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Fukuyama–Mitsunobu alkylation in amine synthesis on solid phase revisited: N-alkylation with secondary alcohols and synthesis of curtatoxins

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Abstract—The Fukuyama–Mitsunobu amination strategy has emerged as an efficient means of N-alkylation of peptides and sulfonamides, as well as a method for synthesis of polyamines on solid phase. Here, an array of reagent combinations for solid-phase alkylation with secondary alcohols was examined in various solvents. The classical reagents DEAD–PPh_3 as well as DEAD–PEt_3 proved applicable for a single alkylation step. Sharply dropping yields in successive alkylation steps were identified as the most serious limitation of the use of Fukuyama–Mitsunobu reaction in SPS of polyamines using primary and in particular secondary alcohols.

1. Introduction

Polyamines and their derivatives play important roles in biochemistry and their pharmacological significance continues to increase. Simple polyamines such as spermidine (**1**) and spermine (**2**) are ubiquitous in eukaryotic cells, where they conduct important roles in cellular physiology, for example, in cell proliferation and DNA synthesis.[1] Relatively simple *n*-alkylated analogs of **2** have been shown to possess anticancer activity in various cell lines.[2] Polyamine-based cationic lipids have proved to be efficient gene-delivery agents.[3] Moreover, certain polyamine derivatives have been shown to interact with ion channels in the central nervous system (CNS).[4] Thus, polyamine neurotoxins isolated from venoms of spiders and wasps antagonize various classes of ionotropic receptors such as nicotinic acetylcholine receptors (nAChRs) and ionotropic glutamate receptors (iGluRs).[5] A variety of polyamine neurotoxins with closely related structures have been isolated from venoms of the funnel web spiders *Hololena curta*[6] and *Agelenopsis aperta*.[7] Some of these indole-containing toxins, known as curtatoxins, are shown in Figure 1. Compounds **4** and **6**, for instance, were isolated from both venom mixtures (which explains the two different names assigned to each of these compounds). Only the *H. curta* venom contains long-chain non-hydroxylated toxins such as compound **5**. The structurally similar wasp toxin component, philanthotoxin-433 (**7**),[8] has been the subject of extensive structure–activity relationship (SAR) studies on various receptor types.[9]

In order to obtain pure natural toxins in useful quantities as well as unnatural analogs for biological studies, efficient synthetic strategies are necessary. Since solution-phase methods for polyamine synthesis[10] often require extensive use of protecting groups as well as tedious purification steps, the development of solid-phase synthesis (SPS) methodologies has received considerable attention in recent years. The subsequent attachment of the amino acid and/or acyl residues to the polyamines may be achieved by well-established solid-phase peptide synthesis (SPPS) protocols. The synthetic strategies for construction of polyamines on solid phase may be classified into three major groups: (1) simple S_N2 alkylation reactions;[11] (2) methods based on reduction of intermediary imines[12] or amides;[13] and (3) Fukuyama amination reactions.[14] In the latter approach,

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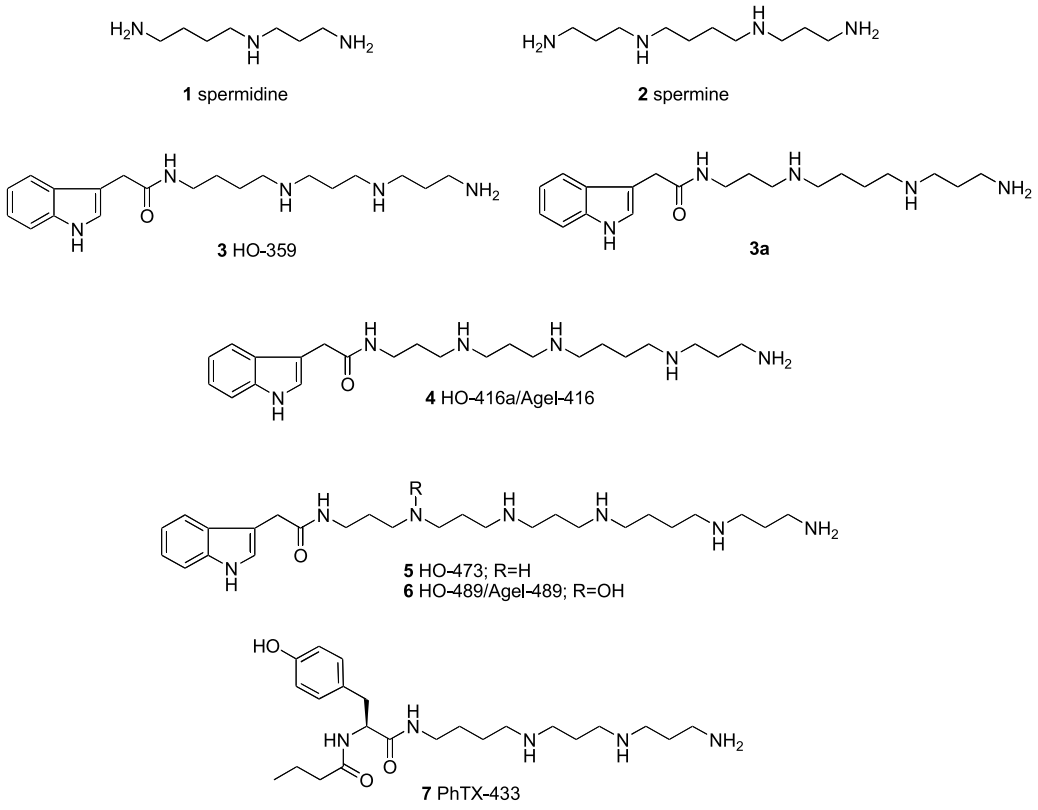


Figure 1. Structures of polyamines and acylpolyamine neurotoxins isolated from venom mixtures of spiders and wasps. The numerals in the names of **3**–**6** denote the molecular masses. In PhTX-433 (**7**) the digits denote the number of methylene groups that separate the amino functionalities, starting from the tyrosine end.

alkylation of secondary sulfonamides is achieved with alkyl halides under mildly basic conditions or with alcohols under Mitsunobu conditions.[15] Fukuyama and co-workers have applied the alkyl bromide approach in mixed solution/solid-phase total syntheses of several spider and wasp toxins. Ns-Protected acylpolyamines (corresponding to **4**[16] and **6**[16b]) were prepared in solution, and the syntheses were completed after anchoring of the terminal amino group to a solid support. Furthermore, two Fukuyama-type approaches based entirely on SPS have been employed in the total synthesis of philanthotoxins,[17] and two SPS Ns-strategies for site-selective N-methylation in peptide synthesis were reported by Miller and Scanlan.[18] The Fukuyama–Mitsunobu conditions have recently emerged as a versatile and general SPS method used, for instance, in N-alkylation of peptides,[19] peptide nucleic acid (PNA) monomer synthesis,[20] preparation of N-alkylated sulfonamides,[21] and in synthesis of polyamine neurotoxins.[22]

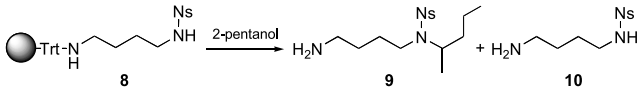
Although a relatively large amount of work has already been devoted to SPS of amines using Fukuyama–Mitsunobu alkylation, we addressed two important issues in order to define the scope and limitations of this strategy. The first issue concerns investigation of alkylation conditions suitable for SPS employing sterically hindered alcohols as building blocks (application of secondary alcohols is also challenging in solution-phase Mitsunobu reactions[23]). The second issue concerns the number of consecutive chain elongation steps that are possible to carry out in a satisfactory overall yield, that is, the length limit of polyamines obtainable by this method. The latter question is of interest, since the Fukuyama–Mitsunobu method has been optimized to give >99% yield in a single alkylation step,[22c] yet the overall yields of philanthotoxins obtained after two alkylations only amounted to 23–40%.[22c,e] Accordingly, the present work reports on the use of Fukuyama–Mitsunobu protocols for the SPS of curtatoxins, which contain polyamine moieties of different lengths, and thus constitutes an interesting test case.

