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Pentaerythrityltetramine Scaffolds for Solid-Phase Combinatorial Chemistry[1]

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Received December 9, 2003

Straightforward synthesis for two pentaerythrityltetramine precursors, 2,2-bis(azidomethyl)propane-1,3-diamine (**1**) and 2-[*N*-(allyloxycarbonyl)aminomethyl]-2-azidomethylpropane-1,3-diamine (**2**), has been described. Both propane-1,3-diamines have been attached by reductive amination to a solid-supported backbone amide linker derived from 4-(4-formyl-3,5-dimethoxyphenoxy)butyric acid. The presence of the two methoxy substituents on the linker is essential to avoid cross-linking between two linkers. The remaining free primary amino group of the propane-1,3-diamine moiety may then be selectively acylated with an appropriately protected amino acid using conventional *N,N*-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBt) activation without any interference by the secondary amino function. The latter group may be subsequently acylated by an anhydride method. Sequential reduction of the azido group and removal of the allyloxycarbonyl protection from **2** allow further coupling of two different amino acids, and hence, this handle may be utilized in construction of branched structures containing four different amino acids or peptides. Solid-supported **1** may, in turn, be used for the synthesis of similar constructs containing two identical branches. It is worth noting that no acid-labile protecting groups are required in this approach, and hence, this dimension may be saved for the cleavage of the linker. The applicability of the scaffolds to library synthesis has been demonstrated by preparation of 11 pentaerythrityl-branched tetra- and octapeptides.

Introduction

Solid-supported scaffolds bearing several orthogonally protected functional groups on a single compact branching unit have recently received increasing interest as handles useful for the generation of combinatorial libraries. In particular, such scaffolds have found applications in parallel synthesis of novel artificial receptors. Monosaccharides containing up to five hydroxy functions that may be derivatized in a selective manner, offer a good example.[2−4] Pentaerythritol-protected with three orthogonally removable groups constitutes another versatile polyol handle.[5] Among polyamine handles, an orthogonally protected *N*-Fmoc-*N*-Alloc-*N*-Boc-triamino analogue of cholic acid has been used for sequential incorporation of amino acids on a solid support[6] and an *o*-NBS/Fmoc/Alloc-strategy has been applied to the assembly of three different peptide chains on a solid-supported triazacyclophane core.[7,8] In addition, we have recently introduced two orthogonally protected pentaerythritol-like handles, viz. *N*-Alloc-*N*-Boc-*N*-Fmoc-α,α-bis(aminomethyl)β-alanine[9] and *N*-Boc-*N*-Fmoc-bis(aminomethyl)malonic acid monoallyl ester.[10] The limited number of orthogonally protected polyamine handles available is somewhat surprising, taking into account that amide bond formation probably is the most thoroughly studied solid-supported reaction.

Syntheses of the orthogonally protected scaffolds described above are rather complicated, and many of them contain TFA-removable protections such as Boc, which undoubtedly limits their applicability. Many strategies are based on exploitation of acid-labile side-chain protections and/or on acidolytic release from the support. Accordingly, it would be beneficial to save the acid-labile dimension for these purposes and not to use acid-labile protecting groups for the branching unit. As an extension

(1) Abbreviations used: AA, amino acid residue; Alloc, allyloxycarbonyl; Boc, *tert*-butoxycarbonyl; DCC, *N,N*-dicyclohexylcarbodiimide; DCM, dichloromethane; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; Fmoc, 9-fluorenylmethoxycarbonyl; HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium hexafluorophosphate 3-oxide; HOAt, 7-aza-1-hydroxybenzotriazole; HOBt, 1-hydroxybenzotriazole; HOSu, *N*-hydroxysuccinimide; NMP, *N*-methylpyrrolidone; *o*-NBS, 2-nitrobenzenesulfonyl; PyAOP, 7-azabenzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate; PyBOP, benzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate; TAM, tetrakis(aminomethyl)methane; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

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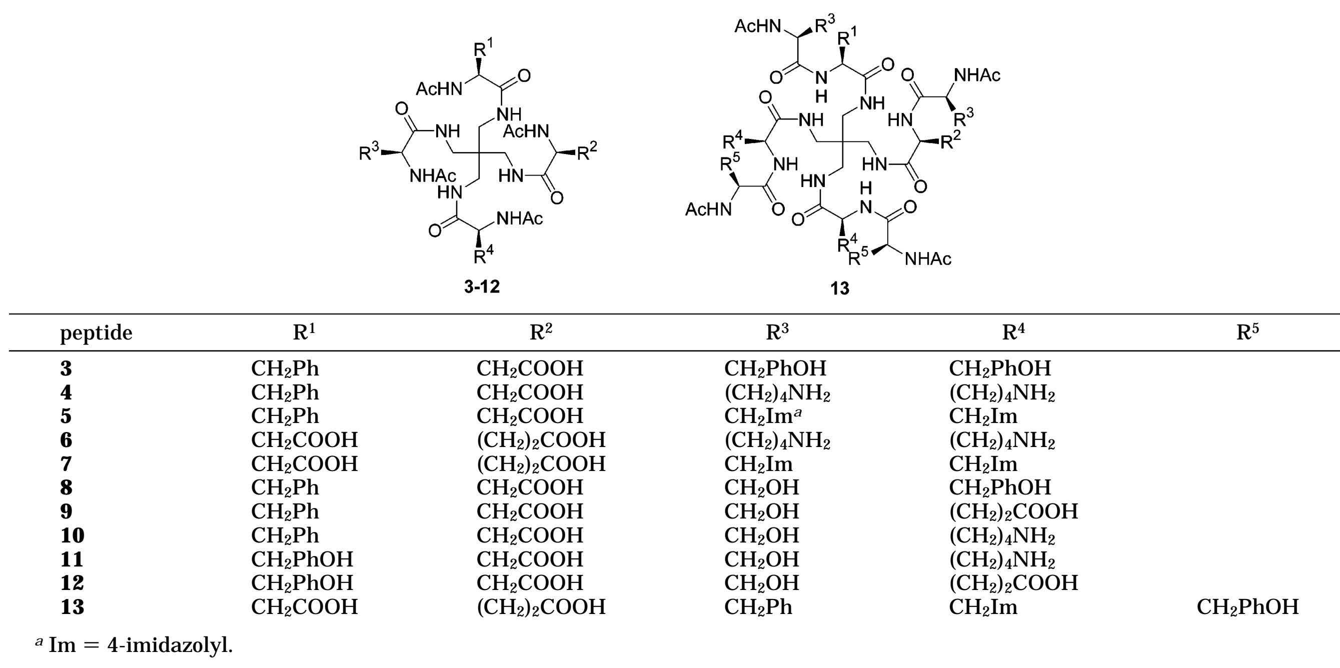
10.1021/jo035801+ CCC: $27.50 © 2004 American Chemical Society

Published on Web 02/17/2004

TABLE 1. Branched Peptides Synthesized



peptide	R^1	R^2	R^3	R^4	R^5
3	CH_2Ph	CH_2COOH	CH_2PhOH	CH_2PhOH	
4	CH_2Ph	CH_2COOH	$(CH_2)_4NH_2$	$(CH_2)_4NH_2$	
5	CH_2Ph	CH_2COOH	CH_2Im[a]	CH_2Im	
6	CH_2COOH	$(CH_2)_2COOH$	$(CH_2)_4NH_2$	$(CH_2)_4NH_2$	
7	CH_2COOH	$(CH_2)_2COOH$	CH_2Im	CH_2Im	
8	CH_2Ph	CH_2COOH	CH_2OH	CH_2PhOH	
9	CH_2Ph	CH_2COOH	CH_2OH	$(CH_2)_2COOH$	
10	CH_2Ph	CH_2COOH	CH_2OH	$(CH_2)_4NH_2$	
11	CH_2PhOH	CH_2COOH	CH_2OH	$(CH_2)_4NH_2$	
12	CH_2PhOH	CH_2COOH	CH_2OH	$(CH_2)_2COOH$	
13	CH_2COOH	$(CH_2)_2COOH$	CH_2Ph	CH_2Im	CH_2PhOH

[a] Im = 4-imidazolyl.

