The Choice of Phosphane Reagent in Fukuyama–Mitsunobu Alkylation: Intramolecular Selectivity Between Primary and Secondary Alcohols in the Preparation of Asymmetric Tetraamine Building Blocks for Synthesis of Philanthotoxins

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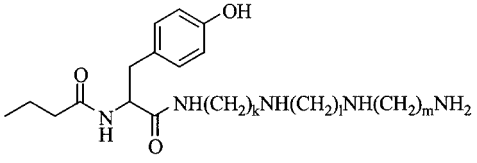
Philanthotoxin-433 (PhTX-433) is a polyamine wasp toxin that antagonizes certain ionotropic receptors noncompetitively. Four analogues of PhTX-433, *C*-methylated in the polyamine chain, were synthesized from (*RS*)-1,3-butanediol, two diamine building blocks, and an activated/protected tyrosine derivative. Use of a phosphane reagent more bulky than trimethylphosphane gave a high intramolecular selectivity between primary and secondary hydroxy groups in the Fukuyama–Mitsunobu reaction. Thus, trimethylphosphane proved to be the only phosphane reagent that enabled alkylation of 2-nitrobenzenesulfonamides with a wide range of secondary alcohols, whereas tributylphosphane was selective for primary alcohol groups. This selectivity was utilized to obtain orthogonally protected, asymmetric, branched tetraamines, employed for solution-phase synthesis of philanthotoxin analogues. The branched philanthotoxin analogues thus obtained were tested in an electrophysiological assay using rat brain ionotropic glutamate receptors expressed in *Xenopus laevis* oocytes. Their potencies proved to be similar to the corresponding nonbranched analogues.

Introduction

Polyamine structural elements are found in various natural products such as antibiotics and toxins from animals and plants. Many important biological activities have been reported for these naturally occurring polyamine derivatives as well as for their synthetic analogues.[1] Philanthotoxins constitute a group of polyamine toxins composed of a polyamine chain connected via an amide bond to a relatively nonpolar head group, consisting of an *N*-acylated amino acid.[2–4] Philanthotoxin-433 (PhTX-433, **1**) was originally isolated from the venom of the female Egyptian digger wasp *Philanthus triangulum* L.[2,3] The structures of PhTX-433 (**1**) and its synthetic analogues PhTX-334 (**2**) and PhTX-343 (**3**) are shown in Figure 1. These toxins antagonize noncompetitively various classes of ionotropic receptors, e.g. nicotinic acetylcholine receptors[4,5] and ionotropic glutamate receptors.[6–9] A large number of philanthotoxin analogues have been synthesized and evaluated pharmacologically in order to obtain structure-activity relationships (SAR).[4,9–12] Despite the recent focus on variations in the polyamine chain of philanthotoxins,[10,12] only two analogues containing a branched polyamine moiety have been described so far.[13,14] These are the PhTX-433 analogues **4** and **5**, containing a methyl or an *n*-butyl group in the 7-position (Figure 2). Using a locust muscle twitch contraction inhibition assay, the *n*-butyl analogue showed a 5.6-fold increase in potency compared to the native toxin **1**.[14] The fact that the biological consequences of the presence of



1 (PhTX-433): $k = 4$, $l = 3$ and $m = 3$
2 (PhTX-334): $k = 3$, $l = 3$ and $m = 4$
3 (PhTX-343): $k = 3$, $l = 4$ and $m = 3$

Figure 1. General structure of philanthotoxins PhTX-*klm*, where numerals *klm* denote the number of methylene groups separating the nitrogen atoms in the polyamine chain

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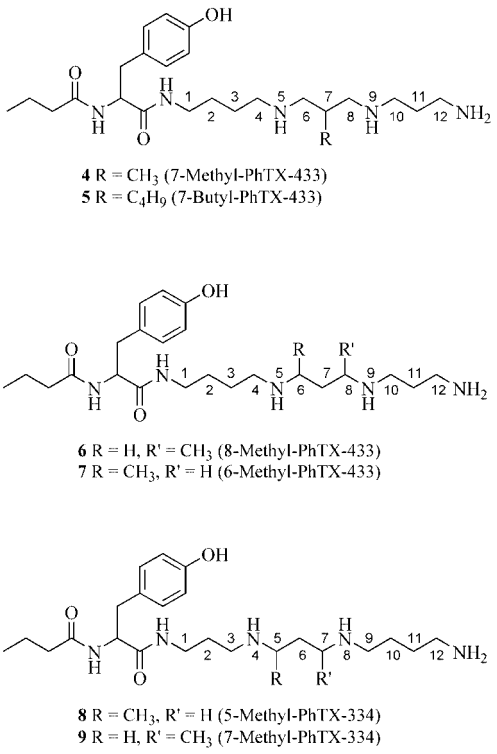


Figure 2. Structures of branched philanthotoxin analogues **4–9**

a branch in the polyamine chain of polyamine toxins have not been investigated systematically is due to the present lack of generally applicable synthetic routes to such philanthotoxin analogues.

The synthetic strategies generally used for construction of polyamines by sequential chain elongation may be classified into three major groups: (i) classical alkylation reactions, (ii) Mitsunobu reactions, and (iii) methods based on reduction of intermediary amides or imines.[15] Thus, in all previously reported procedures, polyamine toxins have been synthesized from diamines (often activated as sulfonamides) in combination with halides,[16,17] amino alcohols,[18–20] amino aldehydes[21,22] or amino acids.[23]

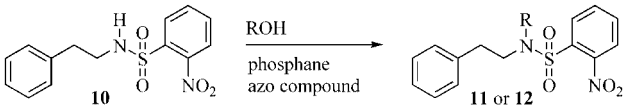
By contrast, the method presented in this work involves preparation of polyamine moieties of philanthotoxin analogues from diamines (activated as sulfonamides) and diols. One of our aims was to develop a general procedure for the incorporation of secondary alcohols into the polyamine chain. The selected diol, (*RS*)-1,3-butanediol, enables synthesis of the four branched analogues **6–9** shown in Figure 2.

Initially, we considered the conventional Fukuyama–Mitsunobu conditions employing diethyl azodicarboxylate and triphenylphosphane in CH_2Cl_2, which allows primary alcohols to alkylate 2-nitrobenzenesulfonamides.[24,25] Earlier work in this area appears to be limited to the alkylation of sulfonamide-activated methylamine derivatives (triflamide or *p*-toluenesulfonamide) with the 1-*O*-benzoyl derivative of 1,3-butanediol under Mitsunobu conditions.[26,27] This type of activation, however, did not seem very appealing since quite harsh Birch conditions[28] are necessary for deprotection of the resulting polyamine. The more recently described Tsunoda conditions, employing tributylphosphane (TBP) and 1,1′-(azodicarbonyl)dipiperidide (ADDP),[29] were reported to give excellent yields in the alkylation of 2-nitrobenzenesulfonamides in the synthesis of polyamine toxins on solid phase.[30] Consequently, this reagent combination was selected, along with the less hindered *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[31] and trimethylphosphane (TMP)[32,33] for our investigation of the alkylation of 2-nitrobenzenesulfonamides (Ns-amides) with secondary alcohols. The Ns group is convenient in both solid and solution phase syntheses, because it is readily removed under mild conditions. Tsunoda et al. obtained 34% and 40% yields in the alkylation of 2-octanol with *N*-methyl-*p*-toluenesulfonamide using ADDP-TBP and TMAD-TBP, respectively.[31]

Results

Using ADDP-TBP or TMAD-TBP and a number of secondary alcohols, no or very little conversion was observed with sulfonamides other than *N*-methyl-*p*-toluenesulfonamide. This emphasizes the need of a careful choice of the test sulfonamide for systematic examination of reagents and optimisation of the reaction conditions for this particular reaction. We have selected 2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (**10**), which is convenient with respect to reactivity, as benzylic or allylic sulfonamides should be avoided due to their often enhanced reactivity. The test alcohols should preferably comprise aliphatic and alicyclic compounds together with allylic, homoallylic and benzylic representatives. The results of alkylations using either 1-butanol or 2-butanol (presented in Table 1), showed that the choice of the azo-reagent in combination with TMP had only a minor effect on the yield. Thus, compounds **11** and **12** (prepared by Method B or C) were obtained in 51–83% yields, the lowest yields being observed with the secondary alcohol. On the other hand, the yield was strongly diminished in the case of 2-butanol when TBP was used (**12**, Method A; in Table 1). This indicated that the alkoxytributylphosphonium intermediate[25] that was presumably involved in the reaction was too sterically congested, or was not formed at all. The combination TMP-ADDP worked satisfactorily with a variety of secondary alcohols to give products **13–18**, as shown in Table 2. It was not possible to isolate any of the expected coupling product **19** using menthol, and since its hydroxy group is particularly hindered, this observation confirms that steric hindrance of the alcohol group is of major importance in the reaction.

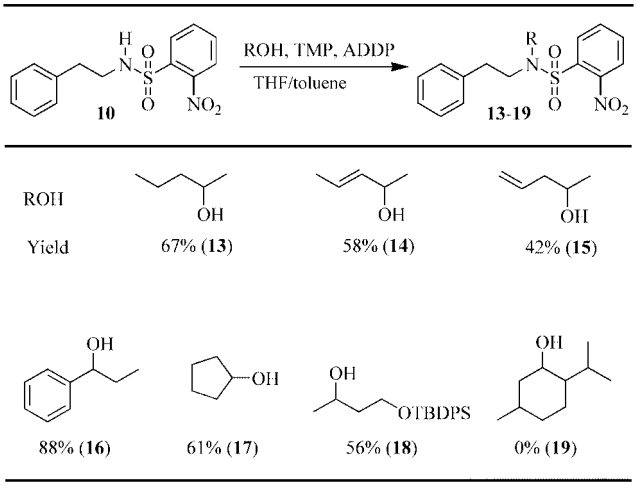
Table 1. Isolated yields from Fukuyama–Mitsunobu reactions between **10** and 1-butanol or 2-butanol



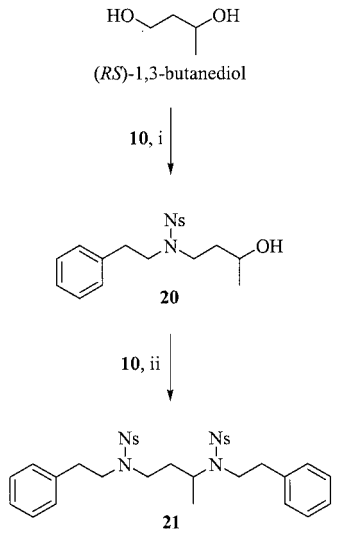
ROH	TBP-TMAD[a]	TMP-TMAD[b]	TMP-ADDP[c]
OH	89% (**11**)	80% (**11**)	83% (**11**)
OH	3% (**12**)	51% (**12**)	71% (**12**)

[a] Method A (toluene). [b] Method B (THF). [c] Method C (THF/toluene).