2. Results and discussion

2.1. Screening of SPS reagent combinations for N-alkylation with secondary alcohols

Numerous combinations of solvents, bases, azo reagents and phosphines[24] have previously been applied in Mitsunobu reactions, and it was decided to select a range of reagents for a combinatorial screening in order to identify suitable conditions for Fukuyama–Mitsunobu SPS alkylations with secondary alcohols. Bycroft and co-workers[22a] as well as Hone and Payne[22b] have employed the traditional reagent pair diethyl azocarboxylate (DEAD) and PPh_3 in their original reports on polyamine SPS using Fukuyama–Mitsunobu amination, and hence these reagents were included in the present investigation. The two azo reagents used under Tsunoda conditions, that is, 1,1′-(azodicarbonyl)dipiperidide (ADDP) and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD),[25] were likewise included, since both of these reagents in combination with PMe_3 were previously found to give acceptable to good yields in alkylation of

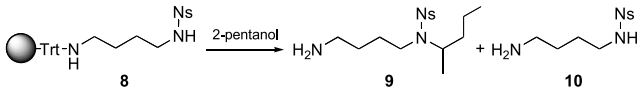
Table 1. Effect of reagent combinations on the yield of single Fukuyama–Mitsunobu solid-phase alkylations with a secondary alcohol in CH_2Cl_2–THF (1:1)[a]



Yields	No base			*i*Pr$_2$EtN		
	TMAD %[a]/%[b]	ADDP %[a]/%[b]	DEAD %[a]/%[b]	TMAD %[a]/%[b]	ADDP %[a]/%[b]	DEAD %[a]/%[b]
PMe_3	46/49	37/39	19/14	51/52	49/53	21/16
PEt_3	60/71	29/47	71/60	71/74	38/54	69/71
PPh_3	24/30	Trace	70/92	14/19	Trace	68/93

[a] Yields estimated from ^{1}H NMR.
[b] Product purities calculated from RP-HPLC as ratios {[9]/([9]+[10])}×100.

Table 2. Effect of various solvents on the yield of single Fukuyama–Mitsunobu solid-phase alkylations with a secondary alcohol[a]



PPh_3, DEAD, *i*Pr$_2$EtN			PEt_3, DEAD, *i*Pr$_2$EtN		
THF–PhMe 1:1	CH_2Cl_2–PhMe 1:1	PhMe	THF–PhMe 1:1	CH_2Cl_2–PhMe 1:1	PhMe
>95%	>95%	76%	53%	82%	38%

[a] Product purities calculated from RP-HPLC as ratios {[9]/([9]+[10])}×100.

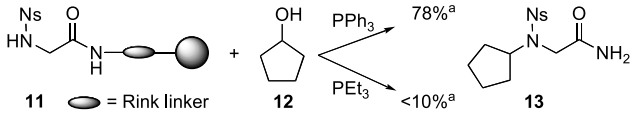
sulfonamides with secondary alcohols in solution.[26] Thus, the phosphines selected were the traditional PPh_3 and the least sterically hindered trialkylphosphine, PMe_3, along with PEt_3. All three phosphines have recently been reported to give acceptable to high conversion in C–C bond formation reactions with secondary benzylic alcohols.[27] Tributylphosphine, which previously has been widely used, was omitted in the present study due to the recently reported lack of reactivity in combination with ADDP and TMAD in solution-phase reactions.[26]

The above-mentioned phosphines and azo reagents comprise nine reagent combinations. The presence of base in Fukuyama–Mitsunobu reactions has previously been reported to enhance the tolerance towards steric bulk of the alcohol (using imidazole[28]) as well as to increase the reaction rate (using *i*Pr$_2$EtN[20]). Hence, the effect of the presence of *i*Pr$_2$EtN was also investigated (Table 1).

In the initial N-alkylation experiments described below we relied on the findings by Strømgaard et al.[22c] concerning the effect of solvent, concentration, order of reagent addition, and the number of repetitions. However, longer reaction times were applied (2×3 and 16 h), as this was found advantageous in our previous solution-phase experiments with secondary alcohols.[26] The results of ^{1}H NMR and RP-HPLC analyses of the product mixtures are shown in Table 1. Subsequently, the two best reagent combinations were further tested in additional solvent mixtures (Table 2).

The general observations about the SPS alkylation of sulfonamide **8** with 2-pentanol that emerged from these investigations are as follows: (1) triphenylphosphine worked well in combination with DEAD; (2) triethylphosphine combinations generally afforded acceptable conversions; (3) the presence of base did not increase the conversion significantly; (4) the reagent pairs DEAD/PPh_3, DEAD/PEt_3 and TMAD/PEt_3 (with and without base) all proved quite efficient in the alkylation. The reagent combinations containing PMe_3 proved not to be superior as opposed to previous solution-phase studies.[26,27] However, acceptable yields were only obtained with this phosphine when combined with ADDP or TMAD, paralleling the previous solution-phase experiments.[26] The RP-HPLC evaluation of the influence of the solvent showed good yields for 1:1 mixtures of THF–PhMe and CH_2Cl_2–PhMe (Table 2), but the ^{1}H NMR spectra of all of the six crude products revealed the presence of more impurities than observed in CH_2Cl_2–THF (1:1). Thus, the latter solvent combination was applied in the subsequent experiments.

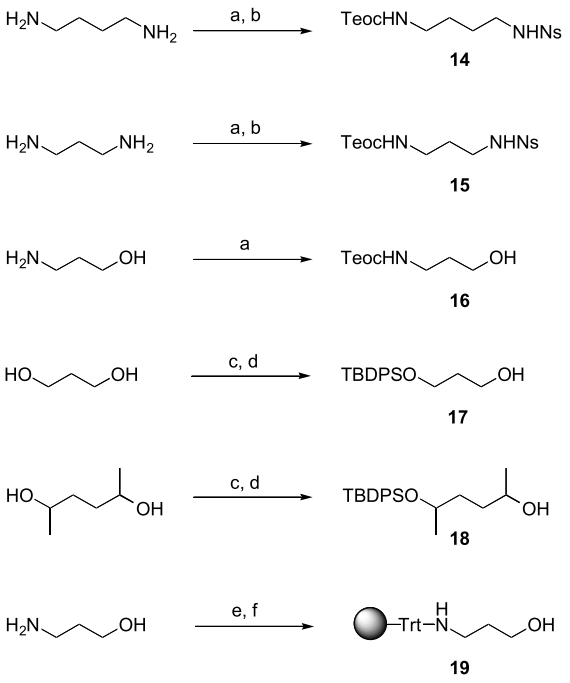
N-Alkylation of the sulfonamide (Ns-derivative) of resin-bound glycine (**11**) with a secondary alcohol (cyclopentanol) was subsequently performed with the most promising reagent combinations found in the above screening. A good yield (78%) was obtained when using PPh_3 as the phosphine, while PEt_3 did not furnish a satisfactory yield (Scheme 1). The two phosphines gave similar conversions in the investigation shown in Tables 1 and 2, which suggests that optimal conditions for N-alkylation is likely to be sensitive to the type of substrate and/or linker used.