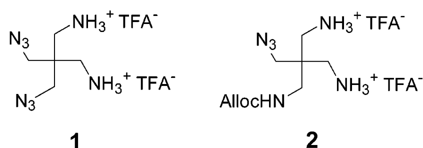


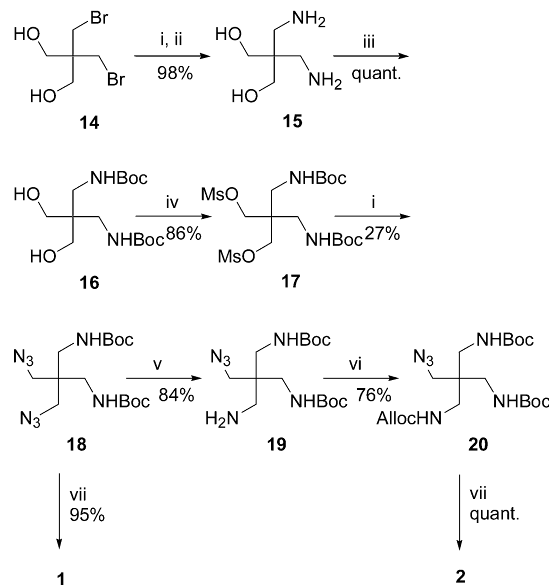
FIGURE 1. Branching units employed.

of our previous studies on pentaerythritol-derived handles, we now report on the synthesis of two pentaerythrityltetramines, viz. 2,2-bis(azidomethyl)-1,3-propanediamine (**1**) and 2-[*N*-(allyloxycarbonyl)aminomethyl]-2-azidomethyl-1,3-propanediamine (**2**), and on their exploitation for the preparation of branched peptides (**3**−**13** in Table 1) on a solid-supported TFA-labile backbone amide linker. Immobilization of **1** or **2** by reductive amination to a backbone amide linker yields a solid-supported tetraamine handle having one secondary amino group, one unprotected primary amino group, and two either similarly (**1**) or differently (**2**) masked primary amino groups. The free primary amino group may first be selectively derivatized with a desired amino acid without acylating the secondary amino group. Accordingly, the immobilization of the tetraamine by reductive amination creates one additional dimension for these partially protected branching units, allowing attachment of three or four different amino acid residues on using **1** or **2**, respectively (Figure 1).

Results and Discussion

Synthesis of Branching Units 1 and 2 (Scheme 1). The first large-scale synthesis of pentaerythrityltetramine [tetrakis(aminomethyl)methane, TAM] was based on displacement of the bromo substituents from pentaerythrityl tetrabromide with *p*-toluenesulfonamide ion and subsequent hydrolysis of the sulfonamide groups with sulfuric acid.[11] The more recent syntheses include treatment of pentaerythrityl tetrachloride with excess of supercritical ammonia and reduction of the explosive tetra azide analogue.[12−14] The conversion of commercially available 2,2-bis(bromomethyl)propane-1,3-diol (**14**) to 2,2-bis(azidomethyl)propane-1,3-diol and further to 2,2-bis(hydroxymethyl)propane-1,3-diamine (**15**), described by Bitha et al.,[15,16] appeared, however, a more appropriate method to obtain the desired branching units **1** and **2**. The amino groups of **15** were Boc-protected (**16**) and the

SCHEME 1. Synthesis of Branching Units 1 and 2



[a] Key: (i) NaN_3, DMF; (ii) H_2, Pd/C, EtOH; (iii) Boc_2O, NaOH, H_2O, MeCN; (iv) MsCl, Py; (v) (1) Ph_3P, THF, (2) NH_4OH, THF; (vi) AllocCl, Et_3N, dioxane; (vii) TFA, DCM.

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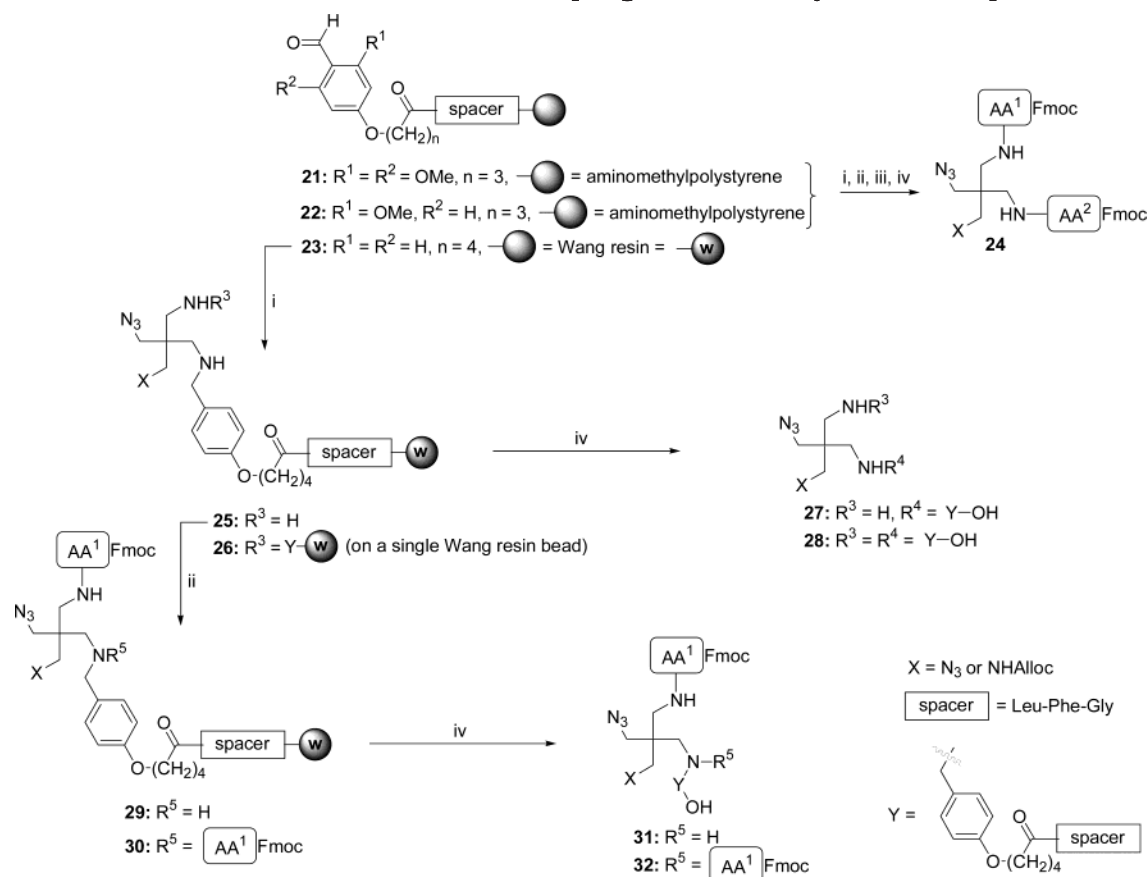
SCHEME 2. Reductive Amination and Selective Coupling to the Primary Amino Group[a]