Table 2. Isolated yields from Fukuyama–Mitsunobu couplings between **10** and secondary alcohols using the TMP-ADDP reagent system



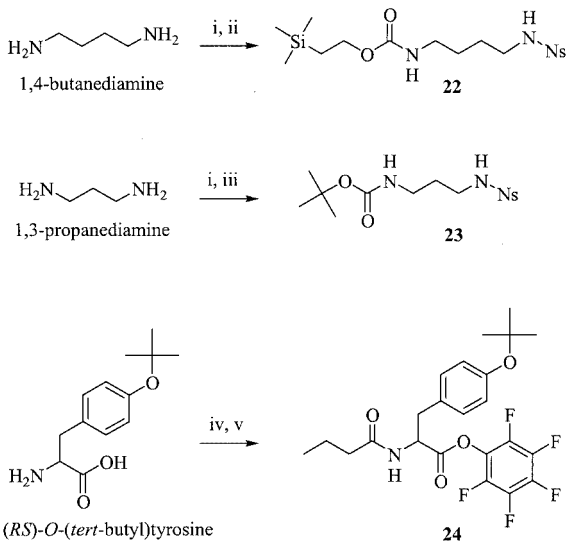
A very high intramolecular selectivity between a primary and a secondary hydroxy group could be obtained by the proper choice of the trialkylphosphane reagent. Thus, when (*RS*)-1,3-butanediol was subjected to alkylation with **10** using the TBP-TMAD reagent pair (Scheme 1), the monoalkylation product **20** was isolated in 63% yield along with only 4% of the dialkylation product **21**. The modest yield of **20** (based on the diol) may be due to an intramolecular ether formation as a side reaction. The obtained sulfonamide **20** could then react further with **10**, using the reagent pair TMP-ADDP, to give the bis-sulfonamide **21** in 66% yield. The observed selectivity in the alkylation with (*RS*)-1,3-butanediol is quite remarkable considering that this secondary alcohol belongs to the least sterically hindered ones.



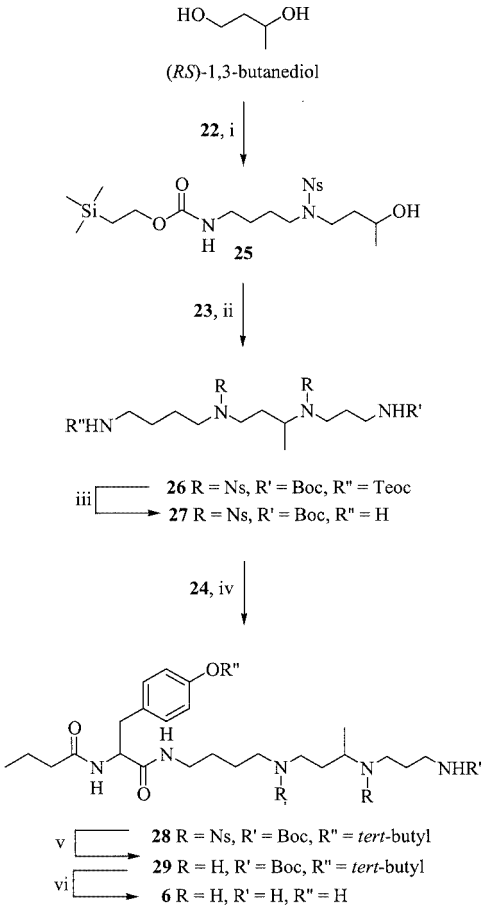
Scheme 1. Reagents: i) TBP, TMAD, THF, 24 h, 63%; ii) TMP, ADDP, THF, 40 h, 66%

The observed intramolecular selectivity in the Fukuyama–Mitsunobu alkylation of primary and secondary alcohol groups was utilized in the synthesis of four branched philanthotoxin analogues, namely 8-methyl-PhTX-433 (**6**), 6-methyl-PhTX-433 (**7**), 5-methyl-PhTX-334 (**8**), and 7-methyl-PhTX-334 (**9**). These four analogues were obtained from only four building blocks: two selectively protected and activated diamine derivatives **22** and **23**, the *N*-acylated tyrosine active ester **24,** and (*RS*)-1,3-butanediol (Scheme 2). Compound **22** was prepared in two steps from 1,4-butanediamine. In the first step, *N*-(2-nitrobenzenesulfonyl)-1,4-butanediamine was prepared by treatment with 2-nitrobenzenesulfonyl chloride (NsCl);[16] the resulting crude product was protected with a 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group using 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate.[34,35] Compound **23** was prepared by treatment of 1,3-propanediamine with NsCl followed by di-(*tert*-butyl) dicarbonate [$(Boc)_2O$] as described by Hidai et al.[36] Conversion of *O*-(*tert*-butyl)tyrosine into **24** was performed by successive acylation with butyryl chloride[37] and formation of the pentafluorophenyl ester (Pfp-ester) using pentafluorophenyl trifluoroacetate.[38]

A six-step synthesis of 8-methyl-PhTX-433 (**6**) from the above-mentioned building blocks was carried out as shown in Scheme 3. In the first step, sulfonamide **22** was *N*-alkylated with 1,3-butanediol, and by choosing the TBP-ADDP reagent system **25** could be isolated in 53% yield. The vacuum liquid chromatography (VLC) purification was, however, quite tedious and some additional, impure fractions of **25** were obtained (analysis by ^1H NMR indicated a total yield of approximately 70%). In the next step, **25** was alkylated with **23** using the TMP-ADDP system to give the fully protected polyamine **26**. The *N*-Teoc group was selectively cleaved with tetrabutylammonium fluoride (TBAF)[39,40] to give **27**, which was acylated using the tyrosine building block **24**.[41] This afforded the fully protected, branched phi-



Scheme 2. Reagents: i) Et_3N, NsCl, CH_2Cl_2, 4 h, 60%; ii) 2-trimethylsilylethyl *p*-nitrophenylcarbonate, DIPEA, THF, 50 °C, 2 h, 89%; iii) Boc_2O, MeOH, N_2, 22 h, 94%; iv) butyryl chloride, THF, 2 M NaOH; v) pentafluorophenyl trifluoroacetate, pyridine, DMF, 5 h, 57% (for iv and v)



Scheme 3. Reagents: i) TBP, ADDP, THF, 24 h, 70%; ii) TMP, ADDP, THF, 40 h, 68%; iii) TBAF, THF, 50 °C, 2 h, 62%; iv) DIPEA, DMF, 2 h, 88%; v) 2-mercaptoethanol, DBU, DMF, 2 h, 67%; vi) TFA, CH_2Cl_2, 3 h, 92%

lanthotoxin analogue **28**, which was treated with diazabicyclo[5.4.0]undec-7-ene (DBU) and 2-mercaptoethanol[42,43] to remove the Ns groups. Finally removal of the *tert*-butyl and Boc groups in **29** using trifluoroacetic acid (TFA) gave 8-methyl-PhTX-433 (**6**) as a tris(TFA) salt.

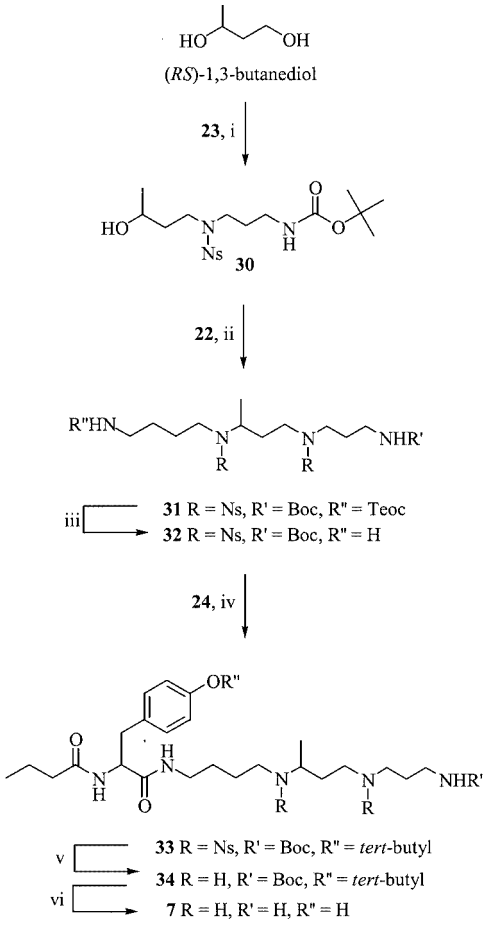
Similarly, a six-step synthesis of 6-methyl-PhTX-433 (**7**) was performed as depicted in Scheme 4. The sequence differs from that described above only with respect to the order of the two Fukuyama–Mitsunobu alkylations. Thus, **23** was alkylated with 1,3-butanediol using TBP-ADDP to give **30**, which was further alkylated with **22** using the TMP-ADDP system. This reversed incorporation of the two building blocks resulted in the fully protected polyamine **31**. Selective cleavage of the *N*-Teoc group, acylation and deprotection were performed as above, to give 6-methyl-PhTX-433 (**7**) as a tris(TFA) salt.