Scheme 1. Resin **11** was alkylated with cyclopentanol (**12**) under Fukuyama–Mitsunobu conditions (DEAD/PPh_3/*i*Pr$_2$EtN or DEAD/PEt_3/*i*Pr$_2$EtN in CH_2Cl_2–THF (1:1), and the product (**13**) was cleaved with TFA–CH_2Cl_2 (95:5). [a]Isolated yields after vacuum liquid chromatography (VLC) based on the original resin loading.

2.2. Building block synthesis

The possibility of synthesizing long-chain polyamines (pentaamines or higher homologs) on solid phase using

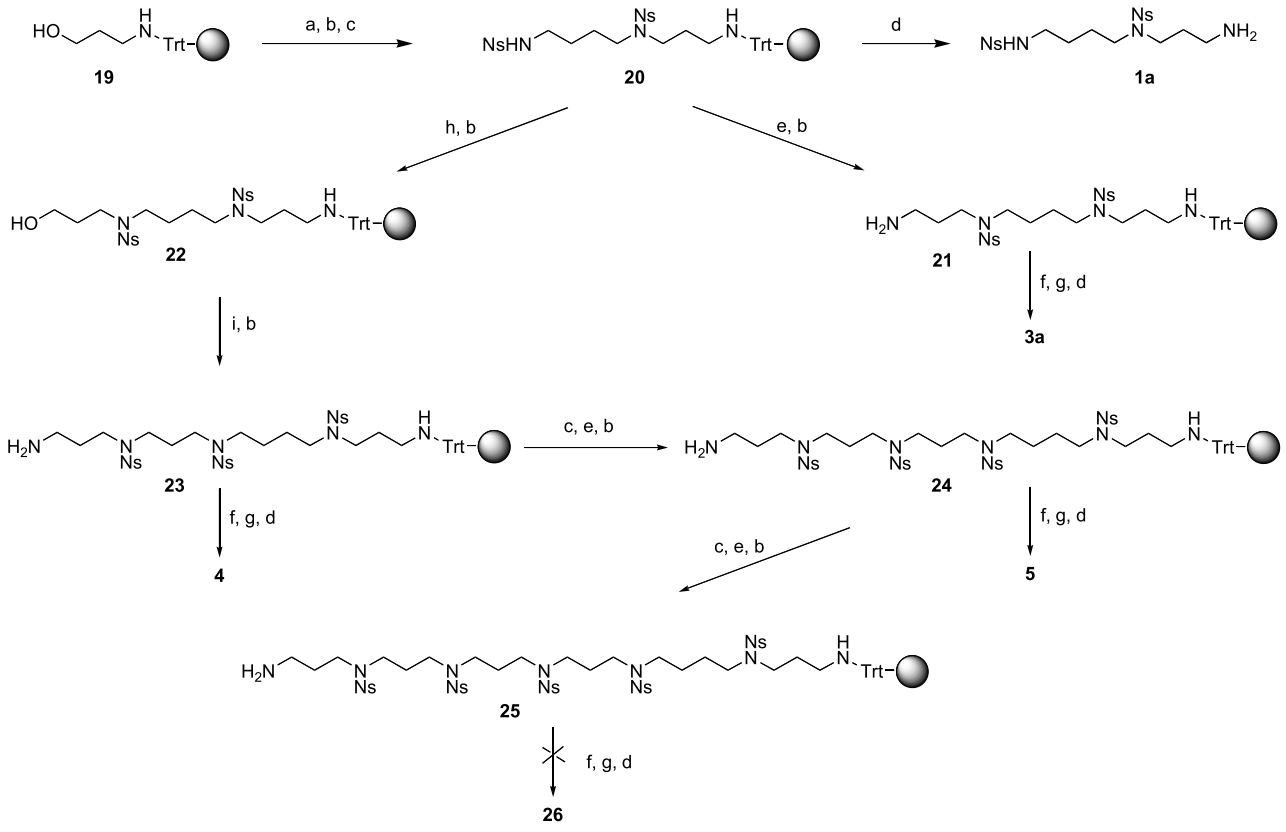


Scheme 2. Reagents and conditions: (a) 2-(trimethylsilyl)ethyl *p*-nitrophenyl carbonate, MeOH, CH_2Cl_2; (b) NsCl, *i*Pr_2EtN, CH_2Cl_2; (c) NaH (1 equiv), THF, 30 min; (d) TBDPS-Cl (1 equiv); (e) TMS-Cl, CH_2Cl_2, 40 °C, then Et_3N at room temperature followed by trityl chloride resin; (f) TBAF, DMF, 50 °C.

the Fukuyama–Mitsunobu approach was examined with curtatoxin analogs as the example. For this purpose, chain elongation building blocks **14**–**18** were prepared along with resin **19**, necessary for synthesis of **3**–**5** and their branched analogs. The diamine building blocks were mono-(2-trimethylsilylethoxy)carbonyl (Teoc) protected and Ns-activated, as previously described.[26] Thus, compounds **14** and **15** were obtained in 70–73% overall yield. Compound **16** was obtained in 80% yield by treatment of 3-amino-1-propanol with (2-trimethylsilyl)ethyl *p*-nitrophenyl carbonate in MeOH–CH_2Cl_2 (1:1), and the crude product was used without further purification. Diols were mono-protected as the *tert*-butyldiphenylsilyl (TBDPS) ethers under the conditions described by Wacowich-Sgarbi and Bundle,[29] affording **17** and **18** in 77 and 73% yield, respectively. It was decided to start from resin **19** shown in Scheme 2. In order to avoid the potential risk of resin cross-linking upon loading with an unprotected amino alcohol, the loading was accomplished with temporarily *O*-trimethylsilyl (TMS) protected 3-aminopropanol, employing similar conditions as used for attachment of amino acids via the N-terminal onto polystyrene trityl resins.[30]

2.3. SPS of curtatoxins using multiple Fukuyama–Mitsunobu amination steps

An efficient SPS strategy for the preparation of pentaamine spider toxins was recently reported by Bienz and co-workers.[11c]



Scheme 3. Reagents and conditions: (a) **14**, PMe_3, ADDP, CH_2Cl_2–THF 1:1; (b) TBAF, DMF, 50 °C; (c) NsCl, *i*Pr_2EtN, CH_2Cl_2; (d) TFA, CH_2Cl_2 1:1; (e) **16**, PMe_3, ADDP, CH_2Cl_2–THF 1:1; (f) indol-3-ylacetic acid, DIC, HOBt; (g) DBU, 2-mercaptoethanol; (h) **17**, PMe_3, ADDP, CH_2Cl_2–THF 1:1; (i) **15**, PMe_3, ADDP, CH_2Cl_2–THF 1:1.

In their case, the polyamine was constructed from the center by bromide displacement reactions. In the present work, however, the aim was to test the efficiency of the Fukuyama–Mitsunobu SPS method for preparation of long-chain polyamines. The sequence shown in Scheme 3 was carried out starting with 500 mg of resin **19**. After the initial Fukuyama–Mitsunobu alkylation with **14** under modified Tsunoda conditions (PMe_3, ADDP),[22e] removal of the Teoc group, and subsequent treatment with NsCl, resin **20** was obtained, which was extensively washed and dried in vacuo.

