or purified via column chromatography.

Representative Experimental Procedure for the Synthesis of *N*-[(benzyloxy)carbonyl]-*N*-(2-hydroxyethyl) phenylalaninamide 8

The product was synthesized using the general procedure for the coupling of ethanolamine: starting material used: *N*-(carbobenzyloxy)-L-phenylalanine (Cbz-Phe-OH) (20 g, 67 mmol) **Yield**: 80%; **m.p.:** 161–164 °C; **IR**: 3311, 1685, 1641, 1530.

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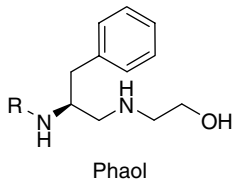


Phaol

Figure 1. Phaol [2-{[(2*S*)-2-amino-3-phenylpropyl]amino}ethanol].

^{1}H NMR (300 MHz, $CDCl_3$, ppm, with $\beta = \alpha CHCH_2Ph$): $\delta = 7{\cdot}38 - 7{\cdot}18$ (m, 10H, Ph), 6·16 (br s, 1H, CONH), 5·43 (s, 1H, OCONH), 5·05 (t (AB), $J = 14$ Hz, 2H, CH_2Cbz), 4·37 (q, $J = 7$ Hz, 1H, αH), $3{\cdot}59 - 3{\cdot}46$ (m, 2H, CH_2OH), $3{\cdot}31 - 3{\cdot}25$ (m, 2H, CH_2 NH), $3{\cdot}15 - 2{\cdot}98$ (d, $J = 7$ Hz, 2H, βH).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = 172{\cdot}2$ (CONH), 156·5 (OCONH), 136·8 + 136·4 (C Phe + Cbz), 129·7 + 129·1 + 129·0 + 128·7 + 128·4 + 127·5 (C Phe + Cbz), 67·5 (CH_2Cbz), 62·0 (CH_2OH), 56·9 (αC), 42·6 (CH_2 NH), 39·2 (βC).

ESI: 365·9 $[M+Na]^+$, 707·0 $[2M+Na]^+$.

General Procedure for Reduction with Red-Al (Sodium bis(2-methoxyethoxy)Aluminum Hydride)

N-protected *N*-(2-hydroxyethyl)phenylalaninamide is dissolved in a mixture of dry THF and dry toluene (ratio 1:2). The mixture is cooled to $-20\,^\circ$C, after which Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) is added very slowly. The reaction mixture is stirred at room temperature. When the reaction is completed, it is quenched with a 2 N NaOH solution at $-20\,^\circ$C. More toluene is added and the organic layer is washed twice with a 2 N NaOH solution, after which the organic layer is dried over Na_2SO_4 and evaporated *in vacuo*. The residue is crystallized from chloroform/*n*-hexane or purified via chromatography.

Representative Experimental Procedure for the Synthesis of Benzyl {1-benzyl-2-[(2-hydroxyethyl)amino]ethyl} Carbamate (Cbz-Phaol) 5

The product was synthesized using the general procedure for the reduction using Red-Al starting from compound **8** (10 g): Reaction time: 10 h; **Yield:** 45–60%; **m.p.:** 70–73 °C; **IR:** 3340, 3290, 3030, 2936, 2908, 2728.

^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 7{\cdot}37 - 7{\cdot}15$ (m, 10H, 2 × Ar), 5·07 (t (AB), $J = 13$ Hz, 2H, CH_2Cbz), 4·89 (br s, 1H, NH or OH), 3·98 (br s, 1H, αH), $3{\cdot}60 - 3{\cdot}57$ (m, 2H, CH_2OH), $2{\cdot}90 - 2{\cdot}59$ (m, 6H, $CH_2NHCH_2 + \beta$H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): 156·7 (CO), 137·9 + 136·9 (C Phe + C Cbz), 129·7 + 128·9 + 128·5 + 128·4 + 127·0 (CH Cbz+ CH Phe), 67·1 (CH_2Cbz), 61·1 (CH_2OH), 52·3 + 52·2 + 51·4 (αC + CH_2 $NHCH_2$), 39·5 (βC).