[a] Key: (i) **1** or **2**, $NaCNBH_3$, solvent, cf. Table 2; (ii) Fmoc-AA^1-OH, coupling reagent, cf. Table 3; (iii) (Fmoc-AA^2)$_2$O, DCM; (iv) TFA, DCM.

hydroxy groups mesylated (**17**). It is worth noting that all these four steps could be performed with relatively high scale (150 mmol) without chromatographic purifications, which gave **17** in 84% overall yield. The next step turned out to be the bottleneck of the synthesis, since urea formation[17] markedly competed with the desired double displacement of the mesyl groups with azide ion.[18] The best but still only moderate 27% yield of the diazide (**18**) was achieved by conventional displacement with sodium azide in DMF (120 °C), but stopping the reaction before completion. The starting material was then recycled. Deblocking of **18** with TFA accomplished the synthesis of branching unit **1**.

Selective reduction of one of the two azido groups of **18** by the Staudinger reaction[19] was the key step for the preparation of the other TAM precursor (**2**). Overnight treatment with triphenylphosphine gave the iminophosphorane intermediate which was hydrolyzed with aqueous ammonia to obtain the desired monoamine (**19**) in an 84% yield. Allyloxycarbonylation of the iminophosphorane intermediate[20] was also attempted, but it gave a poor 10% yield of **20** and a set of unidentified side-products. By contrast, allyloxycarbonylation of the purified amine (**19**) turned out to be the method of choice, giving **20** in 76% yield. Deblocking of **20** with TFA accomplished the synthesis of **2**.

Reductive Amination of Aldehyde Supports (21–23) with the Branching Units (1 and 2) (Scheme 2). The library synthesis was first attempted on support **22** obtained by acylating 4-(4-formyl-3-methoxyphenoxy)-butyric acid[21] to aminomethyl polystyrene derivatized with a tripeptide spacer (loading of 170 μmol g^{-1}). Branching unit **2** was attached by reductive amination to this support and subjected first to selective DCC/HOBt-activated acylation of the primary amino group with Fmoc-Phe and then to acylation of the secondary amino group with Fmoc-Asp anhydride (for the selectivity of acylation, see the discussion below). HPLC-MS analysis of the compound released acidolytically from the support revealed that in addition to the desired product **24** (AA^1 = Phe, AA^2 = Asp), a remarkable amount of the

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(17) Prolonged treatment yielded material, which mainly partitioned into aqueous phase in H_2O/Et_2O extraction. The compound may tentatively be assigned to 5-azidomethyl-5-[*N*-(*tert*-butyloxycarbonyl)-aminomethyl]tetrahydropyrimidin-2-one: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.96 (br, 1H), 6.24 (br, 2H), 3.26 (m, 2H), 2.96 (d, 1H, J = 6.3 Hz), 2.87 (d, 1H, J = 6.3 Hz), 2.80 (s, 4H), 1.38 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.9, 156.1, 78.2, 52.4, 44.0, 40.5, 35.9, 28.1.

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TABLE 2. Reductive Amination of Resin 23 with 2 under Different Conditions[a]

entry	**2** (equiv)	$NaBH_3CN$ (equiv)	solvent	solvent/resin (μL/mg)	time (h)	T (°C)	**27** (%)	**28** (%)
1	5	5	DMF	20	1	25	30	14
2	5	5	DMF	20	3	25	35	36
3	5	5	DMF	20	1	50	38	62
4	10	10	DMF	20	1	25	38	25
5	10	5	DMF	20	1	25	37	22
6	5	5	DMF	5	1	25	53	27
7	10	10	DMF	5	1	25	57	33
8	5	5	THF−DMF (1:3)	20	1	25	32	18
9	5	5	dioxane−DMF (2:1)	20	1	25	35	54
10	5	5	HCOOH−DMF (4:96)	20	1	25	16	45
11	5	5	DMSO−NMP (1:5)	5	1	25	43	13
12	5	5	DMSO−NMP (1:4)	5	1	25	49	10
13	5	5	DMSO−NMP (1:4)	5	3	25	57	27
14	5	5	DMSO−NMP (1:3)	5	1	25	38	12

[a] The amount of the desired (**27**) and the cross-linked (**28**) product compared to the initial amount of the solid-supported linker **23**. The quantification is based on the areas of the HPLC signals of the released products.

corresponding bis(aspartyl) product (**24**, $AA^1 = AA^2 =$ Asp) had been formed.

To study the origin of the unexpected side-product, Wang resin derivatized with a tripeptide spacer and a 5-(4-formylphenoxy)pentanoic acid linker[22] (**23**) was used as a support instead of **22**. The TFA-labile ester bond between the spacer and the Wang resin allowed the release of the entire construct of the branching unit, linker and tripeptide spacer from the support. In this manner, the mode of bonding between the branching unit and the linker could be studied in detail.[23] The HPLC-MS analysis of the product mixture released from the support clearly showed that a branching unit bearing two linker-spacer moieties (**28**) was obtained, in addition to the expected construct (**27**). In other words, the branching unit (**2**) had reacted upon reductive amination by both of its primary amino groups cross-linking two different linkers.

The proportion of the cross-linked product was dependent on the solvent, reaction time, and temperature, but rather independent of the concentration of **1** or **2** (0.04 to 0.17 M) or the density of the aldehyde groups on the resin when the loading was ranged from 80 to 330 μmol g^{-1}. The relative peak areas (%) of the desired (**27**) and cross-linked product (**28**) in the HPLC chromatograms recorded for the reactions of **2** with **23** are listed in Table 2.[24] Prolonged reaction time (3 h at 25 °C, entries 2 and 13) and higher temperature (1 h at 50 °C, entry 3) drove the reductive amination to completion, but simultaneously the extent of cross-linking was remarkably increased. The trend was similar by using an acidic solvent system (4% HCOOH in DMF, entry 10). Addition of a base, such as $CsCO_3$, in turn, completely inhibited the reductive amination (data not shown). In addition to DMF, several solvents exhibiting different polarities and swelling properties were tested. A 1:4 (*v*/*v*) mixture of DMSO and NMP, representing a combination of high solvent polarity and good resin-swelling,[25,26] seemed to be the medium of choice (cf. entries 12 and 6), although even in this case 17% of the solid-supported branching unit was cross-linked to two linkers.

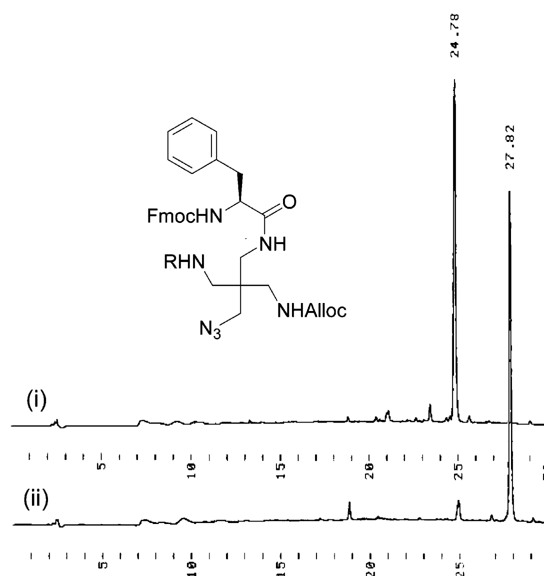

FIGURE 2. HPLC chromatograms of crude peptides released from resin aliquots. Notation: (i) R = Ac, product (24.78 min) released from resin (**33**) after acetic anhydride capping, (ii) R = Fmoc-Asp, **24** (27.82 min) released from resin (**35**). For the chromatographic conditions, see protocol A in the Experimental Section.