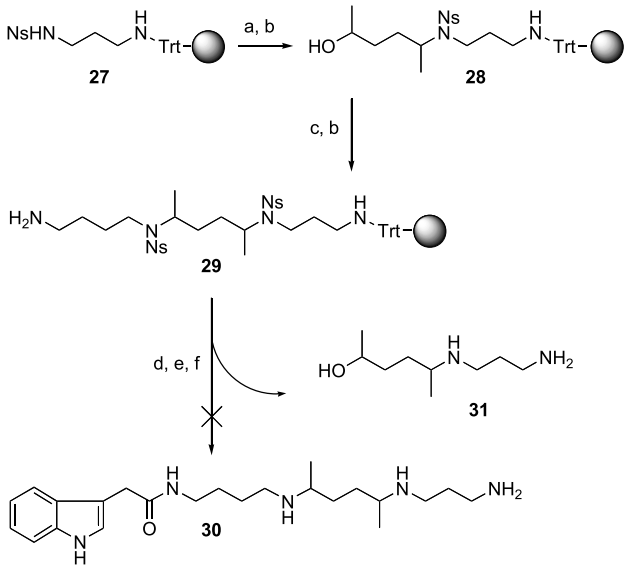
One-fifth of resin **20** was then treated with TFA–CH_2Cl_2 (1:1) to give the dinosylated spermidine derivative **1a** in order to determine the yield after a single alkylation step.

The isolated yield of **1a** was 67% after this 6-step reaction sequence (including the resin loading and cleavage), corresponding to an average yield per step of $>93\%$.

Another one-fifth of the original resin was elongated with the *N*-Teoc-protected aminoalcohol (**16**), and the Teoc group was removed to give resin **21**. The terminal primary amino group was acylated with indol-3-ylacetic acid under activation with DIC and HOBt, the Ns groups were removed, and the resin was treated with TFA–CH_2Cl_2 to furnish **3a** (12% isolated yield).

The remaining three fifths of the original resin were elongated with mono-protected diol **17** to give resin **22**, which was further elongated with the building block **15** to give **23**. Resin **23** was then divided into three equal portions for the acylation to give **4**, and for chain elongations to give **24** and **25**, respectively, as shown in Scheme 3. Thus, the theoretical yields of **1a**, **3a**, **4**, **5**, and **26** represented the same molar amounts, as they were designed to arise from one fifth each of the starting resin **19**. The Ns groups in the fully protected resin-bound products were removed by two treatments with DBU and 2-mercaptoethanol in DMF,[18] for 24 h[16] and for 1 h, respectively, in order to complete the deprotection as indicated by a colorless drain [the absence of the yellow 2-(2-nitrophenylthio)ethanol].[18] The products (**4**, **5**, and **26**) were released from the solid support with TFA–CH_2Cl_2 (1:1) and purified by reversed-phase vacuum liquid chromatography (VLC), a method previously reported to be appropriate for isolation of acylpolyamines.[31] Neither the yields nor the purities were satisfactory after the RP-VLC purification, however, and ^1H NMR spectra demonstrated the presence of relatively complex mixtures, with only minor resonances from the indole moiety present. The samples were therefore analyzed by reversed-phase HPLC and LC–MS.

For compound **4**, the LC–MS analysis was satisfactory. This was not the case for compound **5**, however, and the polyamine **26** was apparently not formed in appreciable amounts after five Fukuyama–Mitsunobu coupling steps (see Supporting Information for chromatograms and MS spectra). The same negative result was obtained when performing five consecutive elongations using the Strømgaard approach (*N*-Teoc protected amino alcohols and ADDP–PBu_3).[22c]



Scheme 4. Reagents and conditions (a) **18**, PPh_3, DEAD, CH_2Cl_2–THF 1:1; (b) TBAF, DMF, 50 °C; (c) **14**, PPh_3, DEAD, CH_2Cl_2–THF 1:1; (d) indol-3-ylacetic acid, DIC, HOBt; (e) DBU, 2-mercaptoethanol; (f) TFA–CH_2Cl_2 1:1.

The optimized conditions developed for alkylation with secondary alcohols were applied in order to prepare di-*C*-methyl branched curtatoxin analog **30** (Scheme 4). Initially, resin **27**[22e] was elongated with the mono protected diol (**18**) using PPh_3 and DEAD in CH_2Cl_2–THF (1:1), and the Teoc group was removed to give resin **28**. The diamine building block **14** was then introduced employing the same Mitsunobu conditions, designed to give resin **29**.

The remaining sequence aimed towards **30** was performed as described above, but no well-defined product could be isolated by RP-VLC. Furthermore, LC–MS analysis of the obtained fractions revealed no traces of **30**, while the most polar fraction contained the diamino alcohol **31**, which indicated that the first alkylation had taken place partially. Thus, the decrease in yield as observed in consecutive alkylations with primary alcohols appears to be even more pronounced when using secondary alcohols.

As shown in Table 3, good isolated yields were obtained after a single alkylation reaction with both primary and secondary alcohols. However, in both cases the isolated yields dropped significantly after the second consecutive alkylation step. We hypothesize that the low yield generally observed in the second SPS Fukuyama–Mitsunobu alkylation step may arise from interference of deposited byproducts and/or excess reagents in the resin pores. This

Table 3. Isolated yields obtained in polyamine solid-phase synthesis using polystyrene trityl resin as shown in Table 1, Schemes 3 and 4

	1st Alkylation	2nd Alkylation	3rd Alkylation
Primary alcohol	67%[a]	12%[a]	Trace
Secondary alcohol	59%[b]	0%[c]	n.p.[d]

[a] Isolated yields obtained in the experiments shown in Scheme 3.
[b] Isolated yield of compound **9** (Table 1).
[c] Yield of **30** (Scheme 4).
[d] Not performed.

explanation seems plausible when considering the problems often encountered with isolation of products from Mitsunobu reactions in general, a subject very recently reviewed by Dembinski[32] as well as by Dandapani and Curran.[33]

3. Conclusions

The experiments described in the present paper show that the Fukuyama–Mitsunobu amination reaction is a versatile but also a limited method for SPS of secondary amines. Superior reagent combinations for Fukuyama–Mitsunobu alkylation of resin-bound 2-nitrobenzenesulfonamides with secondary alcohols have been established by examining a combinatorial array of selected phosphine-reagents and azo reagents, with or without addition of a base. Also, resin-bound Ns-activated glycine was successfully alkylated with a secondary alcohol (cyclopentanol) in good yield, which shows that these results may find extended use in the synthesis of novel peptide analogs. Furthermore, systematic elongation sequences targeting long-chain polyamines (up to a heptaamine), showed that the Fukuyama–Mitsunobu amination method employing primary alcohols is practically limited to two chain elongation steps in SPS, if acceptable yields are to be obtained. However, when using a secondary alcohol, only one alkylation step was feasible under the conditions employed in the present work. Sharply dropping yields in successive alkylation steps are thus the most serious limitation of the use of the Fukuyama–Mitsunobu reaction in SPS of polyamines.