5-Methyl-PhTX-334 (**8**) was synthesized in four steps from fully protected polyamine **26** (Scheme 5). Here the *N*-Boc group was cleaved selectively with *p*-toluenesulfonic acid (TsOH) in diethyl ether; hence the acid-labile *N*-Teoc group proved stable under these conditions, as previously reported by Rosowsky et al.[35,44] The resulting amine **35** was acylated with **24** to give **36**. Deprotection was performed via **37** as already described, yielding the tris(TFA) salt of 5-methyl-PhTX-334 (**8**). A similar pathway starting with **31** and leading, via **38**–**40**, to the tris(TFA) salt of 7-methyl-PhTX-334 (**9**), was performed as shown in Scheme 6. The tris(TFA) salts of **6**–**9** were purified by preparative, reversed-phase HPLC and characterized by HRMS, ^1H and ^{13}C NMR spectroscopy. All four philanthotoxin analogues **6**–**9** represent mixtures of stereoisomers with respect to the stereogenic centers in the polyamine chains.

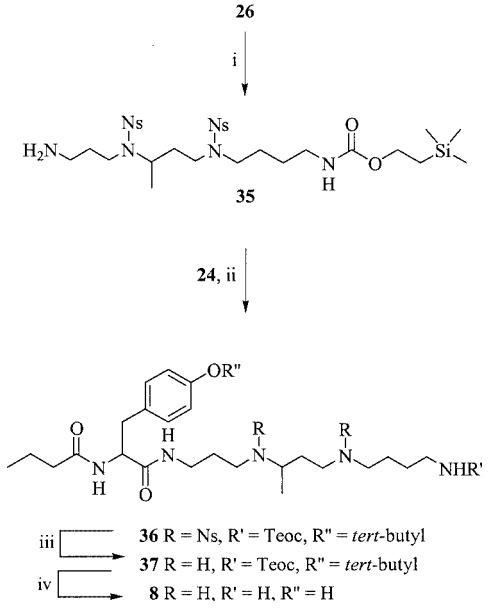
In vitro Electrophysiology: Concentration-inhibition relationships for the four branched philanthotoxin derivatives **6**–**9** and PhTX-343, obtained in an electrophysiological glutamate receptor assay,[7,8] provided the IC_{50} values shown in Table 3. *Xenopus laevis* oocytes were injected with rat brain RNA and incubated at 18 °C for 4–9 days. A two-electrode voltage-clamp (TEVC) was used to record the responses to agonist alone (100 μM kainic acid) and to co-application of agonist (100 μM kainic acid) and each of the philanthotoxin analogues at a holding potential (V_H) of −80 mV. In this assay, responses to kainic acid are mediated by AMPA receptors.[45]

Discussion

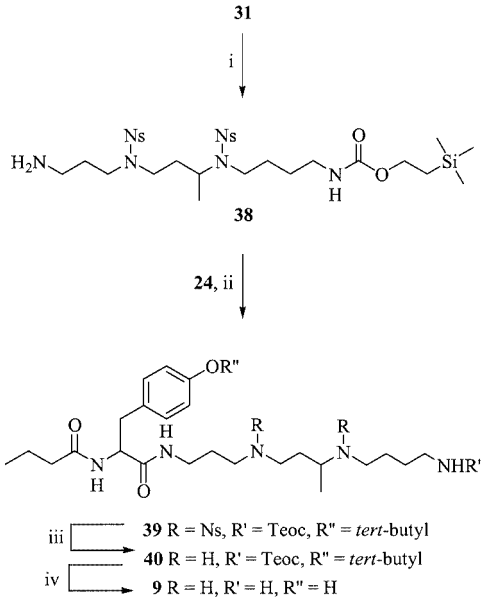
Four novel philanthotoxin analogues **6**, **7**, **8** and **9**, *C*-methylated at α-positions to the nitrogen atoms in the polyamine chain, were synthesized by applying a novel and versatile solution-phase strategy. The intermediate, orthogonally protected tetraamines **26** and **31** were synthesized from two diamine building blocks **22** and **23** and the commercially available (*RS*)-1,3-butanediol, utilizing two trialkyl-



Scheme 4. Reagents: i) TBP, ADDP, THF, 24 h, 56%; ii) TMP, ADDP, THF, 40 h, 69%; iii) TBAF, THF, 50 °C, 2 h, 62%; iv) DIPEA, DMF, 2 h, 91%; v) 2-mercaptoethanol, DBU, DMF, 2 h, 62%; vi) TFA, CH_2Cl_2, 3 h, 96%



Scheme 5. Reagents: i) *p*TsOH, diethyl ether, 50 °C, 1 h, 70%; ii) DIPEA, DMF, 2 h, 76%; iii) 2-mercaptoethanol, DBU, DMF, 2 h, 77%; iv) TFA, CH_2Cl_2, 3 h, 97%



Scheme 6. Reagents: i) *p*TsOH, diethyl ether, 50 °C, 1 h, 63%; ii) DIPEA, DMF, 2 h, 83%; iii) 2-mercaptoethanol, DBU, DMF, 2 h, 54%; iv) TFA, CH_2Cl_2, 3 h, 99%

Table 3. Antagonism by PhTX-343 and branched analogues of rat-brain AMPA receptors expressed in *Xenopus laevis* oocytes

Compound	IC_{50}, μM (n = 5 oocytes)
3 (PhTX-343)	0.13 ± 0.03
6 (8-Methyl-PhTX-433)	0.26 ± 0.08
7 (6-Methyl-PhTX-433)	0.07 ± 0.02
8 (5-Methyl-PhTX-334)	0.13 ± 0.02
9 (7-Methyl-PhTX-334)	0.17 ± 0.03

phosphane reagents (TMP and TBP) to achieve differentiation between primary and secondary hydroxy groups in the Fukuyama–Mitsunobu alkylation method. The applied solution-phase strategy is compatible with an easy scale-up. Moreover, since Fukuyama–Mitsunobu alkylations have previously been applied on solid phase,[30,46,47] we believe that our strategy is applicable to parallel synthesis of polyamines on solid supports.

The protocol presented here employs for the first time diols as building blocks for synthesis of philanthotoxin analogues. This is an advantage because of the variety of diols that are commercially available. This broader availability of diols as compared to, e.g., dihalides or amino alcohols, allows easy synthetic access to a variety of novel philanthotoxin analogues. A major advantage of the present methodology is that protection of the hydroxy groups of diols is not necessary. This may be exploited either in bisalkylation reactions with two mol of a 2-nitrobenzenesulfonamide reagent, or in monoalkylation reactions as those in Scheme 2 and 3, simply by the proper choice of the trialkylphosphane. If monoalkylation of a symmetric diol (with two primary or two secondary hydroxy groups) is required, monoprotec-

tion is necessary. Thus, it was demonstrated that alcohols protected as silyl ethers are compatible with the reaction conditions (e.g. leading to **18**). In such cases an *N*-Boc protected sulfonamide building block should be introduced before an *N*-Teoc protected sulfonamide in order to allow selective removal of the silyl ether protective group.

Selective cleavage of the *N*-Boc and *N*-Teoc groups in the two protected tetraamines **26** and **31** gave rise to four different partially protected polyamines **27**, **32**, **35** and **38**, ready for acylation with the Pfp-ester of an *N*-acylated amino acid such as **24**. In general, the Pfp-ester couplings[40,48] proceeded in high yields (76−92%), whereas the final two-step deprotection gave moderate to good yields (54−75%). The overall yields of the purified final products **6−9**, based on compounds **22** or **23** were in the range 11−17%. The purification was readily achieved by reversed-phase preparative HPLC.

The four branched philanthotoxin analogues **6−9** antagonized AMPA receptors expressed in *Xenopus laevis* oocytes. The observed potencies were all within twofold of the potency of PhTX-343 (**3**), a usual reference compound (Table 3). Thus, the introduction of *C*-methyl groups in PhTX analogues, placed as in **6−9,** does not significantly enhance the antagonistic potency as compared to **3**. Nevertheless, the synthetic methodology presented here is potentially useful for further exploration of the structure-activity relationships of philanthotoxins. In a recent study by Kromann et al.,[49] the position of the secondary amino group in PhTX-83 was systematically moved along the triamine chain. PhTX-56 was shown to be a highly potent antagonist of homomeric GluR1 receptors, with an IC_{50} value in the low nanomolar region.[49] Thus, pharmacological evaluation of philanthotoxins combining the presence of *C*-alkylation sites with altered positions of the secondary amino groups may be of interest.

Experimental Section

General Procedures: Unless otherwise stated, starting materials were obtained from commercial suppliers. *O*-(*tert*-Butyl)tyrosine was obtained from Novabiochem (Läufelingen, Switzerland). Tetrahydrofuran (THF) was distilled under N_2 from sodium/benzophenone immediately before use. Dry dichloromethane was distilled from P_2O_5 and kept over 4 Å molecular sieves. Water for reversed-phase high-performance liquid chromatography (HPLC) was filtered through a 0.22-μm pore filter. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400.13 MHz and 100.62 MHz, respectively, with a Bruker AMX 400 spectrometer, or at 300.06 and 75.45 MHz, respectively, with a Varian Gemini 2000 spectrometer, using $CDCl_3$ or CD_3OD as solvent and tetramethylsilane (TMS) as internal standard. Coupling constants (*J* values) are given in Hertz (Hz) and multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet, br., broad signal. Vacuum liquid chromatography (VLC) was performed using Merck silica gel 60 H, particle size < 45 μm (90%). Preparative HPLC system consisted of a Waters model 590 pump, a Waters Lambda-Max model 481 spectrophotometric detector and a 25 × 2.12 cm Phenomenex Luna 5-C18(2) column, 5 μm. The chromatograph operated isocratically at a flow-rate of 14 mL/min, using water/acetonitrile/TFA, 85:15:0.1 as mobile phase. High-resolution mass (HRMS) measurements for exact mass determination were performed with a Bruker APEX III Fourier transform mass spectrometer equipped with a 7-Tesla superconducting magnet and an external electrospray ion source (Apollo source). The spectra were externally calibrated with a capillary skimmer dissociation spectrum of LHRH (luteinizing hormone releasing hormone). The samples were introduced into the electrospray ion source using a 250-μL syringe, with a syringe pump flow 2 μL/min.