The cross-linking took place less readily on support **22** than on support **23**, but still to a disturbing extent. Fortunately, the more acid labile 4-(4-formyl-3,5-dimethoxyphenoxy)butyrate linker[27] (**21**) turned out to efficiently suppress the cross-linking, even when a prolonged reaction time (3 h) was used [see (ii) in Figure 2]. The only shortcoming of this linker was that the immobilization by reductive amination, quantified by measuring the amount of benzofulvene released after coupling a Fmoc-protected amino acid to the primary amino group, took

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(24) Because of different extinction coefficients, the direct peak area comparison (listed in Tables 2 and 3) is an approximation for corresponding concentration values.

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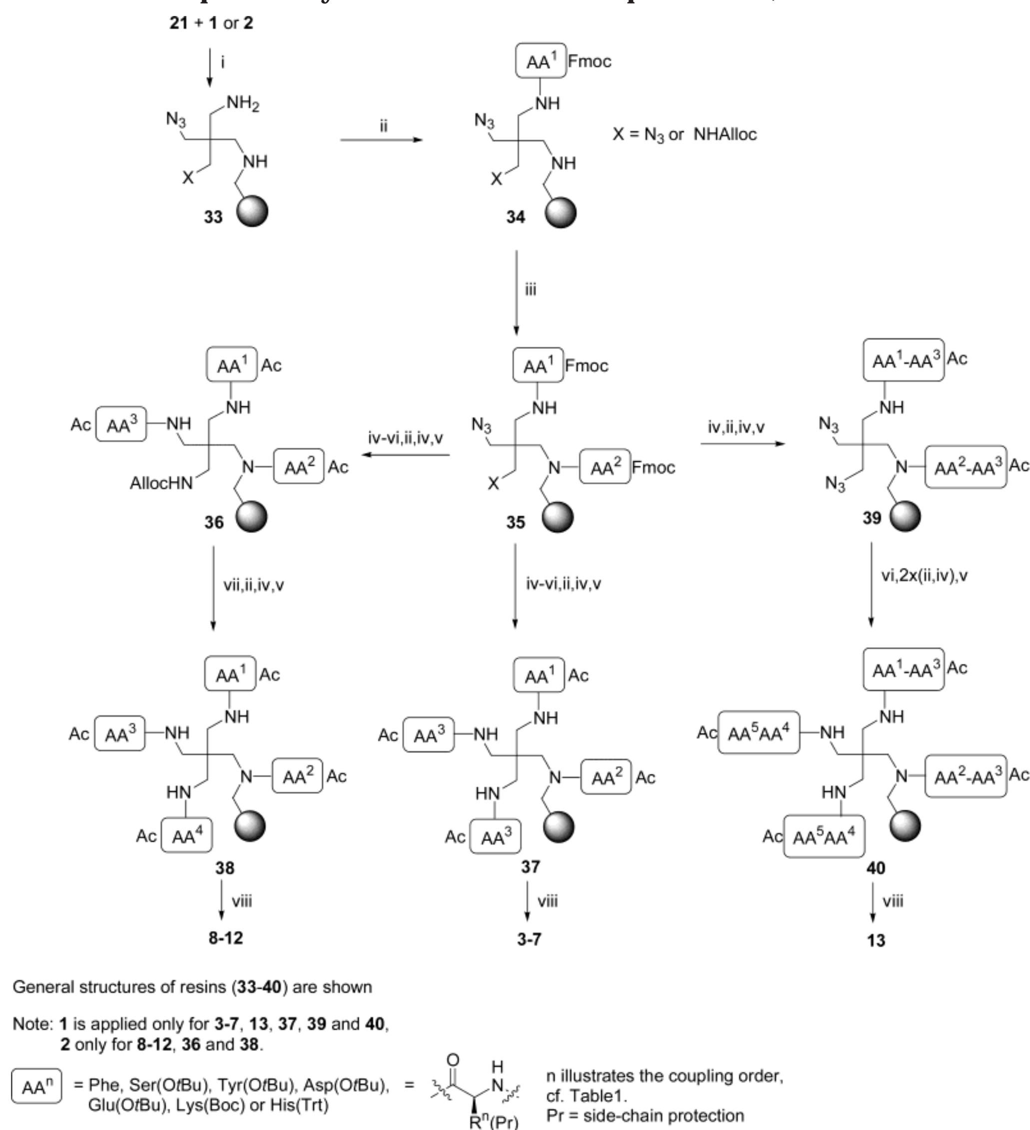
SCHEME 3. General Description of Synthesis of Branched Peptides 3−13, cf. Table 1[a]



[a] (i) $NaCNBH_3$, DMSO, NMP; (ii) Fmoc-AA^n-OH, DCC/HOBt, NMP; (iii) (Fmoc-AA^2)$_2$O, DCM; (iv) piperidine, DMF; (v) Ac_2O-capping; (vi) Me_3P, toluene, H_2O, dioxane; (vii) $Pd(OAc)_2$, Bu_3SnH, PPh_3, AcOH, DCM; (viii) TFA, DCM.

place considerably less readily than reported earlier for simple monoamines.[27,28] In fact, the yield was also lower than with the monomethoxy substituted linker **22**. A satisfactory 90 μmol g^{-1} loading was, however, achieved when **21** (loading 170 μmolg^{-1}) was treated with 5 equiv of **1** or **2** in the presence of 5 equiv of $NaBH_3CN$ for 3 h at room temperature. The unreacted aldehyde groups were then capped with methoxyamine. This support (**33** in Scheme 3) was used in the library syntheses.

Selective Coupling to the Primary Amino Group. Acylation of the secondary amine obtained by reductive amination of a backbone amide linker is known to be difficult with normal coupling reagents.[23,26] This suggests that the primary amino group of **1** and **2** attached to **21** might well be selectively acylated despite the presence of the secondary amino group. The selectivity was first studied on the 5-(4-formylphenoxy)pentanoate derivatized Wang resin (**25**, X = N_3 or NHAlloc). Fmoc-Phe-OH was used as the amino acid and several activation methods (HATU, PyAOP, PyBOP, DCC/HOBt, and DCC/HOSu) were studied. The relative areas (%) of the HPLC signals of the products (**31** and **32**, AA^1 = Phe, X = N_3, Scheme 2) are listed in Table 3. As seen, conventional activation with DCC/HOBt (1 M in NMP) gave the best result: the acylation was selective and the efficiency acceptable (entry 8). The selectivity was expectedly poor with HOAt-based reagents (HATU and PyAOP, data not shown), and PyBOP, a HOBt-based phosphonium salt, also gave a significant amount of the diacylated side-product when in situ activation was used (**32**, R^5 = Fmoc-Phe).[26] A slightly better selectivity was achieved when DMF was replaced with NMP or THF (entries 1−3). Activation with DCC/HOSu exhibited a good regioselectivity, but the coupling efficiency was low. Repeated couplings (2 × 2 h) with HOSu activated Fmoc-Phe-OH (10 equiv), however, gave an acceptable yield (entry 6).