4. Experimental

4.1. Chemicals and instruments

Unless otherwise stated, starting materials were obtained from commercial suppliers and used without further purification. Trityl resins (100–200 mesh, 1% divinylbenzene) were obtained from Novabiochem (Läufelingen, Switzerland) and IRIS Biotech (Marktredwitz, Germany). The Rink amide resin was from IRIS Biotech (Marktredwitz, Germany). Indol-3-ylacetic acid was purchased from Lancaster (Morecambe, England). Tetrahydrofuran (THF) was distilled under N_2 from sodium/benzophenone prior to 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 membrane filter (Millipore, Millipak40). ^{1}H NMR spectra were recorded at 400.14 or 600.13 MHz on a Bruker Avance 400 or Avance 600 spectrometer, respectively, and ^{13}C NMR spectra were recorded at 100.6 MHz on a Bruker Avance 400 spectrometer, using $CDCl_3$ or CD_3OD as solvents and TMS as internal standard. Coupling constants (J values) are given in hertz (Hz). Multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; d, doublet; t, triplet; p, pentet; m, multiplet; br, broad signal. VLC was performed using Merck silica gel 60H, 5–40 μm (average size 15 μm), or Merck LiChroprep RP-18 (40–63 μm) stationary phase. Analytical HPLC was performed on a Shimadzu HPLC-system consisting of an SCL-10A VP controller, an SIL-10AD VP autoinjector, an LC-10AT VP Pump, an SPD-M10A VP diode array detector, and a CTO-10AC VP column oven, using a Phenomenex Luna C18(2) 3 μm column (150×4.6 mm) eluted at a rate of 0.8 mL/min. The system was controlled by Class VP 6 software, and elution was performed with eluent A (MeCN–H_2O–TFA 10:90:0.1) containing 0% of eluent B (MeCN–H_2O–TFA 90:10:0.1) at t=0–5 min, rising linearly to 40% of B during t=5–35 min, and rising linearly to 100% of B during t=35–40 min. LC–MS was performed using a ThermoFinnigan TSQ Quantum Ultra instrument. The preparative HPLC system consisted of a Waters model 590 pump, a Waters Lambda-Max model 481 spectrophotometric detector operating at 215 nm, and a Phenomenex Luna C18(2) 5 μm column (250×21.2 mm). The chromatograph operated isocratically at a flow-rate of 9 mL/min, using water–acetonitrile–TFA 85:15:0.1 as the mobile phase. High-resolution mass spectrometry (HRMS) measurements for exact mass determination were performed on a Bruker APEX Qe 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 CID (collision induced dissociation) spectrum of LHRH (luteinizing hormone releasing hormone) free acid. The samples were introduced into the electrospray ion source using a 250 μL syringe with a syringe pump flow of 2 μL/min.

4.2. General procedures

4.2.1. SPS Fukuyama–Mitsunobu alkylation of resin-bound 2-nitrobenzenesulfonamides (Tables 1 and 2, Schemes 1, 3, and 4). The vacuum dried *N*-nosyl-functionalized resin (typically ~0.1 mmol) was suspended in THF (0.5 mL), and then a secondary alcohol or a monoprotected diol (5 equiv) in CH_2Cl_2 (0.5 mL), a phosphine (6 equiv, ~0.6 mL, 1.0 M in THF) and an azo reagent (5 equiv) in CH_2Cl_2 (0.5 mL) were added. The mixture was shaken at room temperature under N_2 for 3 h. The resin was drained and washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time) and flushed with N_2 for 15 min, after which the procedure was repeated twice. In the final repetition the reaction time was 16 h.

4.2.2. SPS Fukuyama–Mitsunobu alkylation of resin-bound amino alcohols (Schemes 3 and 4). A vacuum-dried resin-bound alcohol (typically ~0.1 mmol) was suspended in THF (0.5 mL), and then *N*-nosyl activated primary amine (5 equiv) in CH_2Cl_2 (0.5 mL), phosphine (6 equiv, ~0.6 mL, 1.0 M in THF) and an azo reagent (5 equiv) in CH_2Cl_2 (0.5 mL) were added. The mixture was shaken at room temperature under N_2 for 3 h. The resin was drained and washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time) and flushed with N_2 for 15 min, after which the procedure was repeated twice. In the final repetition the reaction time was 16 h.

4.2.3. Nosylation of resin-bound amines (Schemes 1 and 3). The resin was dried in vacuo and NsCl (5 equiv) in CH_2Cl_2 was added under a stream of N_2. iPr$_2$EtN (7 equiv) was added, and the mixture was shaken at room temperature for 15 h. Then the resin was washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time) and dried in vacuo before the next chain-elongation step.

4.2.4. Removal of TBDPS or Teoc groups (Schemes 3 and 4)**.** The resin was treated with TBAF·$3H_2O$ (5 equiv) in DMF (3 mL) for 30 min at 50 °C, and washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time).

4.2.5. Introduction of the indol-3-ylacetic acid residue (Schemes 3 and 4)**.** The resin was suspended in dry DMF (1 mL). DIC (5 equiv), HOBt (5 equiv), and indol-3-ylacetic acid (5 equiv) in dry DMF (1 mL) were added and the mixture was shaken at room temperature under N_2 for 4 h. The resulting resin was drained and washed with DMF, CH_2Cl_2 and DMF (3×5 mL, 5 min each time).

4.2.6. Removal of Ns groups on solid phase (Schemes 3 and 4)**.** The resin was treated twice with DBU (10 equiv) in DMF (1 mL) and 2-mercaptoethanol (20 equiv) in DMF (1 mL) for 20 and 1 h, respectively. The resin was drained and washed with MeOH between each repetition until a final colorless drain confirmed complete deprotection. The resin was washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time).

4.2.7. Cleavage from the resins (Tables 1 and 2, Schemes 1, 3, and 4)**.** The products were cleaved by treatment with TFA–CH_2Cl_2 (4 mL, 1:1 for trityl linkers and 95:5 for Rink linker) at room temperature for 2 h. The drained solvent was combined with washings (MeOH (2×5 mL) and CH_2Cl_2 (2×5 mL) and concentrated in vacuo. The products were purified by reversed-phase VLC [H_2O–MeCN–TFA (95:5:0.1, 90:10:0.1, 85:15:0.1 and 80:20:0.1)] or preparative RP-HPLC.

4.2.8. Characterization of compounds 1a, 3a, 9, and 13. *Compound* **1a**. Yield: 44 mg (67%) of a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 2H, Ns), 7.83–7.76 (br m, 6H, Ns), 3.40 (t, J=7.2 Hz, 2H), 3.30 (t, J=6.6 Hz, 2H), 3.02 (t, J=6.6 Hz, 2H), 2.86 (t, J=7.2 Hz, 2H), 1.87 (p, J=7.2 Hz, 2H), 1.58 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 135.5, 135.0 (2C), 134.8, 133.7, 133.6, 133.3, 131.5 (2C), 125.9, 125.6, 49.3, 46.2, 43.7, 38.6, 28.9, 27.8, 26.2. HRMS: *m/z* calcd for $[C_{19}H_{26}N_5O_8S_2]^+$ 516.1217, found 516.1217, ΔM 0.14 ppm.

Compound **3a**. Yield: 11 mg (12%) of a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (d, J=7.9 Hz, 1H), 7.37 (d, J=8.1 Hz, 1H), 7.13 (dd, J=8.1 and 7.9 Hz, 1H), 7.04 (dd, J=8.1 and 7.9 Hz, 1H), 3.69 (s, 2H, CH_2CO), 3.11–3.03 (br m, 6H, 3×CH_2N), 2.98 (t, J=7.6 Hz, 2H, CH_2N), 2.81 (m, 4H, 2×CH_2N), 2.08 (m, 2H), 1.82 (p, J=6.6 Hz, 2H), 1.63 (m, 2H), 1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 138.2, 128.4, 125.2, 122.8, 120.1, 119.3, 112.6, 109.4, 48.2, 48.0, 46.0 (2C), 37.8 (2C), 36.7, 33.9, 27.6, 25.3 (2C). HRMS: *m/z* calcd for $[C_{20}H_{34}N_5O]^+$ 360.2758, found 360.2759, ΔM 0.39 ppm.

Compound **9**. Yield: 12 mg (59%) of a yellow oil after RP-VLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J=7.3 Hz, 1H, Ns), 7.80–7.72 (br m, 3H, Ns), 3.91 (m, 1H, CHNNs), 3.39 (t, J=7.8 Hz, 2H, CH_2NNs), 2.72 (t, J=7.3 Hz, 2H, CH_2NH$_2$), 1.65–1.26 (br m, 8H, 4×CH_2), 1.10 (d, J=6.1 Hz, 3H, CH_3CH), 0.84 (t, J=7.3 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 147.9, 135.1, 132.9, 131.9, 125.2, 55.3, 44.3, 41.7, 38.7, 30.4, 30.0, 20.7, 19.5, 14.1. HRMS: *m/z* calcd for $[C_{15}H_{26}N_3O_2S]^+$ 344.1639, found 344.1640, ΔM 0.32 ppm.