2-Nitro-*N*-(2-phenylethyl)benzenesulfonamide (10): 2-Phenylethylamine (0.42 mL, 3.3 mmol) and Et_3N (0.60 mL, 4.3 mmol) were dissolved in dry CH_2Cl_2 (3 mL) and stirred on an ice-bath. To this solution 2-nitrobenzenesulfonyl chloride (880 mg, 4.0 mmol, 1.2 equiv.) in CH_2Cl_2 (3 mL) was added, the ice-bath was removed, and the mixture was stirred at room temperature overnight. Then the mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (2 × 50 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (3 mL) and loaded onto a VLC column (4 × 4 cm). Elution with hexane, hexane/EtOAc (10:1 and 4:1) afforded **10**[50] (907 mg; 89%) as white crystals (m.p. 90−91 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (t, *J* = 7.0 Hz, 2 H, CH_2Ph), 3.39 (dt, *J* = 6.1 Hz, 2 × 7.0 Hz, 2 H, CH_2N), 5.31 (br. s, 1 H, NH), 7.01 (m, 2 H, Ph), 7.23 (m, 3 H, Ph), 7.72 (m, 2 H, Ns), 7.82 (m, 1 H, Ns), 8.01 (m, 1 H, Ns) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.0, 45.1, 125.7, 127.2, 128.9 (2 C), 129.0 (2 C), 131.2, 133.1, 133.7, 134.0, 137.6 ppm.

***N*-Butyl-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (11). Method A:** 1-Butanol (26 μL, 0.3 mmol, 1.5 equiv.) and **10** (61 mg, 0.2 mmol) were dissolved in toluene (3 mL) and stirred in a septum-sealed flask on an ice-bath. To this solution TBP (75 μL, 0.3 mmol, 1.5 equiv.) and TMAD (51 mg, 0.3 mmol, 1.5 equiv.) were added, and stirring was continued at room temperature for 20 h. Then the mixture was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (2 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane and hexane/EtOAc (15:1 and 7:1) afforded **11** (64 mg; 89%) as a colourless syrup. For spectroscopic data see **11** (Method C) below.

***N*-Butyl-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (11). Method B:** 1-Butanol (26 μL, 0.3 mmol, 1.5 equiv.) and **10** (61 mg, 0.2 mmol) were dissolved in THF (1 mL) and stirred in a septum-sealed flask. To this solution TMP (3 mL, 1.0 M in THF, 0.3 mmol, 1.5 equiv.) and TMAD (51 mg, 0.3 mmol, 1.5 equiv.) were added and stirring was continued at room temperature for 20 h. Then the mixture was concentrated in vacuo, and the residue was taken up in CH_2Cl_2/hexane (1:1) (2 mL) and loaded onto a VLC column (2.7 × 3 cm). Elution with hexane and hexane/EtOAc (15:1 and 6:1) afforded **11** (58 mg; 80%) as a colourless syrup. For spectroscopic data see **11** (Method C) below.

***N*-Butyl-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (11). Method C:** 1-Butanol (26 μL, 0.3 mmol, 1.5 equiv.) and **10** (61 mg, 0.2 mmol) were dissolved in toluene (2 mL) and stirred on an ice-bath in a septum-sealed flask. To this solution TMP (0.3 mL, 1.0 M in THF, 0.3 mmol, 1.5 equiv.) and ADDP (75 mg, 0.3 mmol, 1.5 equiv.) were added and stirring was continued for 20 h at room temperature. Then the mixture was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (2.5 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane and hexane/EtOAc (15:1 and 7:1) afforded **11** (60 mg; 83%) as a reddish oil. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.29 (m, 2 H, CH_2CH_3), 1.54 (m, 2 H, $CH_2CH_2CH_3$), 2.85 (m, 2 H, CH_2Ph), 3.33 (m, 2 H, NCH_2CH_2Ph), 3.51 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 7.15−7.26 (m, 5 H, Ph), 7.60−7.66 (m, 3 H, Ns), 7.96 (m, 1 H, Ns) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 19.8, 30.2, 35.2, 47.6, 48.8, 124.4, 126.9, 128.8 (2 C), 129.0 (2 C), 130.9, 131.8, 133.6, 133.9, 138.3, 148.3 ppm. HRMS: $[C_{18}H_{22}N_2O_4S + Na]^+$ calculated, 385.11925; found, 385.11924.

***N*-(*sec*-Butyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (12). Method A:** 2-Butanol (23 μL, 0.25 mmol, 1.5 equiv.) and **10** (53 mg, 0.17 mmol) were dissolved in toluene (3 mL) and stirred in a septum-sealed flask. To this solution TBP (64 μL, 0.26 mmol, 1.5 equiv.) and TMAD (45 mg, 0.26 mmol, 1.5 equiv.) were added and stirring was continued at room temperature for 20 h. Then another 0.17 mmol (1.0 equiv.) of TBP and TMAD were added and stirring was continued for an additional 22 h. The mixture was then concentrated in vacuo, the residue was taken up in CH_2Cl_2 (2.5 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane and hexane/EtOAc (15:1 and 6:1) afforded **12** (2 mg; 3%) as a colourless syrup, along with unchanged **10** (44 mg; 83%). For spectroscopic data see **12** (Method C) below.

***N*-(*sec*-Butyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (12). Method B:** 2-Butanol (28 μL, 0.3 mmol, 1.5 equiv.) and **10** (61 mg, 0.2 mmol) were dissolved in toluene (2 mL) and stirred in a septum-sealed flask. To this solution TMP (0.3 mL, 1.0 M in THF, 0.3 mmol, 1.5 equiv.) and TMAD (51 mg, 0.3 mmol, 1.5 equiv.) were added and stirring was continued at room temperature for 20 h. Then additional portions of TMP and TMAD (0.2 mmol, 1.0 equiv. of each) were added and stirring was continued for an additional 22 h. The mixture was concentrated in vacuo, and the residue was taken up in CH_2Cl_2/hexane (3:1) (4 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane and hexane/EtOAc (15:1 and 7:1) afforded **12** (37 mg; 51%) as a colourless syrup, along with unchanged **10** (22 mg; 36%). For spectroscopic data see **12** (Method C) below.

***N*-(*sec*-Butyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (12). Method C:** 2-Butanol (28 μL, 0.3 mmol, 1.5 equiv.) and **10** (61 mg, 0.2 mmol) were dissolved in toluene (2.5 mL) and stirred on an ice-bath in a septum-sealed flask. To this solution TMP (0.3 mL, 1.0 M in THF, 0.3 mmol, 1.5 equiv.) and ADDP (75 mg, 0.3 mmol, 1.5 equiv.) were added and stirring was continued for 20 h at room temperature. Then another portion of TMP and ADDP (0.2 mmol, 1.0 equiv. of each) were added and stirring was continued for 22 h. The mixture was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (2.5 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane and hexane/EtOAc (15:1 and 7:1) afforded **12** (51 mg; 71%) as a pale orange syrup. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.16 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 1.55 (m, 2 H, CH_2CH_3), 3.00 (m, 2 H, CH_2Ph), 3.39 (m, 2 H, NCH_2), 3.90 (sextet, *J* = 6.9 Hz, 1 H, NCH), 7.21−7.30 (m, 5 H, Ph), 7.57 (m, 1 H, Ns), 7.66 (m, 2 H, Ns), 8.05 (m, 1 H, Ns) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0, 19.0, 28.5, 38.4, 45.0, 56.1, 124.0, 126.7, 128.7 (2 C), 128.8 (2 C), 130.9, 131.5, 133.4, 134.0, 138.8, 148.0 ppm. HRMS: $[C_{18}H_{22}N_2O_4S + Na]^+$ calculated, 385.11925; found, 385.11921.

***N*-(1-Methylbutyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (13):** Prepared from **10** (61 mg, 0.2 mmol) as described for **12** (Method C) to give **13** (50 mg; 67%) as a pale yellow syrup. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.13 (d, *J* = 6.9 Hz, 3 H, $NCHCH_3$), 1.27−1.44 (4 H, $CH_2CH_2CH_3$), 2.88−3.06 (m, 2 H, CH_2Ph), 3.39 (m, 2 H, NCH_2), 3.99 (sextet, *J* = 6.9 Hz, 1 H, NCH), 7.21−7.31 (m, 5 H, Ph), 7.57 (m, 1 H, Ns), 7.66 (m, 2 H, Ns), 8.03 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.2, 19.6, 37.8, 38.5, 45.1, 54.3, 123.9, 126.6, 128.5, 128.6, 128.7, 128.8, 130.8, 131.4, 133.3, 133.9, 138.7, 148.1 ppm. HRMS: $[C_{19}H_{24}N_2O_4S + Na]^+$ calculated, 399.13490; found, 399.13495.

***N*-(1-Methylbut-2-enyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (14):** Prepared from **10** (61 mg, 0.2 mmol) as described for **12** (Method C) to give **14** (40 mg; 58%) as a colourless syrup. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.9 Hz, 3 H, $NCHCH_3$), 1.66 (dt, *J* = 1.5 Hz, 6.4 Hz, 3 H, $CH{=}CHCH_3$), 2.88−2.95 (m, 2 H, CH_2Ph), 3.38 (m, 2 H, NCH_2), 4.56 (m, 1 H, NCH), 5.44 (dq, *J* = 3 × 7.0 Hz and 15.5 Hz, 1 H, $CH{=}CHCH_3$), 5.58 (m, 1 H, $CH{=}CHCH_3$), 7.16−7.29 (m, 5 H, Ph), 7.60−7.69 (m, 3 H, Ns), 8.03 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.4, 38.1, 45.8, 54.9, 124.0, 126.5, 128.2, 128.6 (2 C), 128.7 (2 C), 130.4, 130.7, 131.5, 133.3, 134.1, 138.6, 148.0 ppm. HRMS: $[C_{19}H_{22}N_2O_4S + Na]^+$ calculated, 397.11925; found, 397.11919.