ESI: 329·5 $[M+H]^+$, 351·4 $[M+Na]^+$, 679·4 $[2M+Na]^+$.

General Procedure for Protection with a Boc-group

The substrate is dissolved in either Et_2O or dichloromethane, depending on the solubility of the specific substrate. Di-*tert*-butyl dicarbonate (Boc_2O, 3 eq.) and TEA (1 eq.) are added. After refluxing the mixture for 12 h, it is washed with 5% $KHSO_4$ solution, 5% $NaHCO_3$ solution and water. The organic fraction is dried over Na_2SO_4 and the solvent is evaporated *in vacuo*, after which the resulting crude product is purified via column chromatography.

Representative Experimental Procedure for the Synthesis of 2-[(2-{[(benzyloxy)carbonyl]amino}-3-phenylpropyl)(*tert*-butoxycarbonyl)amino]Ethyl *tert*-butyl Carbonate (Cbz-Phaol-Boc$_2$) 12

The product was synthesized using the general procedure for protection with a Boc-group: Cbz-Phaol **5** is used as a starting material (1 g, 3 mmol) **Yield:** 85%; **m.p.:** 98–101 °C; **IR:** 3332, 2979, 2939, 1742, 1710, 1685, 1604, 1589, 1531.

The molecule exists as a mixture of two conformers:

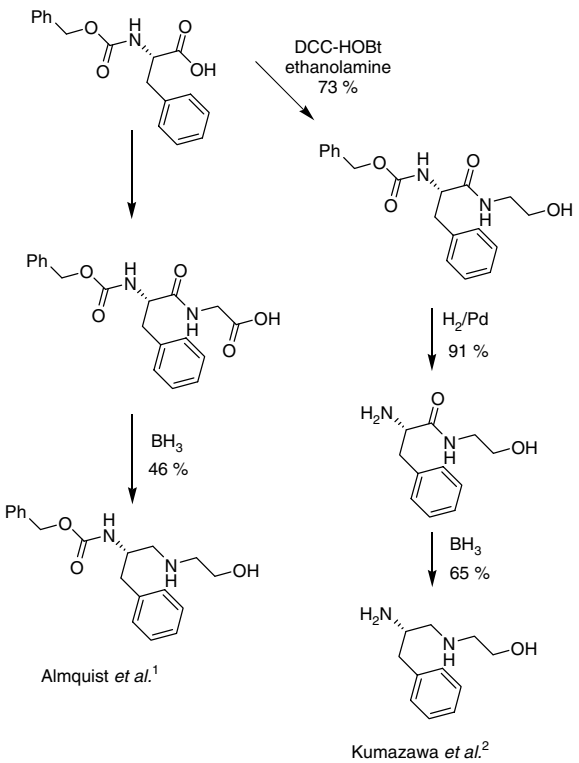
^{1}H NMR (400 MHz, DMSO, ppm): $\delta = 7{\cdot}37 - 7{\cdot}13$ (m, 11H, Ar + NH), $4{\cdot}94 - 4{\cdot}92$ (m, 2H, CH_2Cbz), $4{\cdot}08 - 4{\cdot}05$ (m, 2H, CH_2O), 4·96 (br s, 1H, αH), $3{\cdot}50 - 3{\cdot}02$ (m, 7H, $CH_2NCH_2CH_2 + H_2O$), $2{\cdot}71 - 2{\cdot}60$ (m, 2H, βH), 1·41 (s, 9H, *t*Bu) 1·38 + 1·35 (2 × s, 9H, *t*Bu).

^{13}C NMR (75 MHz, DMSO, ppm): $\delta = 155{\cdot}7$ (CO Cbz), 154·7 (CO O-Boc), 152·8 (CO N-Boc), 138·7 (C Cbz), 137·2 (C Phe) 129·0 + 128·2 + 128·1 + 127·6 + 127·3 + 126·0 (CH Cbz + CH Phe), 81·4 + 78·8 (C Boc), 64·8 (CH_2Cbz), 64·2 + 63·8 (CH_2O), 51·8 + 50·9 (αC), 51·3 ($CH_2NCH_2CH_2$), 46·3 ($CH_2NCH_2CH_2$), 38·7 + 38·2 (βC), 28·0 + 27·3 (*t*Bu).