Compound **13**. Yield: 21 mg (78%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J=7.3 Hz, 1H, Ns), 7.76–7.66 (br m, 3H, Ns), 6.53 (br s, 1H, NHCO), 5.73 (br s, 1H, NHCO), 4.33 (m, 1H, CHN), 3.93 (br s, 2H, H-α), 1.91–1.22 (br m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 134.3, 132.5, 132.1, 131.4, 124.5, 59.6, 46.7, 29.0 (2C), 23.2 (2C). HRMS: *m/z* calcd for $[C_{13}H_{17}N_3O_5SNa]^+$ 350.0781, found 350.0782, ΔM 0.37 ppm.

4.2.9. *N*-[(2-Nitrophenyl)sulfonyl]-N^1-[(2-trimethylsilyl)-ethoxycarbonyl]-1,4-butanediamine (14). (2-Trimethylsilyl)ethyl *p*-nitrophenyl carbonate (4.83 g, 17.05 mmol) in CH_2Cl_2 (25 mL) was added to a stirred solution of 1,4-butanediamine (3.97 g, 45 mmol, 2.6 equiv) in MeOH (25 mL), and the mixture was stirred for 16 h at room temperature. The methanol was removed in vacuo and then EtOAc (250 mL) was added. The organic phase was washed with 2 M aq NaOH (4×100 mL) and brine (2×100 mL), dried (Na_2SO_4), filtered, concentrated, and dried in vacuo to give a sufficiently pure product (2.89 g; 73%). ^{1}H NMR (400 MHz, CD_3OD): δ 4.11 (t, J=8.3 Hz, 2H, CH_2O), 3.10 (t, J=6.4 Hz, 2H, CH_2NHCO), 2.64 (t, J=6.4 Hz, 2H, CH_2NH$_2$), 1.49 (m, 4H, 2×CH_2), 0.98 (t, J=8.3 Hz, 2H, CH_2Si), −0.05 (br s, 9H, $(CH_3)_3$Si). ^{13}C NMR (100 MHz, CD_3OD): δ 159.8, 64.2, 42.7, 41.9, 31.4, 28.8, 19.2, −0.9 (3C). The crude material, *i*Pr$_2$EtN (2.80 mL), and NsCl (3.30 g) were dissolved in CH_2Cl_2 (40 mL) and the solution was stirred at room temperature. After 16 h the mixture was concentrated, the residue was loaded onto a VLC column (7×7 cm), and the column eluted with hexane–EtOAc (10:1, 6:1, 4:1, 2:1, and 1:1) to furnish **14** (4.39 g; 62% overall) as a pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (m, 1H, Ns), 7.86 (m, 1H, Ns), 7.74 (m, 2H, Ns), 5.38 (br t, 1H, $NHSO_2$), 4.57 (br t, 1H, NHCO), 4.13 (m, 2H, CH_2O), 3.12 (m, 4H, 2×CH_2N), 1.55 (m, 4H, 2×CH_2), 0.96 (t, J=7.2 Hz, 2H, CH_2Si), 0.02 [br s, 9H, $(CH_3)_3$Si]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 148.0, 133.7, 133.6, 132.8, 125.4, 63.0, 43.4, 40.2, 27.1, 26.8, 17.8, −1.5 (3C).[26]

4.2.10. *N*-[(2-Nitrophenyl)sulfonyl]-N^1-[(2-trimethylsilyl)ethoxycarbonyl]-1,3-propanediamine (15). The procedure was as described above using 1,3-propanediamine as the starting material, to give **15** (2.15 g; 68% overall) as a pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (m, 1H, Ns), 7.84 (m, 1H, Ns), 7.74 (m, 2H, Ns), 5.95 (br s, 1H, $NHSO_2$), 4.99 (br s, 1H, NHCO), 4.13 (br t, J=8.2 Hz, 2H, CH_2O), 3.25 (q, J=6.4 Hz, 2H), 3.16 (q, J=6.4 Hz, 2H), 1.71 (p, J=6.4 Hz, 2H, CH_2), 0.96 (br t, J=8.2 Hz, 2H, CH_2Si), 0.02 [br s, 9H, $(CH_3)_3$Si]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 147.9, 133.8, 133.5, 132.7, 125.2, 63.0, 40.7, 37.3, 30.2, 17.6, −1.6 (3C). HRMS: *m/z* calcd for $[C_{15}H_{24}N_3O_6SSiNa]^+$ 426.1126, found 426.1127, ΔM 0.40 ppm.

4.2.11. *N*-[(2-Trimethylsilyl)ethoxycarbonyl]-3-amino-1-propanol (16). 3-Amino-1-propanol (552 μL, 2.4 mmol, 1.2 equiv) was dissolved in MeOH (20 mL), (2-trimethylsilyl)ethyl *p*-nitrophenyl carbonate (567 mg, 2.0 mmol) in

CH_2Cl_2 (20 mL) was added, and the mixture was stirred at room temperature for 16 h. Methanol was removed in vacuo, EtOAc (150 mL) was added, and the organic phase was washed with 2 M aq NaOH (4×75 mL), and brine (2×75 mL), dried (Na_2SO_4), filtered and concentrated. Drying in vacuo afforded compound **16** (1.23 g; 79%) as a colorless syrup. ^{1}H NMR (400 MHz, CD_3OD): δ 4.13 (t, J=8.3 Hz, 2H, CH_2O), 3.59 (t, J=6.3 Hz, 2H, CH_2OH), 3.18 (t, J=6.9 Hz, 2H, CH_2N), 1.69 (br p, $J\approx$6.7 Hz, 2H, CH_2), 0.98 (t, J=8.3 Hz, 2H, CH_2Si), 0.05 [br s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (100 MHz, CD_3OD): δ 159.4, 63.7, 60.4, 38.6, 33.7, 18.6, −1.6 (3C).[34]

4.2.12. 3-(*tert*-Butyldiphenylsilyloxy)-1-propanol (17). A mixture of 1,3-propanediol (1.66 mL, 23.0 mmol) and NaH (920 mg, 23 mmol; 60% suspension in oil) in dry THF (20 mL) was stirred at room temperature under N_2 for 30 min. *tert*-Butyldiphenylsilylchloride (5.98 mL, 23.0 mmol) was added during 1 h, and stirring was continued for 16 h. The mixture was then diluted with EtOAc (200 mL), and washed with water (3×100 mL) and brine (2×100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by VLC (hexane–EtOAc 15:1, 8:1, and 6:1) to give **17** (5.58 g; 77%) as a clear syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (m, 4H, Ph), 7.41 (m, 6H, Ph), 3.85 (br t, J=7.2 Hz, 4H, 2×CH_2O), 1.82 (p, J=7.2 Hz, 2H, CH_2), 1.06 [br s, 9H, $(CH_3)_3C$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6 (4C), 133.3 (2C), 129.8 (2C), 127.8 (4C), 63.2, 61.8, 34.4, 26.9 (3C), 19.1. HRMS: *m/z* calcd for $[C_{19}H_{26}O_2SiNa]^+$ 337.1594, found 337.1595, ΔM 0.27 ppm.