***N*-(1-Methylbut-3-enyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (15):** Prepared from **10** (61 mg, 0.2 mmol) as described for **12** (Method C) to give **15** (31 mg; 42%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.9 Hz, 3 H, $NCHCH_3$), 2.22 and 2.33 (ddd, *J* = 6.7 Hz, 6.9 Hz, 13.5 Hz, 2 H, $CH_2CH{=}CH_2$), 2.98 (m, 2 H, CH_2Ph), 3.43 (m, 2 H, NCH_2), 4.06 (m, 1 H, NCH), 4.99 (m, 2 H, $CH_2{=}CH$), 5.67 (m, 1 H, $CH{=}CH_2$), 7.21−7.31 (m, 5 H, Ph), 7.60 (m, 1 H, Ns), 7.66 (m, 2 H, Ns), 8.04 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 38.4, 40.2, 45.4, 54.3, 117.7, 124.0, 126.6, 128.6, 128.7, 128.8 (2 C), 130.9, 131.4, 133.4, 134.0, 134.3, 138.6 148.0 ppm. HRMS: $[C_{19}H_{22}N_2O_4S + Na]^+$ calculated, 397.11925; found, 397.11936.

2-Nitro-*N*-(2-phenylethyl)-*N*-(1-phenylpropyl)benzenesulfonamide (16): Prepared from **10** (61 mg, 0.2 mmol) as described for **12** (Method C) to give **16** (75 mg; 88%) as a reddish oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.81 (m, 1 H, CH_2CH_3), 2.22, 2.77 and 3.29 (m, 4 H, CH_2CH_3 and CH_2Ph), 3.29 and 3.48 (m, 2 H, NCH_2), 5.00 (m, 1 H, $NCHPh$), 6.99 (m, 2 H, Ph), 7.00−7.23 (m, 3 H, Ph), 7.33−7.38 (m, 5 H, Ph), 7.59−7.65 (m, 3 H, Ns), 7.89 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 24.6, 37.7, 46.7, 62.5, 124.0, 126.5 (2 C), 128.3 (2 C), 128.5 (2 C), 128.6 (2 C), 128.7 (2 C), 130.6, 131.5, 133.4, 134.5, 137.6, 138.6, 148.1 ppm. HRMS: $[C_{23}H_{24}N_2O_4S + Na]^+$ calculated, 447.13490; found, 447.13490.

***N*-Cyclopentyl-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (17):** Prepared from **10** (61 mg, 0.2 mmol) as described for **12** (Method C) to give **17** (46 mg; 61%) as a reddish oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42−1.86 (8 H, 4 × CH_2), 2.96 (m, 2 H, CH_2Ph), 3.39 (m, 2 H, NCH_2), 4.20 (m, 1 H, NCH), 7.19−7.33 (m, 5 H, Ph), 7.58 (m, 1 H, Ns), 7.66 (m, 2 H, Ns), 8.02 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2 (2 C), 29.6 (2 C), 38.3, 46.2, 59.5, 124.1, 126.7, 128.7 (2 C), 128.8 (2 C), 130.6, 131.5, 133.4, 134.0, 138.5, 148.0 ppm. HRMS: $[C_{19}H_{22}N_2O_4S + K]^+$ calculated, 413.09319; found, 413.09319.

***N*-[3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (18):** Prepared from **10** (61 mg, 0.2 mmol) as described for **12** (Method C) to give **18** (25 mg; 56%) and 1-*O*-(*tert*-butyl)diphenylsilyl-1,3-butanediol[51] as a 3:2 mixture, which was inseparable by VLC chromatography. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*Bu), 1.16 (d, *J* = 6.9 Hz, 3 H, $NCHCH_3$), 1.57 (m, 2 H, CH_2CH), 2.93 (m, 2 H, CH_2Ph), 3.34

(m, 2 H, NCH_2), 3.56 (m, 2 H, CH_2OSi), 4.16 (m, 1 H, NCH), 7.20−7.67 (m, 18 H, Ph and Ns), 7.99 (m, 1 H, Ns) ppm.

***N*-[4-Methyl-2-(1-methylethyl)cyclohexyl]-2-nitro-*N*-(2-phenylethyl)-benzenesulfonamide (19):** Synthetic procedure starting from **10** (61 mg, 0.2 mmol) and carried out similarly as described above for **12** (Method C) did not result in any isolable product.

***N*-(3-Hydroxybutyl)-2-nitro-*N*-(2-phenylethyl)benzenesulfonamide (20):** 1,3-Butanediol (18 μL, 0.2 mmol) and **10** (92 mg, 0.3 mmol, 1.5 equiv.) were dissolved in THF (1 mL) and stirred in a septum-sealed flask. TBP (80 μL, 0.32 mmol, 1.5 equiv.) and TMAD (51 mg, 0.3 mmol, 1.5 equiv.) were added successively and stirring was continued overnight. After 24 h the mixture was concentrated and the residue was taken up in CH_2Cl_2 (2 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane/EtOAc (5:1, 2:1 and 1:1) afforded **20** (48 mg; 63%) as a colourless syrup, together with a small amount of the di-substituted product **21** (5 mg; 4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.62 and 1.71 (m, 2 H, CH_2CH), (br. s, 1 H, OH), 2.86 (m, 2 H, CH_2Ph), 3.37−3.60 (br. m, 4 H, 2 × CH_2N), 3.88 (m, 1 H, CHOH), 7.15−7.25 (m, 5 H, Ph), 7.60−7.67 (m, 3 H, Ns), 7.92 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 35.2, 37.4, 45.2, 49.4, 64.8, 124.3, 126.8, 128.7 (2 C), 128.9 (2 C), 130.6, 131.8, 133.5, 133.6, 138.6, 148.0 ppm. HRMS: $[C_{18}H_{22}N_2O_5S + Na]^+$ calculated, 401.11416; found, 401.11417.

2-Nitro-*N*-[3-(2-nitrophenyl)sulfonyl-(2-phenylethylamino)butyl]-*N*-(2-phenylethyl)benzenesulfonamide (21): 10 (57 mg, 0.19 mmol, 1.5 equiv.) and **20 (**47 mg, 0.12 mmol) were dissolved in THF (1.5 mL). TMP (0.2 mL, 1.0 M in THF, 0.2 mmol, 1.5 equiv.) and ADDP (47 mg, 0.19 mmol, 1.5 equiv.) in THF (0.3 mL) were added successively, and the mixture was stirred in a septum-sealed flask at room temperature overnight. After 24 h additional portions of TMP (0.2 mL, 1.0 M in THF, 1.5 equiv.) and ADDP (47 mg, 0.19 mmol, 1.5 equiv.) in THF (0.3 mL) were added and stirring was continued for an additional 18 h. The mixture was then concentrated and the residue was taken up in CH_2Cl_2 (3 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane/EtOAc (4:1, 2:1 and 1:1) afforded **21** (55 mg; 66%) as a colourless syrup, together with unchanged **10** (7 mg; 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.68 and 1.86 (m, 2 H, CH_2CH), 2.78 and 2.94 (m, 2 H, CH_2Ph), 3.16−3.47 (br. m, 6 H, 3 × NCH_2), 3.95 (m, 1 H, NCH), 7.10−7.31 (br. m, 10 H, 2 × Ph), 7.55−7.66 (m, 6 H, Ns), 7.89 (m, 1 H, Ns), 8.03 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 34.5, 34.9, 38.2, 45.3, 45.4, 49.2, 52.2, 124.1, 124.2, 126.7 (2 C), 128.6 (2 C), 128.7 (4 C), 128.8 (2 C), 130.7, 131.1, 131.8 (2 C), 132.9, 133.0, 133.6, 133.7, 137.8, 138.3, 148.0 (2 C) ppm. HRMS: $[C_{32}H_{34}N_4O_8S_2 + Na]^+$ calculated, 689.17103; found, 689.17218.

***N*-[(2-Nitrophenyl)sulfonyl]-*N*′-[2-(trimethylsilyl)ethoxycarbonyl]-1,4-butanediamine (22):** 1,4-Butanediamine (16.73 g, 190 mmol, 3 equiv.) and Et_3N (26 mL, 188 mmol, 3 equiv.) were dissolved in dry CH_2Cl_2 (30 mL) and the mixture was stirred under N_2 on an ice-bath. NsCl (14.02 g, 63 mmol) dissolved in dry CH_2Cl_2 (70 mL) was added in 5 portions and stirring was continued at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (200 mL) and water (150 mL) was added. A turbid organic layer was separated and an emulsion was taken aside, dried (Na_2SO_4), filtered and pooled with the organic layer. Finally, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and all the organic extracts were pooled, dried (Na_2SO_4), filtered, concentrated and dried in vacuo. This afforded 10.40 g (60%) of crude *N*-(Ns)-1,4-butanediamine as a yellow syrup, which was used directly in the next step. The syrup was dissolved in THF (100 mL), DIPEA (26.7 mL, 153.3 mmol, 4 equiv.) was added followed by 2-trimethylsilylethyl *p*-nitrophenylcarbonate (11.86 g, 34.9 mmol, 0.9 equiv.), and the mixture was stirred at 50 °C for 2 h, and then at room temperature overnight. After 14 h the solvent was evaporated in vacuo, the residue was diluted with CH_2Cl_2 (250 mL) and washed with 0.1 M HCl (2 × 100 mL), water (2 × 100 mL) and brine (100 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL) and the organic phases were pooled, dried (Na_2SO_4), filtered and concentrated. The residue was taken up in CH_2Cl_2 (25 mL) and loaded onto a VLC column (7 × 9.5 cm). Elution with hexane/EtOAc (10:1 and 2:1) afforded **22 (**14.22 g; 89%) as a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 9 H, $(CH_3)_3$Si], 0.96 (t, *J* = 7.2 Hz, 2 H, CH_2Si), 1.55 (m, 4 H, 2 × CH_2), 3.12 (m, 4 H, 2 × CH_2N), 4.13 (m, 2 H, CH_2O), 4.57 (br. t, 1 H, NHCO), 5.38 (br. t, 1 H, $NHSO_2$), 7.74 (m, 2 H, Ns), 7.86 (m, 1 H, Ns), 8.13 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.5 (3 C), 17.8, 26.8, 27.1, 40.2, 43.4, 63.0, 125.4, 131.1, 132.8, 133.6, 133.7, 148.0, 156.9 ppm. HRMS: $[C_{16}H_{27}N_3O_6Ssi + Na]^+$ calculated, 440.12820; found, 440.12830.