ESI: 551·9 $[M+Na]^+$, 1079·5 $[2M+Na]^+$.

Results and Discussion

Two syntheses of Phaol, on a small scale, have been reported by Almquist *et al*. [3] and Kumazawa *et al*. [1], both using a coupling-reduction scheme. In this scheme first Cbz-Phe-OH is elongated, after which the formed amide is reduced to an amine with borane (Scheme 1). In the first approach (Almquist) glycine is coupled to Cbz-Phe-OH, followed by the reduction of the amide and the carboxylic acid functions with borane, yielding 46% of product.



Scheme 1. Synthesis according to Almquist *et al*. [3] and Kumazawa *et al*. [1].

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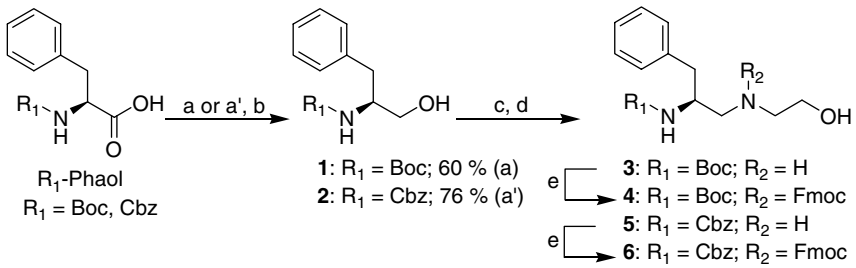
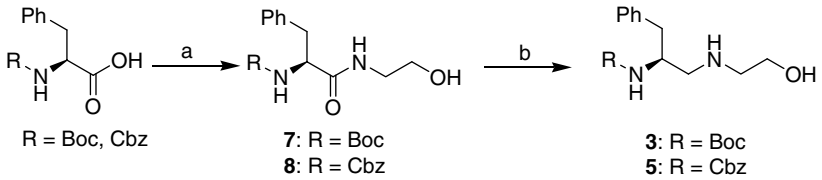


Scheme 2. a: NMM, ethyl chloroformate; a′: *N*-hydroxysuccinimide, DCC; b: $NaBH_4$; c: Et_3N, DMAP, *p*-toluenesulfonyl chloride (TsCl); d: ethanolamine; e: *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu), Na_2CO_3.



Scheme 3. a. Ethanolamine, HOBt, EDC.HCl, NMM; b. Red-Al.

The newly formed amine is protected using Fmoc-chemistry (9*H*-fluoren-9-ylmethyl carbamate).

In a second approach (Kumazawa) ethanolamine is coupled to Cbz-protected (benzyl carbamate) phenylalanine. After deprotection, the substrate is reduced with borane, giving the desired product in 65% yield.

Using Kumazawa's procedure (at a similar scale: 80 and 130 mg) we were unable to obtain the reported yield (65%). Coupling and deprotection steps gave similar results; however, purification posed severe problems. The product was obtained in about 10% yield which was insufficient for our purposes.

With these drawbacks in mind, our goal was to design a robust multigram-scale synthesis of orthogonally protected Phaol. Therefore a new reduction-coupling scheme was proposed (Scheme 2): our approach started from Boc- (*tert*-butyl carbamate) or Cbz-protected phenylalanine which was reduced to the amino alcohol (**1, 2**), by converting it to a mixed anhydride and subsequently reacting it with $NaBH_4$ [4,5]. To introduce the ethanolamine moiety, the alcohol function had to be activated. Conversion of the alcohol to an iodide functional group has already been described several times in literature for nucleophilic substitutions in *N*-protected β-iodoamines [6–9]. Unfortunately, this furnished a product that was too unstable to be useful in a large-scale conversion. Converting the alcohol to a tosylate also resulted in an unstable intermediate. When attempting to substitute this tosylate intermediate with ethanolamine without prior purification, significant amounts of side products were formed.

