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Photochemical Approach to the Preparation of Lariat Crown Ethers Containing Peptide Sidearms

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New types of lariat type crown ethers containing peptide sidearms were prepared by using a novel strategy employing single electron transfer (SET)-induced photocyclization reactions of α-silylether terminated phthalimides. Reactions of chiral substrates in this series produced diastereomeric mixtures of crown ether products as a result of the formation of new stereogenic center generation in the photocyclization process.

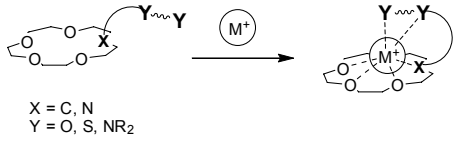
Key Words: Lariat crown ethers, Single electron transfer photochemistry, Peptide tethered macrocycles

Introduction

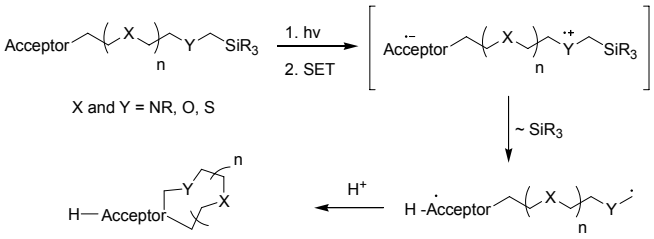
The number of members of the lariat type crown ether family has expanded since the time of the early pioneering studies by Gokel and coworkers. Interest in these systems is a consequence of their unique binding properties toward the variety of cation guests.[1-3] Carbon or nitrogen-pivot lariat crown ethers are typically comprised of one or more heteroatom containing side arms that are joined to a macrocyclic core structure, together providing the framework for capturing cations in the form of chelated structures (Scheme 1). Several recent efforts in this area have focused on development of new types of lariat crown ethers and their use as ion selective sensors,[1-4] and electrodes,[5] for chiral recognition,[6] and as ion transport carriers.[7]

Synthetic approaches for the preparation of lariat crown ether have traditionally depended on ground state thermal polar cyclization reactions that require low concentrations of reactants to minimize competing polymerization processes. In previous studies aimed at the preparation of diverse types of macrocyclic poly-ethers, -thioethers,[8] and -peptides,[10] bis-[9], and lariat[4c,4d,11a] crown ethers we have developed protocols for promoting efficient single electron transfer (SET)-promoted photocylization reactions[11] of acceptor-polydonor substrates that proceed *via* sequential SET-desilylation mechanistic pathways (Scheme 2).

In a recent effort, we have extended the scope of this chemistry to the synthesis of lariat type crown ethers containing