***N*-(*tert*-Butoxycarbonyl)-*N*′-(2-nitrobenzenesulfonyl)-1,3-propanediamine (23):** *N*-(Ns)-1,3-propanediamine (1.04 g, 4.0 mmol), prepared as described above for *N*-(Ns)-1,4-butanediamine, was dissolved in dry MeOH (15 mL) and the solution was stirred under N_2 on an ice-bath. Di-*tert*-butyl dicarbonate (1.33 g, 6.1 mmol, 1.5 equiv.) dissolved in dry MeOH (3 mL) was added over 10 min and the mixture was allowed to reach room temperature, after which it was stirred overnight. After 22 h the solvent was evaporated in vacuo, the residue was taken up in CH_2Cl_2 (5 mL) and loaded onto a VLC column (5 × 5 cm). Elution with hexane/EtOAc (10:1 and 2:1) afforded **23** (1.35 g; 94%) as a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (br. s, 9 H, 3 × CH_3), 1.69 (p, *J* = 6.4 Hz, 2 H, CH_2), 3.15 (dt, *J* = 3.15 Hz and 2 × 6.4 Hz, 2 H, CH_2N), 3.20 (br. dt, *J* = 3.20 Hz, 2 × 6.4 Hz, 2 H, CH_2N), 4.72 (br. s, 1 H, $NHSO_2$), 5.91 (br. s, 1 H, NHCOO), 7.73 (m, 2 H, Ns), 7.84 (m, 1 H, Ns), 8.13 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 28.4, 28.6, 30.6, 37.2, 40.9, 79.6, 125.3, 130.9, 132.8, 133.5, 134.0, 148.1, 156.5 ppm.

***N*-(1-Oxobutyl)-*O*-(*tert*-butyl)tyrosine Pentafluorophenyl Ester (24):** *O*-(*tert*-Butyl)tyrosine (502 mg, 2.12 mmol) was dissolved in 2 M NaOH (2.15 mL, 4.3 mmol, 2 equiv.) and THF (4.3 mL). To this solution butyryl chloride (0.89 mL, 8.5 mmol, 4 equiv.) was added over 30 min and the mixture was stirred at room temperature for 2.5 h. Then EtOAc (100 mL) was added and the organic phase was washed with water (4 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was dried overnight in vacuo (oil-pump) and then taken up in CH_2Cl_2 (4 mL) and loaded onto a VLC column (4 × 4 cm). Elution with hexane/EtOAc (10:1) and EtOAc afforded the crude product (603 mg; 92%), which was dissolved in dry DMF (5 mL) and treated with dry pyridine (0.24 mL) and pentafluorophenyl trifluoroacetate (0.47 mL, 2.74 mmol, 1.3 equiv.) for 5 h. After dilution with EtOAc (50 mL) the organic phase was washed with 0.1 M HCl (2 × 50 mL), saturated aq. $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated and dried in vacuo to give **24** (672 mg; 57%) as a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.34 (br. s, 9 H, 3 × CH_3), 1.62 (sextet, *J* = 7.4 Hz, 2 H, CH_2), 2.19 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.21 (dd, *J* = 6.5 Hz and 14.3 Hz, 2 H, β-CH_2), 3.29 (dd, *J* = 6.1 Hz and 14.3 Hz, 1 H, β-CH_2), 5.21 (ddd, *J* = 6.1 Hz, 6.6 Hz, 7.7 Hz, 1 H, α-CH), 5.90 (br. d, *J* = 7.7 Hz, 1 H, NHCO), 6.96 (m, 2 H, Ph), 7.11 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 17.6, 19.0, 28.3 (3 C), 37.7, 40.0, 53.0, 79.0, 124.0 (2 C), 124.5, 130.9 (3 C), 137.4 (br. d, *J* = 240 Hz, 2 C), 139.3 (br. d, *J* = 252 Hz, 1 C), 140.7 (br. d, *J* = 243 Hz, 2 C), 147.7, 156.8, 173.8 ppm. HRMS: $[C_{23}H_{24}F_5NO_4 + Na]^+$ calculated, 496.15177; found, 496.15176.

Fully Protected Tetraamine 26: Compound **22** (871 mg, 2.09 mmol) was dissolved in freshly distilled THF (20 mL). To this solution 1,3-butanediol (187 μL, 2.09 mmol) and TBP (825 μL, 3.34 mmol, 1.6 equiv.) were added followed by ADDP (790 mg, 3.13 mmol, 1.5 equiv.). The mixture was stirred under N_2 at room temperature overnight. After 18 h the solvent was evaporated in vacuo. VLC [toluene/acetone (20:1, 15:1, 12:1 and 11:1)] afforded compound **25** (543 mg; 53%) as a yellowish syrup. The total yield of **25**, including impure VLC fractions, was 711 mg (70%). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −1.5 (3 C), 17.7, 23.5, 25.3, 27.0, 37.4, 40.0, 44.7, 47.4, 62.9, 64.7, 124.0, 130.3, 131.5, 132.9, 133.3, 147.8, 156.7. Compound **25** (491 mg, 1.0 mmol) was then dissolved in freshly distilled THF (11 mL). To this solution **23** (539 mg, 1.5 mmol) in 7 mL THF and TMP (1.60 mL, 1.0 M in THF, 1.60 mmol, 1.6 equiv.) was added followed by ADDP (378 mg, 1.50 mmol, 1.5 equiv.), and the mixture was stirred under N_2 at room temperature for 6 h. Then additional amounts of TMP (1.60 mL, 1.0 M in THF, 1.60 mmol, 1.6 equiv.) and ADDP (378 mg, 1.50 mmol, 1.5 equiv.) were added and stirring was continued overnight. The solvent was evaporated and the residue was taken up in CH_2Cl_2 (5 mL) and loaded onto a VLC column (5 × 5 cm). Elution with toluene/acetone 20:1, 18:1 and 16:1 afforded **26** (567 mg; 68%) as a yellow foam. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 9 H, $(CH_3)_3Si$], 0.96 (t, *J* = 8.3 Hz, 2 H, CH_2Si), 1.14 (d, *J* = 6.7 Hz, 3 H, NCH*CH*$_3$), 1.45 (br. s, 9 H, 3 × CH_3), 1.46−1.91 (br. m, 8 H, 4 × CH_2), 3.14 (m, 5 H, CH_2N), 3.27 (m, 5 H, CH_2N), 3.92 (m, 1 H, NCH), 4.12 (m, 2 H, CH_2O), 5.01 (m, 2 H, 2 × NHCO), 7.60 (m, 2 H, Ns), 7.70 (m, 4 H, Ns), 7.93 (m, 1 H, Ns), 8.02 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.6 (3 C), 17.6, 19.0, 25.3, 26.9, 28.2, 28.3, (2 C), 31.8, 34.6, 37.7, 40.0, 41.0, 45.1, 47.6, 52.0, 62.7, 79.0, 124.0 (2 C), 130.3, 130.9, 131.7 (2 C), 132.7, 133.0, 133.5, 133.6, 147.7, 147.9, 156.0, 156.8 ppm. HRMS: $[C_{34}H_{55}N_6O_{12}S_2Si]^+$ calculated, 831.30832; found, 831.30900.

Fully Protected Tetraamine 31: Compound **23** (517 mg, 1.44 mmol) was dissolved in freshly distilled THF (15 mL). To this solution 1,3-butanediol (150 μL, 1.67 mmol, 1.16 equiv.) and TBP (570 μL, 2.3 mmol, 1.6 equiv.) were added followed by ADDP (547 mg, 2.16 mmol, 1.5 equiv.). The mixture was stirred under N_2 at room temperature overnight. After 20 h the solvent was evaporated in vacuo. VLC [toluene/acetone (20:1, 15:1, 13:1, 12:1 and 11:1)] afforded compound **30** (347 mg; 56%). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 28.5 (3 C), 28.7, 37.6, 45.2, 45.8, 47.3, 79.3, 124.3, 130.3, 131.9, 133.0, 133.7, 148.1, 156.2 ppm. Compound **30** (193 mg, 0.45 mmol) was then dissolved in freshly distilled THF (10 mL). To this solution **22** (281 mg, 0.67 mmol, 1.5 equiv.) and TMP (0.72 mL, 1.0 M in THF, 0.72 mmol, 1.6 equiv.) were added followed by ADDP (170 mg, 0.68 mmol, 1.5 equiv.), and the mixture was stirred under N_2 at room temperature for 8 h. Then additional amounts of TMP (0.72 mL, 1.0 M in THF, 0.72 mmool, 1.6 equiv.) and ADDP (170 mg, 0.68 mmol, 1.5 equiv.) were added and stirring was continued overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (5 mL) and loaded onto a VLC column (4 × 5 cm). Elution with hexane/EtOAc (3:1, 5:2, 2:1 and 1:1) afforded **31** (256 mg; 69%) as a yellow foam. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 [s, 9 H, $(CH_3)_3Si$], 0.97 (t, *J* = 8.3 Hz, 2 H, CH_2Si), 1.12 (d, *J* = 6.7 Hz, 3 H, CH*CH*$_3$), 1.43 (br. s, 9 H, 3 × CH_3), 1.45−1.95 (br. m, 8 H, 4 × CH_2), 3.10−3.33 (br. m, 10 H, 5 × CH_2N), 3.92 (m, 1 H, NCH), 4.13 (m, 2 H, CH_2O), 5.01 (m, 2 H, 2 × NHCO), 7.62 (m, 2 H, Ns), 7.71 (m, 4 H, Ns), 7.93 (m, 1 H, Ns), 8.02 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.6 (3 C), 17.6, 19.0, 27.3, 28.2 (2 C), 28.3 (2 C), 28.5, 34.6, 37.3, 40.0, 43.1, 45.5, 45.7, 51.9, 62.6, 79.0, 123.9, 124.0, 130.3, 130.8, 131.7, 131.8, 132.6, 133.1, 133.5, 133.6, 147.7, 147.9, 156.0, 156.8 ppm. HRMS: $[C_{34}H_{55}N_6O_{12}S_2Si]^+$ calculated, 831.30832; found, 831.30931.