Although the desired product **3** was sufficiently stable to be purified, the separation was problematic due to the many side products. Reaction conditions of the nucleophilic substitution with ethanolamine were varied, both with substrates **1** and **2** to improve the result: The reaction was performed in ethanolamine as the solvent at 100 °C, in acetonitrile with two equivalents of ethanolamine, at 70 °C and at room temperature. However, approximately the same amount of side products were formed in all instances. Furthermore, all attempts to purify the Boc-protected compound **3**, either by crystallization or column chromatography, failed. After the subsequent protection with an Fmoc-group of the secondary amine, pure product **4** could be isolated, using a medium-pressure gradient column. The obtained yield, from Boc-L-phenylalaninol (Boc-Phe-ol) **1** to Boc-Phaol(Fmoc) **4** (Scheme 2), was 27% (Phaol(X)-Y: X is the protecting group of the secondary amine; Y is the protecting group of the alcohol function). In this way, an orthogonally protected amino acid derivative, was synthesized. The Fmoc protection of the secondary amine was suggested by Almquist *et al*. [3].

Benzyl {1-benzyl-2-[(2-hydroxyethyl)amino]ethyl}carbamate (Cbz-Phaol) **5** was obtained via tosylation of Cbz-L-phenylalaninol (Cbz-Phe-ol) **2** and substitution with ethanolamine in an overall yield of 27%, after purification using crystallization. Protection of the secondary amine of substrate **5** with an Fmoc-group was achieved with Fmoc-OSu in yields of 90–95%.

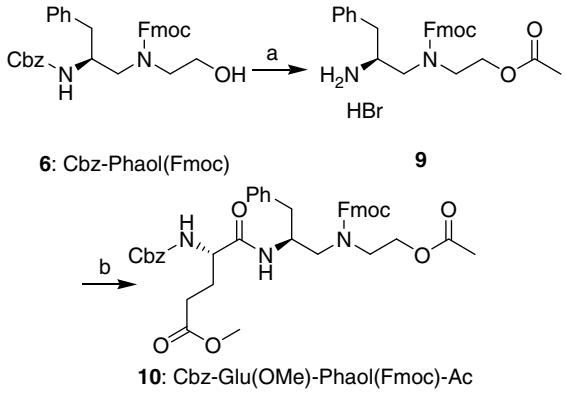
In light of the low yield and the inefficient coupling, an alternative coupling-reduction scheme was devised (Scheme 3) in which Boc- or Cbz-protected phenylalanine was coupled to ethanolamine. The products **7** and **8** formed were reduced using sodium bis(2-methoxyethoxy)aluminum hydride solution (Red-Al), in lieu of borane. The rationale behind this method was based on a report by Voight *et al*. [10], who reported the use of Red-Al for the synthesis of *N*-Boc-protected amino acid-derived secondary amines. The chiral integrity of the Phaol moiety was not affected by this reduction, nor by the protection or deprotection steps. This was checked using chiral derivatization. (Refer later in text).

The reduction of **7** to Boc-Phaol **3** produced a significant amount of unidentified side products according to TLC, which were not easily removed by column chromatography. Even more side products were formed if the reaction time was extended. After several trials, an optimal reaction time of 6 h was found, which gave a yield of 60% of **3** on small reaction scale (0·2 g; 0·65 mmol). On a larger scale (1 g, 3·25 mmol), the separation was more difficult. The crude product **3** was therefore not purified and directly protected with Fmoc-chemistry, giving Boc-Phaol(Fmoc) (**4**) in 55% yield.

The reactions were repeated using Cbz-Phe-OH to synthesize Cbz-Phaol **5**. The results for the reduction of **8** are described in Table 1. From these results, it can be seen that the yield of this reaction goes through a maximum in function of time. Under the conditions used, a reaction time of about 10 hours seems to be optimal for the formation of **5**.