Consistent with the results on Wang resins (**25**, X = N_3 or NHAlloc), the acylations of the primary amino functions of **1** and **2** attached to **21** on a aminomethyl polystyrene resin (**33**, X = N_3 or NHAlloc) were carried

TABLE 3. Selective Coupling of Fmoc-Phe-OH to the Primary Amino Group of Resin 25 (X = N_3)[a]

entry	Fmoc-Phe-OH (equiv)	reagent (equiv)	base (equiv)	solvent	time (h)	**31** (%)	**32** (%)
1	1.5	PyBOP (1.5)	DIEA (3.0)	DMF	2	65	13
2	1.5	PyBOP (1.5)	DIEA (3.0)	NMP	2	65	8
3	1.5	PyBOP (1.5)	DIEA (3.0)	THF	2	68	5
4	10	DCC/HOSu (10)		DMF	2	65	0
5	10	DCC/HOSu (10)		DMF	17	71	0
6	10	DCC/HOSu (10)		DMF	2 × 2	83	0
7	10	DCC/HOBt (10)		NMP	2	84	0

[a] The amount of the desired monoacylated (**31**) and diacylated (**32**) product compared to the initial amount of primary amino groups on support **33**. The quantification is based on the areas of the HPLC signals of the released products.

out with Fmoc-Phe-OH (10 equiv) using DCC/HOBt activation. The reaction time was 2 h and the coupling was repeated until the Fmoc loading remained unchanged, usually twice. The secondary amine site (**34**) was then acylated with acetic anhydride and the product was released from an aliquot of the resin and analyzed by HPLC. As seen from Figure 2 (i), the crude mixture was free from the diacylated side product [see also (ii) in Figure 2]. The general applicability of the method was then demonstrated with two additional amino acids, viz. Fmoc-Tyr(OtBu)-OH and Fmoc-Asp(OtBu)-OH, without any marked difficulties.

Conversion of the Azido Groups to Amino Groups. It has been recently reported that an azido functionality can be converted to an amino functionality on a solid support by mild trimethylphosphine treatment, which is completely orthogonal to the removal of Fmoc groups and TFA-labile protections.[29,30] These findings prompted us to use azido group as a masked amino group in the pentaerythrityltetramine precursors (**1**,**2**). This choice remarkably simplified the synthesis route (Scheme 1). The azido masks (**35** and **39**, Scheme 3) were removed with trimethylphosphine (1 M Me_3P in toluene, 12 equiv/azido group, 2 h at rt, N_2 atm] in a 1:4 (*v*/*v*) mixture of water and dioxane. Other tertiary phosphines were also tested.[31] Triphenylphosphine gave cleanly the iminophosphorane intermediate, which was unexpectedly stable. Attempts to hydrolyze this iminotriphenylphosphorane, including treatments with 0.1 M solutions of NaOH, NH_3 or K_2CO_3 in aqueous dioxane, failed. The first step of the on-resin Staudinger reaction with tributylphosphine was, in turn, difficult and only a trace amount of the corresponding iminophosphorane was obtained. It should be noted that the reductive conditions used for the Alloc deprotection of solid-supported **2** should not be applied when the azido group is still present.

Synthesis of Branched Peptides (3−13). Straightforward synthesis of the branched peptide-like constructs (**3**−**13**) is outlined in Scheme 3, in which the general structures of the resin-bound intermediates (**33**−**40**) are shown (cf. Table 1). To further demonstrate the applicability of the approach based on selective coupling, the primary amino group on resins **33** (X = N_3 or NHAlloc, a 300 mg sample, loading 90 μmolg-1) was acylated with Fmoc-Tyr(O*t*Bu)-OH or Fmoc-Asp(O*t*Bu)-OH, in addition to Fmoc-Phe-OH, using the same DCC/HOBt activation. No marked differences in coupling yields and purity occurred. After this initial regioselective coupling, the secondary amino group was acylated with Fmoc-Asp(O*t*Bu)-OH or Fmoc-Glu(O*t*Bu)-OH using an anhydride method to obtain resins (**35**). The Fmoc groups were removed and the exposed amino groups were capped with acetic anhydride. The azido masks were then removed with trimethylphosphine and the third amino acid, viz. Fmoc-Ser(O*t*Bu)-OH to obtain **36** and Fmoc-Tyr(O*t*Bu)-OH, Fmoc-Lys(Boc)-OH or Fmoc-His(Trt)-OH to obtain **37**, was coupled. The Fmoc groups were removed and the exposed amino groups were capped with acetic anhydride to obtain resins **36** and **37**. The Alloc group was removed from **36** by a palladium catalyzed hydrostannolysis[32,33] and the last amino acid, either Fmoc-Lys(Boc)-OH, Fmoc-Glu(O*t*Bu)-OH or Fmoc-Tyr-(O*t*Bu)-OH, was then coupled. The Fmoc groups were removed and the exposed amino groups were again capped with acetic anhydride to obtain **38**. The fully protected solid-supported tetrapeptides (**37**, **38**) were finally released with a mixture of TFA-DCM (1:1) and purified in a standard manner to obtain **3**−**7** and diastereomeric mixtures of **8**−**12**. Figure 3 gives an example of a crude product mixture, and Figure 4 show the analytical RP HPLC chromatograms of the purified peptide constructs. The isolated yields of the tetrapeptides (**3**−**12**) ranged from 19 to 30%.

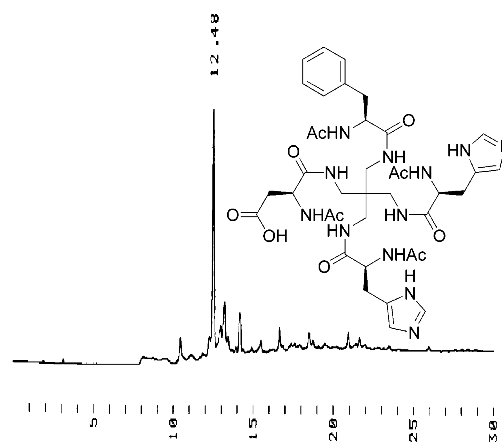


FIGURE 3. Analytical RP HPLC chromatogram of the crude product mixture of a branched tetrapeptide prepared (**5**, 12.48 min). For the chromatographic conditions, see protocol A in the Experimental Section.

The applicability of branching unit **1** was further demonstrated by synthesis of an octapeptide (**13**), in

(29) Lundquist, IV, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781.
(30) Lundquist, J. T., IV; Pelletier, J. C. *Org. Lett.* **2002**, *4*, 3219.
(31) Malkinson, J. P.; Falconer, R. A.; Toth, I. *J. Org. Chem.* **2000**, *65*, 5249.
(32) Guibé, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, *27*, 2365.
(33) Guibé, F.; Zhang, H. X.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 623.