4.2.13. 5-(*tert*-Butyldiphenylsilyloxy)-2-hexanol (18). A mixture of 2,5-hexanediol (809 mg, 6.9 mmol) and NaH (280 mg, 6.9 mmol; 60% suspension in oil) in dry THF (10 mL) was stirred at room temperature under N_2 for 30 min. *tert*-Butyldiphenylsilylchloride (1.78 mL, 6.9 mmol) was added during 30 min, and stirring was continued for 16 h. The mixture was then diluted with EtOAc (100 mL), and washed with water (3×75 mL) and brine (2×75 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by VLC (hexane–EtOAc 15:1, 8:1, and 6:1) to give **18** (1.78 g; 73%) as a clear syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (m, 4H, Ph), 7.39 (m, 6H, Ph), 3.88 (m, 1H, C*H*OH), 3.69 (m, 1H, CHOSi), 1.65–1.44 (br m, 4H, 2×CH_2), 1.14–1.04 (br m, 15H, 5×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0 (2C), 135.9 (4C), 129.6 (2C), 127.5 (4C), 69.5/69.4* (1C), 68.3/68.0* (1C), 35.5/35.1* (1C), 34.7/34.5* (1C), 27.1 (3C), 23.4, 23.1/22.8* (1C), 19.2 (diastereoisomers). HRMS: *m/z* calcd for $[C_{22}H_{32}O_2Si]^+$ 357.2244, found 357.2244, ΔM 0.03 ppm.

4.2.14. Preparation of N-resin-bound 3-amino-1-propanol (19). 3-Amino-1-propanol (1.03 mL, 13.5 mmol, 10 equiv) was dissolved in dry CH_2Cl_2 (20 mL) and TMS-Cl (1.71 mL, 13.5 mmol, 10 equiv) was added. The mixture was stirred at 40 °C under N_2 for 1.5 h, and Et_3N (3 mL, 16 equiv) was added upon cooling to room temperature, followed by trityl chloride resin (1.0 g, 1.35 mmol/g, 1.35 mmol). The mixture was stirred at room temperature under N_2 overnight. The resin was drained, washed with MeOH and treated with 20% iPr$_2$EtN in MeOH (30 mL) for 30 min to cap unreacted trityl chloride functionalities. The resin was washed with DMF, MeOH and CH_2Cl_2 (3×5 mL), and then it was treated with TBAF (426 mg, 6.75 mmol, 5 equiv) in DMF (10 mL) at room temperature for 2 h. Finally the resin was drained, washed with DMF, MeOH and CH_2Cl_2 (3×5 mL), and freeze-dried to give the functionalized resin (**19**, 1.25 g, 1.283 mmol/g assuming that complete conversions had been achieved).

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Supplementary data

Supplementary data associated with this article can be found at 10.1016/j.tet.2005.04.027

References and notes

1. Cohen, S. S. *A guide to polyamines*; Oxford University Press: New York, 1998.
2. (a) Bergeron, R. J.; McManis, J. S.; Liu, C. Z.; Feng, Y.; Weimar, W. R.; Luchetta, G. R.; Wu, Q.; Ortiz-Ocasio, J.; Vinson, T. J. R.; Kramer, D.; Porter, C. *J. Med. Chem.* **1994**, *37*, 3464–3476. (b) Reddy, V. K.; Valasinas, A.; Sarkar, A.; Basu, H. S.; Marton, L. J.; Frydman, B. *J. Med. Chem.* **1998**, *41*, 4723–4732. (c) Casero, R. A.; Woster, P. M. *J. Med. Chem.* **2001**, *44*, 1–26. (d) Valasinas, A.; Sarkar, A.; Reddy, V. K.; Marton, L. J.; Basu, H. S.; Frydman, B. *J. Med. Chem.* **2001**, *44*, 390–403.
3. (a) Byk, G.; Dubertret, C.; Escriou, V.; Frederic, G.; Jaslin, G.; Rangara, R.; Pitard, B.; Crouzet, J.; Wils, P.; Schwartz, B.; Scherman, D. *J. Med. Chem.* **1998**, *41*, 224–235. (b) Yingyongnarongkul, B.-e.; Howarth, M.; Elliott, T.; Bradley, M. *Chem. Eur. J.* **2004**, *10*, 463–473. (c) Yingyongnarongkul, B.-e.; Howarth, M.; Elliott, T.; Bradley, M. *J. Comb. Chem.* **2004**, *6*, 753–760.
4. (a) Scott, R. H.; Sutton, K. G.; Dolphin, A. C. *Trends Neurosci.* **1993**, *16*, 153–160. (b) Williams, K. *Biochem. J.* **1997**, *325*, 289–297. (c) Igarashi, K.; Kashiwagi, K. *Biochem. Biophys. Res. Commun.* **2000**, *271*, 559–564.
5. For recent reviews, see: (a) Strømgaard, K.; Andersen, K.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Mini Rev. Med. Chem.* **2001**, *1*, 317–338. (b) Strømgaard, K.; Mellor, I. R.