Table 1. Synthesis of Cbz-Phaol (5) by reduction with Red-Al (5 eq.) in THF : toluene 1 : 2 (0.5 g 8 : 10 ml; 2 g 8 : 32 ml: 10 g 8 : 200 ml) at room temperature

Amount of **8** (g)	Reaction time (h)	Isolated yield of **5** (%)
0.5	4.5	23
0.5	9	60
0.5	24	19
2	8.5	45
2	14	36
10	8.5	40
10	10	64
10	15	30

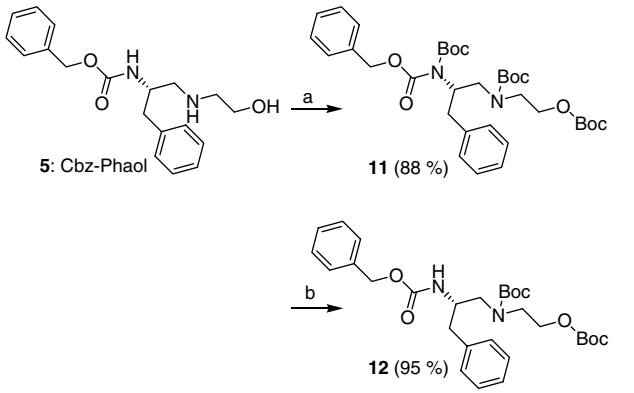


Scheme 4. a. HBr in acetic acid; b. HOAt, EDC, DIPEA.

As Cbz-Phaol is easily purified by crystallization and since it can be obtained in a reasonably good yield (also on a larger scale) this product was deemed useful for incorporation into peptides like septocylindrin B. The secondary amine of **5** was protected with an Fmoc-group in an excellent yield.

Initial attempts to test the orthogonality of this partial protection scheme (the alcohol function is not protected) uncovered that the Fmoc-group of **6** did not survive the hydrogenolytic Cbz removal during coupling reactions with the amino acid *N*-alpha-benzyloxycarbonyl-L-glutamic acid gamma-methyl ester (Cbz-Glu(OMe)-OH). More test reactions also revealed the susceptibility of the alcohol function to unintended coupling with the activated acid function of an amino acid. To solve both the problem of Fmoc-deprotection and the undesired coupling with the alcohol function, a different method was developed. In this case, Cbz-deprotection was performed using HBr in acetic acid [11]. This was accompanied by protection of the alcohol moiety as an acyl ester. The deprotected derivative was coupled to Cbz-Glu(OMe)-OH giving product Cbz-Glu(OMe)-Phaol(Fmoc)-Ac (**10**) in a yield of 94% (Scheme 4). This methodology gives rise to a fully orthogonally protected Phaol **9**, which can be easily purified.

Unfortunately, in view of the instability of the Fmoc-group under hydrogenation, scaffold **9** is of little use in the synthesis of the acid labile peptaibols where peptide buildup via Cbz or Fmoc strategy is mandatory. Hence a new protecting scheme was required. In this scheme, Boc-chemistry is used to protect the amine as well as the alcohol. Normally a Boc-group is deprotected with an acid, but the scope of this method can be broadened to acid-sensitive substrates by using Lewis acids, like $BiCl_3$ [12]. This is necessary



Scheme 5. protection with a Boc-group of **5**: a. Boc_2O (5 eq.), TEA, DMAP, THF; b. Boc_2O (2 eq), TEA, Et_2O or dichloromethane.

for the incorporation of Phaol into acid-sensitive peptides, like peptaibols, which have an acid-sensitive Aib(2-Aminoisobutyric acid) -Pro(proline) bond.

Cbz-Phaol **5** was protected with a Boc-group, to give Cbz-Phaol-Boc_2 (**12**), in a good yield. The synthesis needed to be optimized however, because the product had the tendency to protect three times with a Boc-group (Scheme 5): the nitrogen atom of the carbamate of **5** was also protected with a Boc-group to give molecule **11**, as confirmed by NMR. The optimized reaction was conducted at reflux temperature in diethyl ether or dichloromethane, with Boc-anhydride and TEA (instead of using THF and DMAP). Using these conditions the protection with a Boc-group was limited to the secondary amine and the primary alcohol, giving **12**. Subsequent deprotection with TFA was quantitative.