Scheme 1



Scheme 2

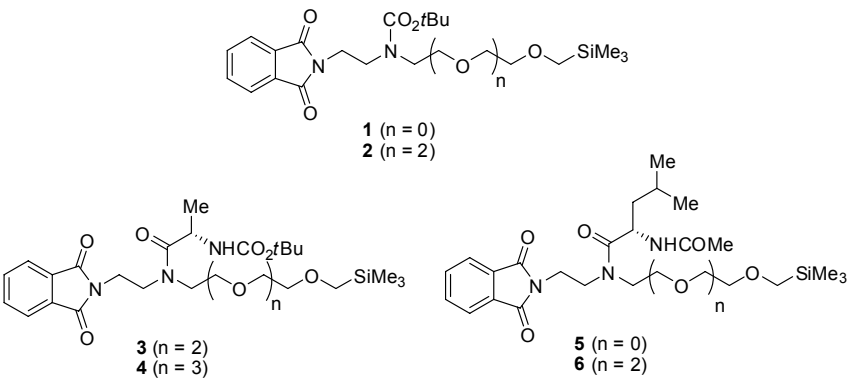


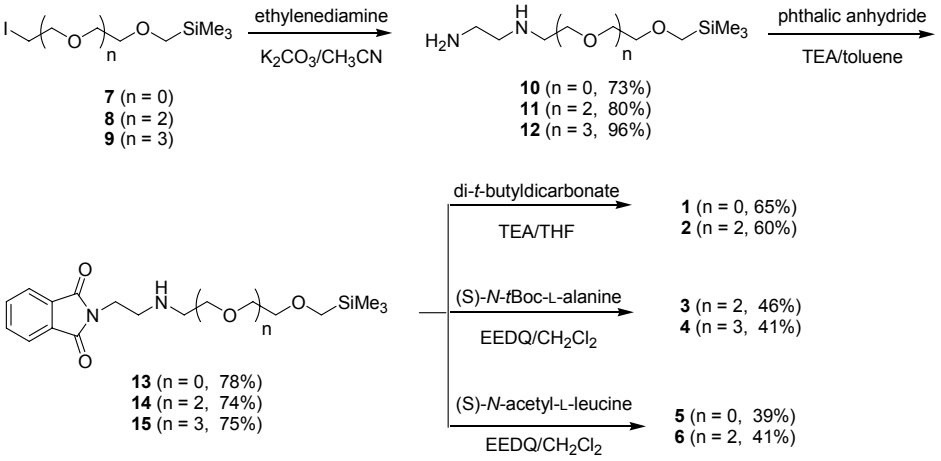
Figure 1. Substrates for SET promoted photocyclization reactions that produce peptide tethered lariat crown ethers.

peptide sidearms. For this purpose, α-trimethylsilylether terminated polyethers containing *N*-linked bulky peptide side chains and phthalimide acceptor groups (**1-6**, Figure 1) were prepared and used as reactants in SET-promoted photocyclization reactions that efficiently generate the lariat crown ether targets.

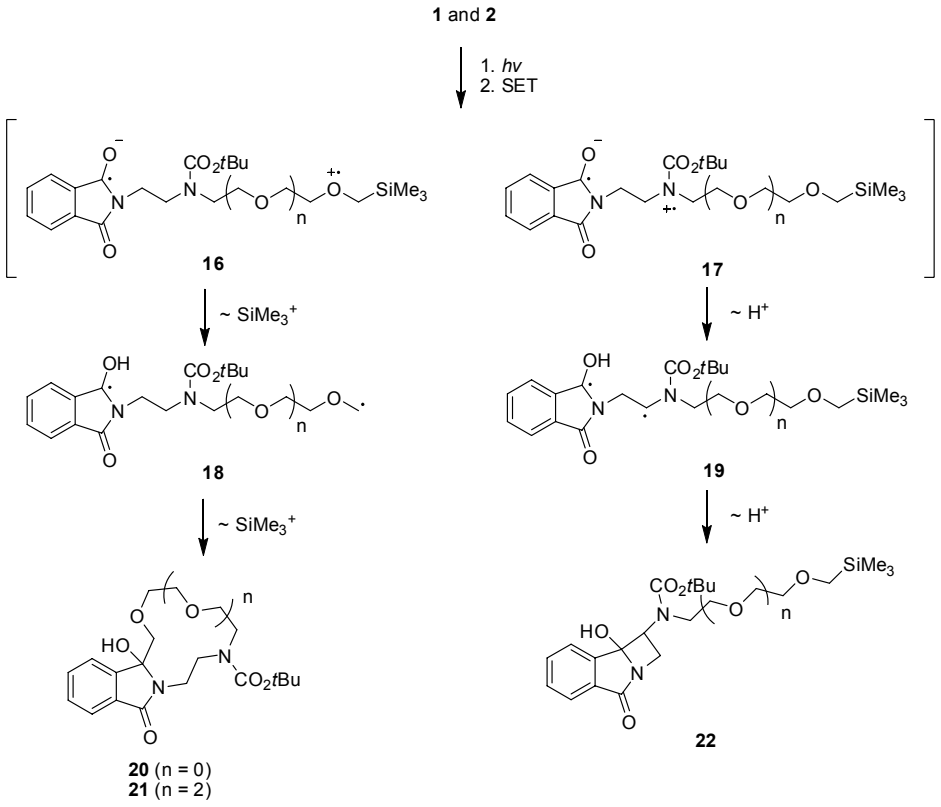
Results and Discussion

Preparation of Peptide Tethered Lariat Crown Ethers 20-21, 23-24, and 26-27. The preparation of photoreaction substrates **1-6** began with *N*-alkylation reactions between ethylenediamine and the known trimethylsilylmethyl-polyethyleneoxy iodides **7-9**[8] under basic conditions that generate the trimethylsilylmethyl-polyethyleneoxyaminoethylamines **10-12** (Scheme 3). Reactions of phthalic anhydride with amines **10-12** in the presence of triethylamine lead to formation of the corresponding phthalimide **13-15** in high yields (74 - 78%).