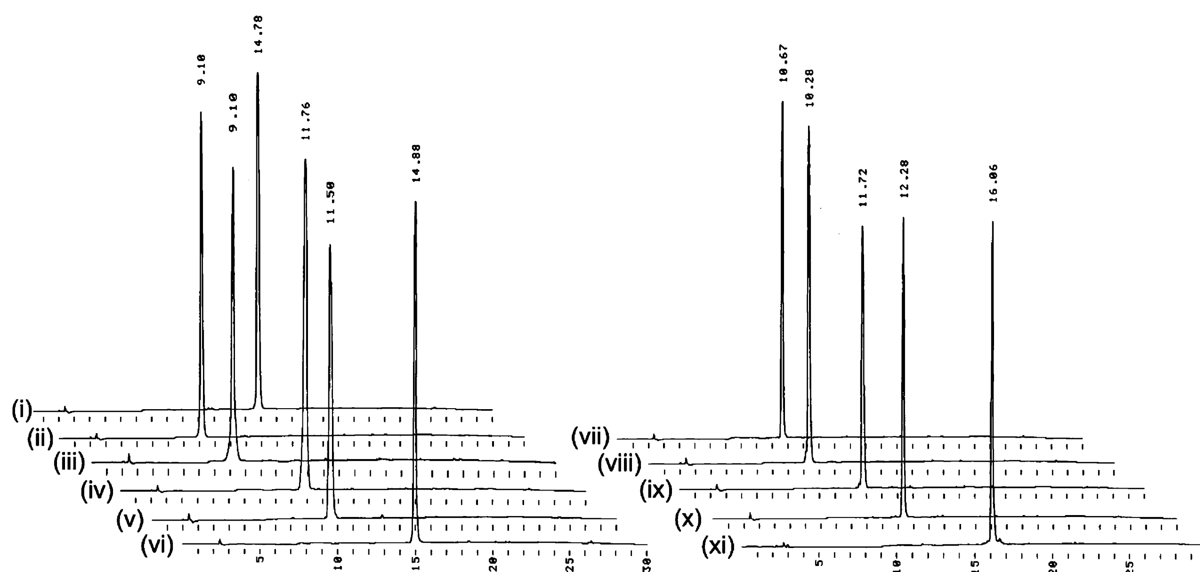


FIGURE 4. Analytical RP HPLC chromatograms of purified peptides **3**–**13**. Notation: (i) **13** (14.78 min), (ii) **7** (9.10 min), (iii) **6** (9.10 min), (iv) **5** (11.76 min), (v) **4** (11.50 min), (vi) **3** (14.88 min), (vii) **12** (10.67 min), (viii) **11** (10.20 min), (ix) **10** (11.72 min), (x) **9** (12.28 min), (xi) **8** (16.06 min). For the chromatographic condition, see protocol A in the Experimental Section.

TABLE 4. LC/ES–HRMS Molecular Masses for the Peptides Prepared (3–13)

peptide	$[M+1H^+]_{found}$	$[M + 1H^+]_{req}$
3	889.4095	889.4090
4	819.4724	819.4723
5	837.3973	837.4002
6	801.4441	801.4465
7	819.3724	819.3744
8	813.3743	813.3777
9	779.3600	779.3570
10	778.4107	778.4094
11	794.4074	794.4043
12	795.3546	795.3519
13	720.3256[a]	720.3226[b]

[a] $[(M + 2H^+)/2]_{found}$. [b] $[(M + 2H^+)/2]_{req}$.

which each of the four amino groups of **1** were derivatized with a dipeptide. The Fmoc groups of the doubly acylated resin [**35**, X = N_3, AA^1 = Asp(O*t*Bu), AA^2 = Glu(O*t*Bu)] were removed and double coupling with Fmoc-Phe-OH was performed, followed by Fmoc removal and capping with acetic anhydride (**39**). The azido masks were removed and two acetyl capped dipeptide arms were simultaneously assembled, giving a solid-phase anchored achiral octapeptide (**40**). The isolated yield of **13** after the cleavage (TFA-DCM) and standard purification was 9%. Figure 4 shows the RP HPLC chromarogram of the purified product.

The authenticity of all peptides (**3**-**13**) was verified by HRMS (Table 4). In addition, **3** and diastereomers of **8** were characterized by ^{1}H NMR spectroscopy (see the Experimental Section).

Conclusions

The results of the present report may be summarized as follows: (i) A straightforward synthesis for two pentaerythrityltetramine precursors (**1**, **2**) was developed. (ii) Experiments on immobilization of these branching units by reductive amination indicated the limitations of the pseudodilution approach; bridging of two aldehyde linkers by **1** or **2** could only be avoided by proper choice of the aldehyde structure anchored to the solid support. (iii) The primary and secondary amino groups of **1** and **2** attached by reductive amination to a BAL-type linker could be regioselectively acylated. Accordingly, one additional dimension to these partially protected branching units was provided. (iv) The applicability of branching units **1** and **2** was demonstrated by synthesis of 11 branched peptide constructs (**3**–**13**). Each of the four amino groups of the pentaerythrityltetramine core (**2**) could be selectively acylated on a solid support without using a single acid-labile protecting group.

Experimental Section

***N,N*'-Bis(*tert*-butoxycarbonyl)-2,2-bis(aminomethyl)-propane-1,3-diol (16).** 2,2-Bis(aminomethyl)propane-1,3-diol (**15**) was first prepared essentially as described earlier.[15] Accordingly, a mixture of NaN_3 (40 g, 620 mmol) and 2,2-bis-(bromomethyl)propane-1,3-diol (40.0 g, 150 mmol) in DMF (300 mL) was stirred at 120 °C overnight and filtered. Volatiles were removed, and the residue was dissolved in DCM (300 mL). The resulting precipitate was filtered off, the filtrate was evaporated to dryness, and the residue was subjected to a standard Et_2O/aq NaCl workup. The organic phase was dried with Na_2SO_4 and evaporated to dryness to yield 28.5 g (quantitative) of crude 2,2-bis(azidomethyl)propane-1,3-diol as a colorless oil. The azide (28.5 g, 153 mmol) was dissolved in ethanol (150 mL), and nitrogen was bubbled through the mixture. Pd/C (6 g, 10% Pd/C, 50% wet with water) was added to the mixture, and the bubbling was continued with hydrogen overnight. The mixture was filtered, and the filtrate was evaporated to dryness to yield 20.0 g (98%) of crude **15** as white solids. The reactions described above were monitored by ^{1}H NMR spectroscopy. 2,2-Bis(azidomethyl)propane-1,3-diol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.61 (s, 4H), 3.41 (s, 4H), 2.71 (br, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 63.4, 51.6, 44.8. **15**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.30 (s, 4H), 2.76 (br, 4H), 2.48 (s, 4H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 63.2, 43.3, 43.0. Compd. **15** (20.0 g, 150 mmol) was dissolved in MeCN (200 mL), and aqueous NaOH (12 g, 300 mmol in 100 mL of H_2O) and then

Boc_2O (80 g, 370 mmol) were added. The mixture was stirred for 5 h, and the resulting white precipitate was collected and washed several times with water and MeCN. The white powder obtained was dried by repeated coevaporations with dry pyridine and residual volatiles were removed under vacuum to yield 50 g (quantitative) of **16**: ^1H NMR (DMSO-d_6, 400 MHz) δ 6.57 (t, 2H, $J = 6.4$ Hz), 4.29 (t, 2H, $J = 5.8$ Hz), 3.19 (d, 4H, $J = 5.8$ Hz), 2.86 (d, 4H, $J = 6.4$ Hz), 1.37 (s, 18H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.6, 78.1, 61.2, 45.2, 40.4, 28.2; HRMS (EI) M^+ requires 334.2104, found 334.2108.