Using this new method, fully protected Phaol can be synthesized on gram scale, providing an interesting scaffold that can be used for peptide synthesis.

The chiral integrity of the Phaol moiety was not affected, nor by the reduction, nor by the protection with a Boc-group of the amine- and alcohol-function. This was checked, using chiral derivatization. Cbz-Phaol-Boc_2 **12** was coupled to Cbz-Glu(OMe)-OH, giving rise to the diastereomer Cbz-Glu(OMe)-Phaol-Boc_2. The optical purity was checked by NMR and HPLC, thus proving that the synthesis did not affect the chirality of the substrates. More details can be found in the supporting information. Since all Phaol derivatives and analogs were synthesized using the same methods, their chiral integrity can be deduced from these results.

To check the scope and limitation of the Red-Al reduction method, analogs were synthesized.

For the synthesis of molecule **13**, diethanolamine was coupled to Cbz-Phe-OH. Test reactions pointed out that the secondary amine was not nucleophilic enough in comparison to the primary alcohol functions. Therefore, the alcohol functions needed prior protection for this coupling. To this end, the diethanolamine was protected with a TBDMS group using *tert*-butyl(chloro)dimethylsilane (TBDSCl), after which it was coupled to Cbz-Phe-OH. The resulting product **18** was then deprotected with TBAF, to minimize the steric hindrance, and reduced to give molecule **13** in 38% yield (Scheme 6).

While attempting to synthesize molecules **14** and **15**, a new problem arose: both the amide and the carbamate function underwent reduction (Figure 2). This unwanted side reaction resulted in lower yields of the isolated products.

The results of the optimization of the synthesis of **14** and **15** are described in Tables 2 and 3. For the synthesis of **14**, a short

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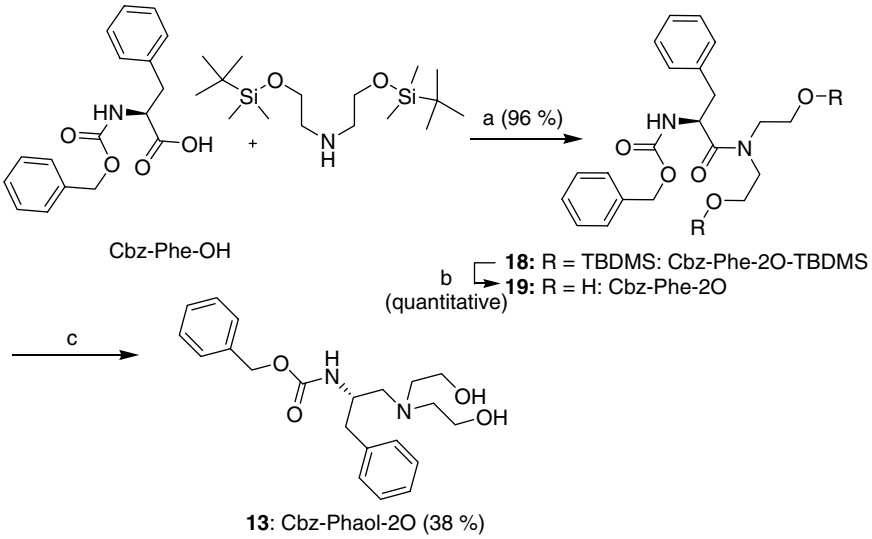

Scheme 6. (a) EDC.HCl, HOAt, NMM; (b) TBAF; (c) Red-Al.