In contrast to the strategy employed in our previous approaches to the synthesis of lariat crown ethers,[4c,4d] the one used in the current effort relies on early introduction of peptide side chains through amide linkages to the amine centers in **13-15**. The selection of this protocol is based on the prediction that



Scheme 3



Scheme 4

Table 1. Photoreactions of phthalimide derivatives **1**-**6**

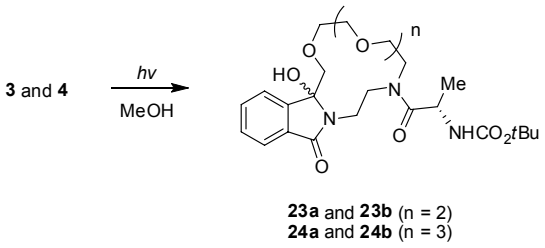
Reactant	Reaction condition	Conversion (%)	Product (%)*
1	2.5 h/MeOH	60	**20** (95)
2	3 h/MeOH	70	**21** (93)
3	3 h/MeOH	89	**23a** (23), **23b** (47)
4	3 h/MeOH	83	**24a** (27), **24b** (57)
5	1 h/MeOH	98	**26a** (19), **26b** (71)
6	2.5 h/MeOH	96	**27a** (12), **27b** (71)

*Yields are based on consumed reactants.

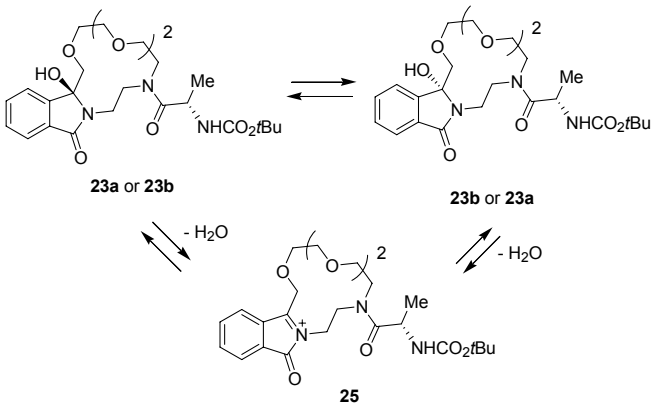
SET-promoted reactions of the substances that contain amide and α-silylether electron donor sites would undergo reactions selectively *via* sequential SET-desilyaltion pathways.[10,11] As a result, *N*-acylation reactions of amine **13**-**15** were carried out with di-*t*-butyldicarbonate, (S)-*N*-*t*Boc-L-alanine and (S)-*N*-acetyl-L-leucine to generate peptide linked phthalimides **1**-**6** in the yields ranging from 41 - 65% (Scheme 3). Owing to the existence of slow amide rotation, NMR spectra of phthalimides **1**-**6** show the existence of mixtures of rotatomers in ratios that range from 1:1.5-1:3.[12]

Irradiation (> 290 nm) of methanol solutions of phthalimides **1** and **2** leads to formation of the respective *N*-*t*Boc tethered lariat azacrown ethers **20** and **21** exclusively (Scheme 4 and Table 1). As expected,[4c,4d,8-11] cyclization reactions of **1** and **2** take place *via* a pathway involving sequential SET-desilylation from the terminal silylmethyl ether donor site. In these processes, long range SET to the phthalimide excited state produces the zwitterionic biradicals **16** that undergo methanol promoted desilylation to form biradicals **18**, which then cyclized by C-C bond formation to generate the crown ethers **20** and **21**. A noteworthy feature of these reactions is their remarkable chemoselectivity. Alternative routes initiated by intramolecular SET from the carbamate nitrogen donor to the excited state of the phthalimide acceptor, although thermodynamically feasible, do not result in the formation of cyclization products that would arise, for example, by intramolecular proton transfer in zwitterionic biradicals **17** followed by cyclization of the diradical **19**. This finding is consistent with the results of our earlier studies which demonstrated that processes of this type take place under Curtin-Hammet control in which the reactivity ($rate_{desilylation} > rate_{deprotonation}$) of the competitively formed zwitterionic biradicals governs the reaction pathway followed.