2,2-Bis(azidomethyl)-*N,N*-bis(*tert*-butoxycarbonyl)propane-1,3-diamine (18). Mesyl chloride (7.0 mL, 90 mmol) was added dropwise to a mixture of **16** (10.0 g, 30 mmol) in dry pyridine (100 mL) at 0 °C. The reaction mixture was stirred for 5 h at room temperature and then poured into ice−water. After 30 min of aqueous quenching, the mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with aq NaCl, and dried with Na_2SO_4. Volatiles were removed and the residue was coevaporated several times with dry toluene to yield 12.6 g (86%) of **17** as white powder: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.53 (br, 2H), 4.06 (s, 4H), 3.12 (d, 4H, $J = 7.1$ Hz), 3.10 (s, 6H), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 80.1, 67.1, 44.7, 38.6, 37.3, 28.3. The mesylate intermediate (**17**, 12.5 g, 26 mmol) and NaN_3 (8.4 g, 130 mmol) was dissolved in DMF (50 mL) and the mixture was stirred at 120 °C for 1.5 h. Ice was added, and then the mixture was extracted three times with Et_2O. The organic phase was washed with aq NaCl, dried with Na_2SO_4, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (30 to 60% EtOAc in petroleum ether) to yield 2.7 g (27%) of **18** as colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.24 (br, 2H), 3.29 (s, 4H), 3.05 (d, 4H, $J = 6.8$ Hz), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 79.8, 52.7, 44.2, 41.2, 28.3; HRMS (FAB) $[M + H]^+$ requires 385.2312, found 385.2328.

2-(Aminomethyl)-2-azidomethyl-*N,N*-bis(*tert*-butoxycarbonyl)propane-1,3-diamine (19). Triphenylphosphine (5.4 g, 21 mmol) was slowly added to a mixture of **18** (7.9 g, 21 mmol) in dry THF (25 mL), and the reaction was stirred overnight at room temperature. Aqueous ammonia (3.4 mL, 15% NH_3 in water) was added, and the mixture was refluxed for 3 h. Volatiles were removed and the residue was purified by silica gel chromatography (3−5% MeOH in DCM) to yield 6.2 g (84%) of **19** as white solid flakes: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.39 (br, 2H), 3.31 (s, 2H), 3.13 (dd, 2H, $J = 14.4$, 7.9 Hz), 2.79 (dd, 2H, $J = 14.4$, 5.9 Hz), 2.47 (s, 2H), 1.44 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 79.6, 52.5, 44.6, 42.1, 40.8, 28.4; HRMS (ESI) $[M + H]^+$ requires 359.2401, found 359.2391.

2-[*N*-(Allyloxycarbonyl)aminomethyl]-2-azidomethyl-*N,N*-bis(*tert*-butoxycarbonyl)propane-1,3-diamine (20). Allyloxycarbonyl chloride (2.4 mL, 23 mmol) was added dropwise to a mixture of **19** (6.1 g, 17 mmol) and triethylamine (3.2 mL, 22 mmol) in dioxane (60 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and then evaporated to dryness. The residue was dissolved in DCM, washed with aq $NaHCO_3$, dried with Na_2SO_4, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (15−20% EtOAc in petroleum ether) to yield 5.7 g (76%) of **20** as a white foam: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.06 (br, 1H), 5.93 (m, 1H), 5.52 (br, 2H), 5.27 (m, 2H), 4.57 (d, 2H, $J = 5.6$ Hz), 3.18 (s, 2H), 3.07−2.94 (m, 4H), 2.86 (dd, 2H, $J = 14.4$, 6.6 Hz), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 157.0, 132.8, 117.7, 79.7, 65.8, 52.1, 44.6, 40.6, 40.2, 28.3; HRMS (FAB) $[M + H]^+$ requires 443.2618, found 443.2622.

2,2-Bis(azidomethyl)propane-1,3-bis(ammonium trifluoroacetate) (1). Compound **18** (2.5 g, 6.5 mmol) was dissolved in DCM (20 mL), and TFA (20 mL) was added. The mixture was allowed to stir at ambient temperature for 3 h and evaporated to dryness. The resulted yellowish oil was coevaporated with ethanol and dried on KOH under vacuum. The product was precipitated from DCM/ethanol, filtered, washed with cold DCM, and dried to yield 2.5 g (95%) of **1** as white solid. ^1H NMR (DMSO-d_6 400 MHz) δ 8.14 (br, 6H), 3.63 (s, 4H), 2.89 (s, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 50.2, 39.7, 39.6 (TFA related peaks not listed); HRMS (ESI) $[M + H]^+$ requires 185.1258, found 185.1262.

2-[*N*-(Allyloxycarbonyl)aminomethyl]-2-azidomethylpropane-1,3-bis(ammonium trifluoroacetate) (2). Compound **20** (2.5 g, 5.6 mmol) was treated with TFA as described above for the conversion of **18** to **1** to yield 2.6 g (quantitative) of **2** as hygroscopic white solid: ^1H NMR (DMSO-d_6, 500 MHz) δ 8.02 (br, 6H), 7.55 (br, 1H), 5.91 (m, 1H), 5.28 (m, 1H), 5.18 (m, 1H), 4.50 (m, 2H), 3.59 (s, 2H), 3.15 (s, 2H), 2.85 (s, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.5, 133.3, 117.3, 65.1, 50.2, 40.7, 40.2, 40.1 (TFA related peaks not listed); HRMS (ESI) $[M + H]^+$ requires 243.1564, found 243.1575.

Resins (33, X = N_3 or NHAlloc). 4-(4-Formyl-3,5-dimethoxyphenoxy)butyric acid was first attached by HATU-promoted coupling to an aminomethyl polystyrene resin derivatized with a tripeptide (Leu-Phe-Gly) spacer to obtain resin (**21**). The loading before the linker attachment was 170 μmol g^{-1} (determined by the release of benzofulvene). A sample of **21** (2.0 g) was treated with a mixture of **1** (700 mg, 5 equiv) or **2** (800 mg, 5 equiv) and $NaBH_3CN$ (107 mg, 5 equiv) in DMSO−NMP (1:4, 10 mL) for 3 h at room temperature. The resin was collected and washed with DMF, DCM, and MeOH, and the unreacted formyl groups were capped with a mixture of methoxyamine (50 mg, 0.60 mmol) and K_2CO_3 (90 mg, 0.65 mmol) in H_2O−THF (1:9, 10 mL). After 1 h of shaking, the suspension was filtered, and the resin was washed with DMF, DCM, and MeOH and dried (**33**, X = N_3 or NHAlloc). The primary amino group on a small resin aliquot was then acylated with excess of Fmoc-Phe-OH using DCC/HOBt coupling. The treatment was repeated until the Fmoc loading remained unchanged. In this manner, a loading of 90 μmol g^{-1} (53%) of solid-supported **1** or **2** was obtained.

Synthesis of Branched Peptides (3−13, Scheme 3).