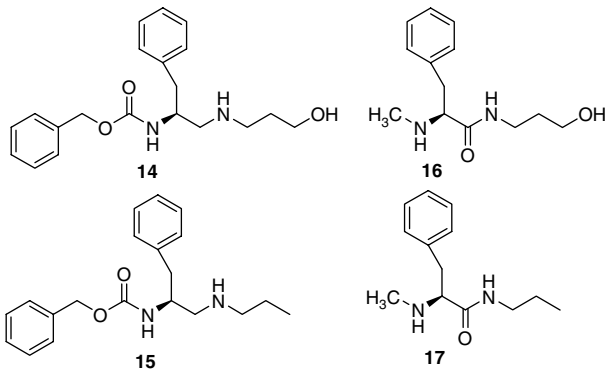

Figure 2. Phaol analogs **14** and **15** with side products **16** and **17**.

Table 2. Results of synthesis of 14 on a 0.5 g scale (1.4 mmol) with 5 eq. of Red-Al, at room temperature

Reaction time (h)	Yield **14** (%)	Yield **16** (%)
3	62	35
6	70	24
14	28	27
20	31	27
2[a]	27	29

[a] Reaction at 50 °C.

Table 3. Results of synthesis of 15 on a 0.5 g scale (1·4 mmol) with 5 eq. of Red-Al, at room temperature

Reaction time (h)	Yield **15** (%)	Yield **17** (%)
3	30	1
5	18	17
6	22	14
14	19	21
20	27	18
2[a]	34	12

[a] Reaction at 50 °C.

reaction time up to 6 h appeared to be optimal, although **16** is always formed in comparable amounts. If the reaction is allowed to run for more than 6 h, the excess equivalents of Red-Al probably cause further reduction of **14**, leading to lower yields. The same conclusions can be drawn for the synthesis of **15**, except that an even shorter reaction time is needed.

The unwanted side reaction, the reduction of the carbamate, has been reported with reductions using $LiAlH_4$ as reductant [13,14], in the literature, no such problems have been mentioned when using Red-Al however [10]. It seems that the presence of a $-NCH_2CH_2OH$ moiety is beneficial for the selectivity of the reduction, in view of the fact that in the synthesis of **3**, **5** and **13,** this side reaction was not observed. The reason could be that the complexation with these molecules brings the reactive centre at the correct position to reduce the amide instead of the carbamate. By synthesizing the analogs, a hitherto unknown side reaction of Red-Al has been uncovered.

To use the Phaol analogs in peptide synthesis, orthogonal protection is needed. In molecule **13** the alcohol function was TBDMS-protected, giving molecule **22** (Figure 3) and was later easily deprotected with TBAF. The free amine functionality and alcohol functions of molecules **14** and **15** were protected with a Boc-group, resulting in molecules **20** and **21**. Boc-deprotection did not pose a problem.

Conclusions

A reproducible large-scale synthesis of Phaol was developed. The scope of this method was investigated by synthesizing three analogs. This uncovered some limitations of this method by identifying a previously unreported Red-Al reduction of carbamates. All the Phaol analogs were further orthogonally protected, making them suitable for use in peptide synthesis. Deprotection of these derivatives was carried out successfully and without any complications.

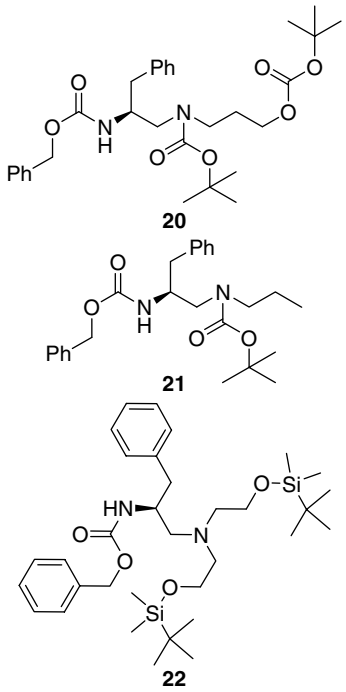

Figure 3. Cbz-Phaol-N3O-Boc_2 (**20**), Cbz-Phaol-N3-Boc (**21**) and Cbz-Phaol-2O-TBDMS (**22**).

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Supporting information

Supporting information may be found in the online version of this article.

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