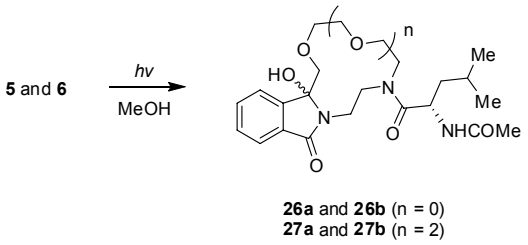
Based on the result coming from studies with **1** and **2**, it was expected that photocyclization reactions of more complex chiral-peptide linked, α-silylether terminated phthalimides would efficiently produce macrocyclic ethers that contain chiral side chains. Substances of this type could play a role in chiral recognition of cationic guests. In order to test this proposal, photoreactions of the respective *N*-*t*Boc-alanine derivatives **3** and **4** were explored. In each case, irradiation of methanol solution of the substrate leads to formation of separable mixtures (ca. 1:2) of the diastereomeric cyclization products **23a**-**23b** and **24a**-**24b** (Scheme 5 and Table 1). In reality, the product ratios are not as high as expected based on earlier findings which showed that epimerization reactions at the amidol centers *via*



Scheme 5



Scheme 6



Scheme 7

N-acyliminum cations **25** (for **23a** in Scheme 6) in macrocycles of this type do not take place rapidly under neutral conditions. If true in these cases, the lack of epimerization means that the ratios of the diastereomeric products are governed by the kinetics of biradical cyclization. Thus it appears that the chiral center in the peptide side chain has only a minimal effect on the diatereoselectivities of these photocyclization reactions. It should be noted that owing to the complexity of the spectroscopic data for and noncrystalline natures of **23a**-**23b** and **24a**-**24b**, the relative configurations at the two chiral centers in these substances could not be assigned.

In a similar manner, photocyclization reactions of the *N*-acetyl-leucine linked phthalimides **5** and **6** in methanol give rise to high yielding formation of the respective macrocyclic ethers containing chiral peptide side chains (Scheme 7 and Table 1). Interestingly, these processes yield *ca*. 1:6 ratios of the diastereomeric products that are higher than those associated with formation of **3** and **4**. This difference could be a consequence of the presence of the more bulky isobutyl group present in the leucine side chain, which might project a higher degree

of steric control over the key biradical cyclization reactions.

In recent preliminary studies, the ability of peptide-tethered crown ethers, **23a-24b**, to complex (S)-α-phenethylammonium perchlorate were explored by using of ^{1}H-NMR spectroscopy. However, in contrast to our expectations, the existence of mixtures of rotamers and the low binding affinity of the ammonium salt for crown ethers **23a-24b** caused difficulty in observing any significant changes in ^{1}H-NMR resonance of protons in the crown ethers and ammonium salt. Further studies are underway at the current time to develop sensitive methods to determine the binding affinities of (S)-α-phenethylammonium perchlorate and other ammonium salts to **23a-24b**.

In summary, the results of the study described above show that SET-promoted photocyclization processes can serve as key reactions in synthetic approaches for the preparation of chiral sidearm containing lariat-crown ethers. Moreover, the remarkably high degrees of chemoselectivity of the photocyclization processes give further evidence to the importance of Curtin-Hammet control in SET-promoted photoreactions of linked acceptor-polydonor systems.

Experimental

General Procedures. The chemical shifts of resonances in the ^{1}H- and ^{13}C-NMR (300 MHz) spectra (recorded on $CDCl_3$ solutions) are reported in parts per million relative to $CHCl_3$ peak (7.24 ppm) as an internal standard. High resolution (HRMS) mass spectra were obtained by using electron impact (EI) ionization unless otherwise noted. Preparative photochemical reactions were conducted in an apparatus consisting of a 450 W Hanovia medium vapor pressure mercury lamp surrounded by a Pyrex glass filter in a water-cooled quartz immersion well surrounded by the solution being irradiated. The solutions were purged with nitrogen before and during irradiation. The photolysates were concentrated *in vacuo*, giving residues, which were subjected to silica gel column chromatography. All starting materials used in the reactions described below, were derived from commercial sources. All new compounds are isolated as oils in purity (> 90% by NMR analysis) unless noted otherwise.