Fully Protected 8-Methyl-PhTX-433 (28): $Bu_4NF{\cdot}3H_2O$ (95 mg, 0.30 mmol, 2.5 equiv.) and **26** (100 mg, 0.12 mmol) were dissolved in THF (5 mL) and stirred at 50 °C for 4 h. The mixture was then diluted with EtOAc (50 mL) and the organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, concentrated and dried in vacuo. The resulting syrup was taken up in CH_2Cl_2 (2 mL) and loaded onto a VLC column (3 × 3 cm). Elution with CH_2Cl_2/MeOH (200:5) and CH_2Cl_2/MeOH/concd. ammonia (150:10:1) afforded **27** (51 mg; 62%) as a light yellow syrup, along with unchanged **26** (28 mg; 28%). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 25.6, 28.4 (2 C), 28.5, 30.2, 32.0, 34.6, 37.9, 41.2, 41.4, 45.2, 47.9, 52.2, 79.2, 124.1, 124.2, 130.6, 131.1, 131.8, 131.9, 133.1, 133.2, 133.6, 133.7, 147.9, 148.1, 156.2 ppm. Compound **27** (51 mg, 0.07 mmol) and DIPEA (20 μL, 0.11 mmol, 1.6 equiv.) were dissolved in dry DMF (2 mL), and **24** (42 mg, 0.09 mmol, 1.3 equiv.) dissolved in dry DMF (1 mL) was added. The mixture was stirred under N_2 for 2 h and then diluted with EtOAc (50 mL). The organic solution was washed with water (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL) and loaded onto a VLC column (3 × 3 cm). Elution with toluene and toluene/acetone (4:1) afforded **28** (63 mg; 88%) as a light yellow syrup. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.3 Hz, 3 H, *CH*$_3$CH$_2$), 1.14 (d, *J* = 6.5 Hz, 3 H, *CH*$_3$CH), 1.30 (br. s, 9 H, 3 × CH_3, Tyr-*t*Bu), 1.45 (br. s, 9 H, 3 × CH_3, *N*Boc), 1.36−1.56 (br. m, 6 H, 3 × CH_2), 1.66−1.93 (br. m, 4 H, 2 × CH_2), 2.12 (m, 2 H, CH_2CO), 2.96 (m, 2 H, β-CH_2), 2.99−3.29 (br. m, 10 H, 5 × CH_2N), 3.94 (m, 1 H, NCH), 4.58 (dd, *J* = 7.3 Hz and 7.7 Hz, 1 H, α-CH), 6.88 (d, *J* = 8.4 Hz, 2 H, Ph), 7.00 (d, *J* = 8.4 Hz, 2 H, Ph), 7.61 (m, 2 H, Ns), 7.69 (m, 4 H, Ns), 7.93 (m, 1 H, Ns), 8.02 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.0, 25.5, 26.4, 28.3, 28.4, 28.5, 28.6, 28.7, 28.8, 28.9, 32.1, 35.0, 37.5, 38.3, 38.5, 41.2, 45.4, 47.7, 52.3, 54.5, 54.7, 78.4, 79.1, 124.2, 124.3, 129.0, 129.6 (2 C), 129.7, 129.8, 130.5, 130.6, 131.7, 131.9, 133.0, 133.2, 133.6, 133.7, 148.0, 148.1, 154.2, 156.3, 171.3, 173.2 ppm. HRMS: $[C_{45}H_{65}N_7O_{13}S_2 + Na]^+$ calculated, 998.39740; found, 998.39820.

Fully Protected 6-Methyl-PhTX-433 (33): Deprotection of **31** (100 mg), carried out as described above for **26**, afforded **32** (35 mg; 42%) as a light yellow syrup, together with unchanged **31** (49 mg; 49%). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 28.3, 28.4, 28.5, 28.8, 29.0, 30.9, 35.0, 37.4, 41.5, 43.6, 45.7, 45.9, 52.1, 79.2, 124.1, 124.2, 130.6, 131.1, 131.8, 131.9, 132.9, 133.5, 133.6, 133.7, 147.9, 148.1, 156.0 ppm. Compound **32** (35 mg; 0.04 mmol) and DIPEA (13 μL, 0.07 mmol, 1.75 equiv.) were dissolved in dry DMF (2 mL), and **24** (29 mg, 0.06 mmol, 1.5 equiv.) dissolved in dry DMF (1 mL) was added. The mixture was stirred under N_2 for 2 h and then diluted with EtOAc (50 mL). After workup and purification as described above for **28**, **33** (46 mg; 92%) was obtained as a light yellow syrup. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 3 H, *CH*$_3$CH$_2$), 1.12 (d, *J* = 6.5 Hz, 3 H, *CH*$_3$CH), 1.31 (br. s, 9 H, 3 × CH_3, Tyr-*t*Bu), 1.44 (br. s, 9 H, 3 × CH_3, *N*Boc), 1.45−1.75 (br. m, 8 H, 4 × CH_2), 1.86 (m, 2 H, CH_2), 2.12 (m, 2 H, CH_2CO), 3.00 (m, 2 H, β-CH_2), 3.01−3.35 (br. m, 10 H, 5 × CH_2N), 3.92

(m, 1 H, NCH), 4.59 (dd, J = 7.3 Hz and 7.8 Hz, 1 H, α-CH), 6.89 (d, J = 8.4 Hz, 2 H, Ph), 7.09 (m, J = 8.4 Hz, 2 H, Ph), 7.61 (m, 2 H, Ns), 7.69 (m, 4 H, Ns), 7.93 (m, 1 H, Ns), 8.02 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.0, 26.9, 28.4 (2 C), 28.5, 28.6 (2 C), 28.7, 28.8 (2 C), 28.9, 35.1, 37.5, 38.3, 38.5, 43.3, 45.9, 46.1, 52.2, 54.5, 54.6, 78.4, 79.1, 124.1, 124.2, 124.3, 128.3, 129.6, 129.7, 129.8, 130.5, 131.0, 131.8, 131.9, 132.8, 133.3, 133.7 (2 C), 148.0, 148.1, 154.2, 156.1, 171.3, 173.2 ppm. HRMS: $[C_{45}H_{65}N_7O_{13}S_2 + Na]^+$ calculated, 998.39740; found, 998.39795.

Fully Protected 5-Methyl-PhTX-334 (36): *p*-Toluenesulfonic acid (TsOH) (46 mg, 0.24 mmol) and **26** (200 mg, 0.24 mmol) were suspended in diethyl ether (5 mL) and placed on a rotary evaporator at 50 °C for 1 h. The residue was then dissolved in EtOAc (50 mL) and the organic layer was washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated and dried in vacuo. The resulting syrup was taken up in CH_2Cl_2 (2 mL) and loaded onto a VLC column (3 × 3 cm). Elution with CH_2Cl_2/MeOH (200:5 and CH_2Cl_2/MeOH/concd. ammonia (200:10:1) afforded **35** (122 mg; 70%) as a white foam, along with unchanged **26** (21 mg; 11%). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.5 (3 C), 17.8, 19.1, 25.5, 27.0, 28.4, 35.0, 39.6, 40.2, 41.5, 45.4, 47.8, 52.2, 62.9, 124.2 (2 C), 130.7, 131.1, 131.8 (2 C), 133.0, 133.5, 133.6, 133.7, 148.0, 148.1, 156.9 ppm. Compound **35** (67 mg, 0.09 mmol) and DIPEA (24 μL, 0.14 mmol, 1.55 equiv.) were dissolved in dry DMF (2 mL), and **24** (52 mg, 0.11 mmol, 1.25 equiv.) dissolved in dry DMF (1 mL) was added. The mixture was stirred under N_2 for 2 h and was diluted with EtOAc (50 mL). The organic solution was washed with water (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL) and loaded onto a VLC column (3 × 3 cm). Elution with toluene and toluene/acetone (4:1) afforded **36** (71 mg; 76%) as a light yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 [br. s, 9 H, $(CH_3)_3Si$], 0.80 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 0.96 (t, J = 8.1 Hz, 2 H, CH_2Si), 1.13 (d, J = 6.7 Hz, 3 H, CH_3CH), 1.30 (br. s, 9 H, 3 × CH_3, Tyr-*t*Bu), 1.45−1.53 (br. m, 6 H, 3 × CH_2), 1.67−1.94 (br. m, 4 H, 2 × CH_2), 2.12 (m, 2 H, CH_2CO), 2.94 (m, 2 H, β-CH_2), 3.01−3.35 (br. m, 10 H, 5 × CH_2N), 3.94 (m, 1 H, NCH), 4.13 (t, J = 8.1 Hz, 2 H, CH_2O), 4.59 (dd, J = 6.9 Hz and 7.8 Hz, 1 H, α-CH), 6.89 (d, J = 8.3 Hz, 2 H, Ph), 7.10 (d, J = 8.3 Hz, 2 H, Ph), 7.60 (m, 2 H, Ns), 7.70 (m, 4 H, Ns), 7.92 (m, 1 H, Ns), 8.01 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.5 (3 C), 13.6, 17.8, 18.8, 19.1, 25.5, 27.1, 28.7, 28.8, 28.9, 31.1, 35.0, 36.6, 37.2, 38.3, 40.3, 40.9, 45.5, 47.9, 52.2, 54.5, 63.0, 78.4, 124.0, 124.2, 124.3, 129.5, 129.6 (2 C), 129.7, 130.5, 131.8, 131.9, 132.0, 133.0, 133.1, 133.7, 133.7, 147.9, 148.1, 154.2, 157.0, 171.5, 173.4 ppm. HRMS: $[C_{46}H_{70}N_7O_{13}S_2Si]^+$ calculated, 1020.42368; found, 1020.42451.