Tetrapeptides 3 and 8. The primary amino groups of a 300 mg sample of the resin (**33**, N_3 or NHAlloc, loading 90 μmol g^{-1}) were acylated with Fmoc-Phe-OH (10 equiv) using standard DCC/HOBt activation (1 M DCC and 1 M HOBt in NMP). Reaction time of 2 h was used and the coupling was repeated. The secondary amino group that remained unreacted was then acylated by treating the resin (**34**, X = N_3 or NHAlloc) with $[Fmoc\text{-}Asp(O\textit{t}Bu)]_2O$ (20 equiv in DCM, 5 h at 25 °C) to obtain **35** (X = N_3 or NHAlloc). The Fmoc groups were removed (20% piperidine in DMF), and the exposed α-amino groups were capped with a mixture of Ac_2O, 2,6-lutidine, *N*-methylimidazole and THF (5:5:8:82). The azido masks were removed by shaking the resin 2 h in a mixture of trimethylphosphine (1 M Me_3P in toluene, 12 equiv/an azido group, 2 h at 25 °C, N_2 atm) in H_2O-dioxane (1:4), and then next amino acid [10 equiv Fmoc-Ser(OtBu)-OH (**36**) and 20 equiv Fmoc-Tyr(OtBu)-OH (**37**)] was coupled using DCC/HOBt activation. Reaction time of 2 h was used for the coupling, the Fmoc groups were removed and the exposed amino groups were capped with Ac_2O to obtain resins **36** and **37**. The Alloc group of resin **36** was removed by a palladium catalyzed hydrostannolysis [2 equiv of $Pd(OAc)_2$, 12 equiv of $P(Ph)_3$, 12 equiv of AcOH, 12 equiv of Bu_3SnH in DCM, 30 min at rt, argon atm] and then the last amino acid [Fmoc-Tyr(OtBu)-OH, 10 equiv] was coupled using DCC/HOBt activation, as described above. Fmoc deprotection followed by Ac_2O capping yielded resin **38**. The fully protected and solid-supported branched peptide (**3**, **8**) was cleaved from the support (**37**, **38**) with a mixture of TFA and DCM (1:1, *v/v*). Volatiles were removed, and the crude peptide (**3**, **8**) was precipitated from cold ether and purified by HPLC. Peptide **8** was obtained as a pair of diastereomers (**8a**, **8b**), which were separated by an isocratic elution (13% MeCN in 0.1% aq TFA). The isolated yields of peptides were 19% (**3**) and 20% (sum of diastereomers of **8**). **3**: ^1H NMR (D_2O, 500 MHz) δ 7.26−7.10 (m, 5H), 7.00 (d, 2H, $J = 8.5$ Hz), 6.98 (d, 2H, $J = 8.6$ Hz), 6.74 (d, 2H, $J = 8.5$ Hz), 6.73 (d, 2H, $J = 8.6$ Hz), 4.41 (t, 1H, $J = 6.1$ Hz), 4.27

(dd, 1H, $J = 8.9$, 7.0 Hz), 4.18 (m, 2H), 2.97 (dd, 1H, $J = 13.7$, 7.0 Hz), 2.92 (dd, 2H, $J = 13.6$, 6.5 Hz), 2.81 (dd, 1H, $J = 13.7$, 8.9 Hz), 2.75–2.70 (m, 3H), 2.70 (dd, 1H, $J = 13.6$, 4.6 Hz), 2.25 (d, 1H, $J = 14.7$ Hz), 2.11–2.05 (m, 6H), 1.95 (s, 3H), 1.88 (s, 6H), 1.87 (s, 3H), 1.77 (d, 1H, $J = 14.2$ Hz); HRMS (ESI) $[M + H]^+$ requires 889.4090, found 889.4095. **8a**: ^{1}H NMR (D_2O, 500 MHz) δ 7.35–7.22 (m, 5H), 7.11 (d, 2H, $J = 8.6$ Hz), 6.82 (d, 2H, $J = 8.6$ Hz), 4.55 (t, 1H, $J = 6.3$ Hz), 4.43 (dd, 1H, $J = 8.4$, 7.2 Hz), 4.35 (dd, 1H, $J = 8.7$, 6.9 Hz), 4.24 (dd, 1H, $J = 5.4$, 4.4 Hz), 3.86 (dd, 1H, $J = 11.7$, 5.4 Hz), 3.80 (dd, $J = 11.7$, 4.4 Hz), 3.07 (dd, 1H, $J = 13.8$, 7.2 Hz), 3.02 (dd, 1H, $J = 13.8$, 6.9 Hz), 2.98 (dd, 1H, $J = 13.8$, 8.4 Hz), 2.88 (dd, 1H, $J = 13.8$, 8.7 Hz), 2.86 (d, 2H, $J = 6.3$ Hz), 2.57 (d, 1H, $J = 14.6$ Hz), 2.50–2.43 (m, 6H), 2.22 (d, 1H, $J = 14.3$ Hz), 2.08 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H); HRMS (ESI) $[M + H]^+$ requires 813.3777, found 813.3745. **8b**: ^{1}H NMR7.34–7.22 (m, 5H), 7.09 (d, 2H, $J = 8.5$ Hz), 6.79 (d, 2H, $J = 8.5$ Hz), 4.53 (t, 1H, $J = 6.3$ Hz), 4.41 (dd, 1H, $J = 8.1$, 7.4 Hz), 4.34 (dd, 1H, $J = 8.6$, 6.8 Hz), 4.23 (dd, 1H, $J = 5.5$, 4.4 Hz), 3.84 (dd, 1H, $J = 11.7$, 5.5 Hz), 3.79 (dd, 1H, $J = 11.7$, 4.4 Hz), 3.06 (dd, 1H, $J = 13.8$, 7.5 Hz), 2.99 (dd, 1H, $J = 13.5$, 6.8 Hz), 2.97 (dd, 1H, $J = 13.8$, 8.1 Hz), 2.86 (dd, 1H, $J = 13.5$, 8.6 Hz), 2.84 (d, 2H, $J = 6.4$ Hz), 2.56–2.38 (m, 7H), 2.24 (d, 1H, $J = 14.8$ Hz), 2.07 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H); HRMS (ESI) $[M + H]^+$ requires 813.3777, found 813.3741 (the avarage MS value of **8a** and **8b** is shown in Table 4).

Tetrapeptides 4–7 and 9–12. The other branched tetrapeptides were synthesized analogously with **3** and **8**. However, double coupling of Fmoc-His(Trt)-OH proved to be difficult (peptides **5** and **7**), and hence, PyAOP/DIEA was used for coupling instead of DCC/HOBt (10 equiv of Fmoc-His(Trt)-OH, 10 equiv of PyAOP, 20 equiv of DIEA, relative to amino groups, 2 h at 25 °C). The analytical RP HPLC chromatogram of the crude product mixture of **5** is shown in Figure 3. The isolated yields of the tetrapeptides (**4**–**7**, **9**–**12**) ranged from 20 to 30%. HRMS (ESI): see Table 4.

Octapeptide (13). The Fmoc groups were removed from resin **35** [X = N_3, AA^1 = Asp(O*t*Bu), AA^2 = Glu(O*t*Bu), a 300 mg sample] with 20% piperidine in DMF and a double coupling with Fmoc-Phe-OH (20 equiv) using DCC/HOBt activation was performed. After 2 h coupling time, the Fmoc groups were removed and the exposed α-amino groups were capped with Ac_2O to obtain resin **39**. The azido masks were removed by treating the resin for 2 h with trimethylphosphine, as described above, and the capped dipetides [Ac-Tyr(O*t*Bu)-His-(Trt)] were then simultaneously assembled (see coupling of Fmoc-His(Trt)-OH above). The fully protected solid-supported octapeptide (**40**) was released from the support and purified as the tetrapeptides. The isolated yield of the achiral octapeptide (**13**) was 9%. HRMS (ESI): see Table 4.

Acknowledgment. We thank Dr. Petri Heinonen for performing the ^{1}H and ^{13}C NMR analysis.

Supporting Information Available: General procedures and spectral data for compounds **1**–**13**, **16**, and **18**–**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035801+