Med. Res. Rev. **2004**, *24*, 589–620. (c) Mellor, I. R.; Usherwood, P. N. R. *Toxicon* **2004**, *43*, 493–508.
6. Quistad, G. B.; Reuter, C. C.; Skinner, W. S.; Dennis, P. A.; Suwanrumpha, S.; Fu, E. W. *Toxicon* **1991**, *29*, 329–336.
7. (a) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Philips, D.; Rosnack, K. J.; Saccomano, N. A.; Stroh, J. G.; Volkmann, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6696–6704. (b) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Phillips, D.; Rosnack, K. J.; Forman, J. T.; Saccomano, N. A.; Stroh, J. G.; Volkmann, R. A. *J. Org. Chem.* **1992**, *57*, 1814–1820. (c) Adams, M. E. *Toxicon* **2004**, *43*, 509–525.
8. (a) Eldefrawi, A. T.; Eldefrawi, M. E.; Konno, K.; Mansour, N. A.; Nakanishi, K.; Eugene, O.; Usherwood, P. N. R. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4910–4913. (b) Piek, T.; Fokkens, R. H.; Karst, H.; Kruk, C.; Lind, A.; van Marle, J.; Tong, Y. C. In *Neurotox 8: molecular basis of drug and pesticide action*; Lunt, G. G., Ed.; Elsevier: Amsterdam, 1988; pp 61–76.
9. (a) Nakanishi, K.; Goodnow, R., Jr.; Konno, K.; Niwa, M.; Bukownik, R.; Kallimopoulos, T.; Usherwood, P. N. R.; Eldefrawi, A. T.; Eldefrawi, M. E. *Pure Appl. Chem.* **1990**, *62*, 1223–1230. (b) Bruce, M.; Bukownik, R.; Eldefrawi, A. T.; Eldefrawi, M. E.; Goodnow, R., Jr.; Kallimopoulos, T.; Konno, K.; Nakanishi, K.; Niwa, M.; Usherwood, P. N. R. *Toxicon* **1990**, *28*, 1333–1346. (c) Goodnow, R., Jr.; Bukownik, R.; Nakanishi, K.; Usherwood, P. N. R.; Eldefrawi, A. T.; Anis, N. A.; Eldefrawi, M. E. *J. Med. Chem.* **1991**, *34*, 2389–2394. (d) Nakanishi, K.; Choi, S.-K.; Hwang, D.; Lerro, K.; Orlando, M.; Kalivretenos, A. G.; Eldefrawi, A. T.; Eldefrawi, M. E.; Usherwood, P. N. R. *Pure Appl. Chem.* **1994**, *66*, 671–678. (e) Choi, S.-K.; Kalivretenos, A. G.; Usherwood, P.; Nakanishi, K. *Chem. Biol.* **1995**, *2*, 23–32. (f) Nakanishi, K.; Huang, X.; Jiang, H.; Liu, Y.; Fang, K.; Huang, D.; Choi, S.-K.; Katz, E.; Eldefrawi, M. E. *Bioorg. Med. Chem.* **1997**, *5*, 1969–1988. (g) Huang, D.; Jiang, H.; Nakanishi, K.; Usherwood, P. N. R. *Tetrahedron* **1997**, *53*, 12391–12404. (h) Strømgaard, K.; Brierley, M. J.; Andersen, K.; Sløk, F. A.; Mellor, I. R.; Usherwood, P. N. R.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *J. Med. Chem.* **1999**, *42*, 5224–5234. (i) Bixel, M. G.; Krauss, M.; Liu, Y.; Bolognesi, M. L.; Rosini, M.; Mellor, I. R.; Usherwood, P.; Melchiorre, C.; Nakanishi, K.; Hucho, F. *Eur. J. Biochem.* **2000**, *267*, 110–120. (j) Bixel, M. G.; Krauss, M.; Weise, C.; Bolognesi, M. L.; Rosini, M.; Usherwood, P. N. R.; Melchiorre, C.; Hucho, F. *Farmaco* **2001**, *56*, 133–135. (k) Bixel, M. G.; Weise, C.; Bolognesi, M. L.; Rosini, M.; Brierley, M. J.; Mellor, I. R.; Usherwood, P.; Melchiorre, C.; Hucho, F. *J. Biol. Chem.* **2001**, *276*, 6151–6160. (l) Mellor, I. R.; Brier, T. J.; Pluteanu, F.; Strømgaard, K.; Saghyan, A.; Eldursi, N.; Brierley, M. J.; Andersen, K.; Jaroszewski, J. W.; Krogsgaard-Larsen, P.; Usherwood, P. N. R. *Neuropharmacology* **2002**, *44*, 70–80. (m) Brier, T. J.; Mellor, I. R.; Tikhonov, D.; Neagoe, I.; Shao, Z.; Brierley, M. J.; Strømgaard, K.; Jaroszewski, J. W.; Krogsgaard-Larsen, P.; Usherwood, P. N. R. *Mol. Pharmacol.* **2003**, *64*, 954–964. (n) Jørgensen, M. R.; Olsen, C. A.; Mellor, I. R.; Usherwood, P. N. R.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *J. Med. Chem.* **2005**, *48*, 56–70.
10. For recent reviews, see: (a) Karigiannis, G.; Papaioannou, D. *Eur. J. Org. Chem.* **2000**, 1841–1863. (b) Kuksa, V.; Buchan, R.; Lin, P. K. T. *Synthesis* **2000**, 1189–1207.
11. (a) Renault, J.; Lebranchu, M.; Lecat, A.; Uriac, P. *Tetrahedron Lett.* **2001**, *42*, 6655–6658. (b) Manov, N.; Bienz, S. *Tetrahedron* **2001**, *57*, 7893–7898. (c) Manov, N.; Tzouros, M.; Chesnov, S.; Bigler, L.; Bienz, S. *Helv. Chim. Acta* **2002**, *85*, 2827–2846. (d) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2003**, *5*, 4183–4185. (e) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2004**, *6*, 1935–1938. (f) Picard, S.; Le Roch, M.; Renault, J.; Uriac, P. *Org. Lett.* **2004**, *6*, 4711–4714.
12. (a) Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett.* **2000**, *41*, 1095–1098. (b) Jönsson, D. *Tetrahedron Lett.* **2002**, *43*, 4793–4796. (c) Jönsson, D.; Unden, A. *Tetrahedron Lett.* **2002**, *43*, 3125–3128.
13. (a) Paikoff, S. J.; Wilson, T. E.; Cho, C. Y.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5653–5656. (b) Nefvi, A.; Ostresh, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931–934. (c) Ostresh, J. M.; Schoner, C. G.; Hamashin, V. T.; Nefvi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622–8623. (d) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Org. Lett.* **2001**, *3*, 2797–2799. (e) Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698–699. (f) Wang, F.; Manku, S.; Hall, D. G. *Org. Lett.* **2000**, *2*, 1581–1583. (g) Manku, S.; Laplante, C.; Kopac, D.; Chan, T.; Hall, D. G. *J. Org. Chem.* **2001**, *66*, 874–885. (h) Manku, S.; Wang, F.; Hall, D. G. *J. Comb. Chem.* **2003**, *5*, 379–391. (i) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *J. Org. Chem.* **2004**, *69*, 6149–6152.
14. For reviews, see: (a) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359. (b) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
15. Mitsunobu, O. *Synthesis* **1981**, 1–28.
16. (a) Hidai, Y.; Kan, T.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 4711–4714. (b) Hidai, Y.; Kan, T.; Fukuyama, T. *Chem. Pharm. Bull.* **2000**, *48*, 1570–1576.
17. (a) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 1338–1340. (b) Andersen, T. F.; Strømgaard, K. *Tetrahedron Lett.* **2004**, *45*, 7929–7933.
18. (a) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301–2302. (b) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1998**, *120*, 2690–2691.
19. (a) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243–1246. (b) Reichwein, J. F.; Wels, B.; Kruitjzer, J. A. W.; Versluis, C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3684–3687. (c) Brouwer, A. J.; Liskamp, R. M. J. *J. Org. Chem.* **2004**, *69*, 3662–3668. (d) Lin, X. D.; Dorr, H.; Nuss, J. M. *Tetrahedron Lett.* **2000**, *41*, 3309–3313.
20. Viirre, R. D.; Hudson, R. H. E. *Org. Lett.* **2001**, *3*, 3931–3934.
21. Dankwarth, S. M.; Smith, D. B.; Porco, J. A., Jr.; Nguyen, C. H. *Synlett* **1997**, 854–856.
22. (a) Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett.* **2000**, *41*, 1099–1102. (b) Hone, N. D.; Payne, L. J. *Tetrahedron Lett.* **2000**, *41*, 6149–6152. (c) Strømgaard, K.; Andersen, K.; Ruhland, T.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Synthesis* **2001**, 877–884. (d) Kromann, H.; Krikstolaityte, S.; Andersen, A. J.; Andersen, K.; Krogsgaard-Larsen, P.; Jaroszewski, J. W.; Egebjerg, J.; Strømgaard, K. *J. Med. Chem.* **2002**, *45*, 5745–5754. (e) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Synlett* **2004**, 473–476.
23. Hughes, D. L. In *Organic reactions*; Paquette, L. A., Ed.; Wiley: New York, 1992; Vol. 42, pp 335–656.
24. Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317–334.
25. (a) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539–542.
26. Olsen, C. A.; Jørgensen, M. R.; Witt, M.; Mellor, I. R.;

Usherwood, P. N. R.; Jaroszewski, J. W.; Franzyk, H. *Eur. J. Org. Chem.* **2003**, 3288–3299.
27. Hillier, M. C.; Desrosiers, J.-N.; Marcoux, J.-F.; Grabowski, J. *Org. Lett.* **2004**, *6*, 573–576.
28. Falck, J. R.; Lai, J.-Y.; Cho, S.-D.; Yu, J. *Tetrahedron Lett.* **1999**, *40*, 2903–2906.
29. Wacowich-Sgarbi, S. A.; Bundle, D. R. *J. Org. Chem.* **1999**, *64*, 9080–9089.
30. Barlos, P. *Liebigs Ann. Chem.* **1988**, 1079–1081.
31. Wellendorph, P.; Jaroszewski, J. W.; Hansen, S. H.; Franzyk, H. *Eur. J. Med. Chem.* **2003**, *38*, 117–122.
32. Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772.
33. Dandapani, S.; Curran, D. P. *Chem. Eur. J.* **2004**, *10*, 3130–3138.
34. Kita, Y.; Haruta, J.-I.; Yasuda, H.; Fukunaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697–2700.