Fully Protected 7-Methyl-PhTX-334 (39): Deprotection of **31** (100 mg) with TsOH, performed as described above for **26**, afforded **38** (55 mg; 63%) as a yellow syrup, along with unchanged **31** (11 mg; 11%). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.6 (3 C), 17.6, 19.0, 27.4, 28.7, 31.6, 34.8, 38.8, 40.0, 43.2, 45.4, 45.7, 52.0, 62.7, 123.9, 124.0, 124.1 (2 C), 130.5, 130.9, 131.7, 131.8, 133.2, 133.6, 147.8, 148.0, 156.9 ppm. Compound **38** (55 mg, 0.08 mmol) and DIPEA (20 μL, 0.11 mmol, 1.4 equiv.) were dissolved in dry DMF (2 mL), and **24** (43 mg, 0.09 mmol, 1.15 equiv.) in dry DMF (1 mL) was added. The mixture was stirred under N_2 for 2 h and then diluted with EtOAc (50 mL). After workup and purification as described above for **36**, **39** (64 mg; 83%) was obtained as a light yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 [br. s, 9 H, $(CH_3)_3Si$], 0.82 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 0.96 (t, J = 8.1 Hz, 2 H, CH_2Si), 1.12 (d, J = 6.9 Hz, 3 H, CH_3CH), 1.29 (br. s, 9 H, 3 × CH_3, Tyr-*t*Bu), 1.48−1.70 (br. m, 8 H, 4 × CH_2), 1.93 (m, 2 H, CH_2), 2.12 (m, 2 H, CH_2CO), 2.94 (m, 2 H, β-CH_2), 3.05−3.30 (br. m, 10 H, 5 × CH_2N), 3.92 (m, 1 H, NCH), 4.13 (t, J = 8.1 Hz, 2 H, CH_2O), 4.61 (dd, J = 6.9 Hz and 7.6 Hz, 1 H, α-CH), 6.89 (d, J = 8.4 Hz, 2 H, Ph), 7.09 (d, J = 8.4 Hz, 2 H, Ph), 7.60 (m, 2 H, Ns), 7.70 (m, 4 H, Ns), 7.92 (m, 1 H, Ns), 8.02 (m, 1 H, Ns) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.5 (3 C), 13.6, 17.8, 19.0, 27.5, 28.0, 28.6, 28.7, 28.8, 28.9, 29.0, 35.3, 36.1, 37.3, 38.3, 40.2, 43.4, 46.1, 46.2, 52.2, 54.5, 62.9, 78.4, 124.0, 124.1, 124.3, 124.4, 129.6, 129.7, 130.4, 130.9, 131.8 (2 C), 132.0, 132.5, 133.4, 133.7 (2 C), 147.9, 148.1, 154.2, 157.0, 171.4, 173.4 ppm. HRMS: $[C_{46}H_{70}N_7O_{13}S_2Si]^+$ calculated, 1020.42368; found, 1020.42468.

8-Methyl-PhTX-433 (6): Compound **28** (53 mg, 0.05 mmol) was dissolved in dry DMF (3 mL) and treated with 2-mercaptoethanol (40 μL, 0.57 mmol, 11 equiv.) and DBU (40 μL, 0.27 mmol, 5 equiv.). After stirring for 2 h under N_2 the mixture was diluted with EtOAc (50 mL), the organic solution was washed with water (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (2 mL) and loaded onto a VLC column (2 × 2 cm). Elution with CH_2Cl_2/MeOH/concd. ammonia (180:10:1, 150:10:1 and 70:10:1) afforded **29** (22 mg; 67%) as a colourless syrup. Compound **29** (20 mg, 0.03 mmol) was then dissolved in TFA/CH_2Cl_2 (1:9) (2.5 mL) and stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and **6** was isolated as the tris(TFA) salt by reversed-phase HPLC. Yield: 24 mg (92%). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.85 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 1.38 (d, J = 6.2 Hz, 3 H, CH_3CH), 1.49−1.59 (br. m, 6 H, 3 × CH_2), 1.91−2.36 (br. m, 4 H, 2 × CH_2), 2.16 (t, J = 7.6 Hz, 2 H, CH_2CO), 2.94−3.17 (br. m, 12 H, 5 × CH_2N and β-CH_2), 3.31 (br. s, 1 H, NCH), 4.42 (dd, J = 7.0 Hz and 7.6 Hz, 1 H, α-CH), 6.70 (d, J = 8.6 Hz, 2 H, Ph), 7.05 (d, J = 8.6 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 16.1, 20.3, 24.3, 25.5, 27.2, 30.6, 37.8, 38.2, 38.7, 39.3, 43.2, 45.0, 48.6, 53.5, 56.9, 116.2, 116.3, 129.1, 131.3, 131.4, 157.3, 174.1, 176.1 ppm. HRMS: $[C_{24}H_{44}N_5O_3]^+$ calculated, 450.34387; found, 450.34376.

6-Methyl-PhTX-433 (7): Deprotection of **33** (42 mg, 0.04 mmol) was performed as described above for **28**, to give **34** (16 mg; 62%) as a colourless syrup. Compound **34** (16 mg, 0.03 mmol) was then dissolved in TFA/CH_2Cl_2 (1:9) (2 mL) and stirred at room temperature for 3 h, the mixture was concentrated in vacuo, and **7** was isolated as the tris(TFA) salt by reversed-phase HPLC. Yield: 20 mg (96%). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.85 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.36 (d, J = 6.2 Hz, 3 H, CH_3CH), 1.50−1.59 (br. m, 6 H, 3 × CH_2), 1.87−2.36 (br. m, 4 H, 2 × CH_2), 2.16 (t, J = 7.5 Hz, 2 H, CH_2CO), 2.76−3.06 (br. m, 6 H, 2 × CH_2N and β-CH_2), 3.25 (m, 6 H, 3 × CH_2), 3.45 (br. s, 1 H, NCH), 4.41 (dd, J = 7.0 Hz and 8.1 Hz, 1 H, α-CH), 6.70 (d, J = 8.6 Hz, 2 H, Ph), 7.02 (d, J = 8.6 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 16.3, 20.3, 24.4, 25.4, 27.3, 30.5, 37.8, 38.2, 38.7, 39.2, 45.3, 45.8, 46.0, 53.1, 56.9, 116.2 (2 C), 129.1, 131.3 (2 C), 157.3, 174.2, 176.1 ppm. HRMS: $[C_{24}H_{44}N_5O_3]^+$ calculated, 450.34387; found, 450.34388.

5-Methyl-PhTX-334 (8): Deprotection of **36** (69 mg, 0.07 mmol) was performed as described above for **28**, to give **37** (34 mg, 77%) as a colourless syrup. Compound **37** (34 mg, 0.05 mmol) was dissolved in TFA/CH_2Cl_2 (1:9) (4 mL) and stirred at room temperature for 3 h, the mixture was concentrated in vacuo, and **8** was isolated as the tris(TFA) salt by reversed-phase HPLC. Yield: 40 mg (97%). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.86 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 1.34 (d, J = 6.4 Hz, 3 H, CH_3CH), 1.54 (m, 2 H, CH_2CH_3), 1.77−2.20 (br. m, 8 H, 4 × CH_2), 2.18 (t, J =

7.5 Hz, 2 H, CH_2CO), 2.86 (m, 2 H, β-CH_2), 2.95−3.31 (br. m, 11 H, 5 × CH_2N and CHN), 4.39 (dd, J = 7.0 Hz and 7.4 Hz, 1 H, α-CH), 6.72 (d, J = 8.4 Hz, 2 H, Ph), 7.05 (d, J = 8.4 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 16.3, 20.3, 24.4, 25.4, 27.3, 30.5, 37.8, 38.2, 38.7, 39.2, 45.3, 45.8, 46.0, 53.1, 56.9, 116.2 (2 C), 129.1, 131.3 (2 C), 157.3, 174.2, 176.1 ppm. HRMS: $[C_{24}H_{44}N_5O_3]^+$ calculated, 450.34387; found, 450.34385.

7-Methyl-PhTX-334 (9): Deprotection of **39** (62 mg, 0.06 mmol) was performed as described above for **28**, to give **40** (21 mg; 54%) as a colourless syrup. Compound **40** (18 mg, 0.03 mmol) was dissolved in TFA/CH_2Cl_2 (1:9) (2 mL) and stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and **9** was isolated as the tris(TFA) salt by reversed-phase HPLC. Yield: 22 mg (> 99%). ^1H NMR (400 MHz, CD_3OD): δ = 0.86 (t, J = 7.5 Hz, 3 H, CH_3CH_2), 1.38 (d, J = 6.4 Hz, 3 H, CH_3CH), 1.55 (m, 2 H, CH_2CH_3), 1.77−2.20 (br. m, 8 H, 4 × CH_2), 2.18 (t, J = 7.5 Hz, 2 H, CH_2CO), 2.87 (m, 2 H, β-CH_2), 2.94−3.30 (m, 10 H, 5 × CH_2N, 3.42 (br. s, 1 H, CHN), 4.38 (dd, J = 7.0 Hz and 7.4 Hz, 1 H, α-CH), 6.71 (d, J = 8.4 Hz, 2 H, Ph), 7.05 (d, J = 8.4 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 16.2, 20.2, 24.4, 25.6, 27.3, 30.7, 36.8, 37.9, 38.6, 40.0, 45.2, 45.4, 46.4, 53.2, 57.1, 116.3 (2 C), 128.9, 131.3 (2 C), 157.4, 175.1, 176.3 ppm. HRMS: $[C_{24}H_{44}N_5O_3]^+$ calculated, 450.34387; found, 450.34386.

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