Preparation of ω-(Trimethylsilylmethoxy)polyethyleneoxyaminoethyl Amines 10 and 12. Independent solutions of ethylenediamine (8.7 g, 144 mmol for **7**; 8.7 g, 144 mmol for **8**; 8.4 g, 140 mmol for **9**) in CH_3CN (100 mL) containing potassium carbonate (6.0 g, 43 mmol for **7**; 6.0 g, 43 mmol for **8**, 5.78 g, 42 mmol for **9**) in 100 mL CH_3CN were stirred at 80 °C for 30 min. To each was added ω-(trimethylsilylmethoxy)polyethyleneoxy iodide **7** (3.7 g, 14 mmol), **8** (5.0 g, 14 mmol) and **9** (5.0 g, 14 mmol) and the resulting solutions were stirred at 110 °C for 15 h. Concentration of solutions *in vacuo* gave residues which were diluted with ether. The ether solutions were washed with water, dried with Na_2SO_4 and concentrated *in vacuo* to afford **10** (2.0 g, 73%), **11** (3.2 g, 80%) and **12** (3.9 g, 96%).

10: ^{1}H-NMR ($CDCl_3$) δ 0.01 (s, 9H), 1.47 (s, 3H), 2.66 (t, 2H, J = 6.0 Hz), 2.71-2.79 (m, 4H), 3.09 (s, 2H), 3.48 (t, 2H, J = 4.5 Hz); ^{13}C-NMR ($CDCl_3$) δ −3.5, 41.3, 48.5, 51.9, 64.6, 74.1; HRMS (FAB) *m/z* 191.1582 (M+1, $C_8H_{23}N_2OSi$ requires 191.1580).

11: ^{1}H-NMR ($CDCl_3$) δ −0.03 (s, 9H), 1.52 (s, 3H), 2.64 (t, 2H, J = 5.5 Hz), 2.76 (t, 4H, J = 5.0 Hz), 2.99 (s, 2H), 3.50-3.63 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ −3.5, 41.1, 48.6, 51.8, 64.8, 69.8, 70.1, 74.2; HRMS (FAB) *m/z* 279.2106 (M+1, $C_{12}H_{31}N_2O_3Si$ requires 279.2104).

12: ^{1}H-NMR ($CDCl_3$) δ −0.02 (s, 9H), 1.43 (s, 3H), 2.63 (t, 2H, J = 6.0 Hz), 2.75 (t, 4H, J = 4.4 Hz), 3.09 (s, 2H), 3.49-3.60 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ −3.4, 41.5, 48.8, 51.2, 65.0, 70.0, 70.2, 70.3, 74.3; HRMS (FAB) *m/z* 323.2360 (M+1, $C_{14}H_{35}N_2O_4Si$ requires 323.2366).

Preparation of *N*-[*N'*-((ω-Trimethylsilylmethoxy)polyethyleneoxy)amino]ethylphthalimides 13 and 15. To each of three solutions of toluene (50 mL) containing phthalimide (1.1 g, 7 mmol for **10**; 1.1 g, 7 mmol for **11**; 2.0 g, 14 mmol for **12**) and triethylamine (1.5 g, 14 mmol for **10**; 1.5 g, 14 mmol for **11**; 2.8 g, 28 mmol for **12**) were added amines **10** (1.4 g, 7 mmol), **11** (2.0 g, 7 mmol) and **12** (4.0 g, 14 mmol). The resulting solutions were stirred at 140 °C for 18 h with water removal using a Dean-Stark apparatus. Concentration of the solutions *in vacuo* gave residues which were diluted with CH_2Cl_2 and washed with 10% aq K_2CO_3. The organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to yield **13** (1.8 g, 78%), **14** (2.2 g, 74%) and **15** (4.2 g, 75%).

13: ^{1}H-NMR ($CDCl_3$) δ −0.06 (s, 9H), 2.73 (t, 2H, J = 4.5 Hz), 2.88 (t, 2H, J = 6.3 Hz), 3.03 (s, 2H), 3.41 (t, J = 5.4 Hz), 3.76 (t, 2H, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$) δ −3.2, 37.7, 47.5, 48.5, 65.0, 74.3, 123.1, 133.7, 132.1, 168.3; HRMS (FAB) *m/z* 321.1637 (M+1, $C_{16}H_{25}N_2O_3Si$ requires 321.1634).

14: ^{1}H-NMR ($CDCl_3$) δ −0.03 (s, 9H), 2.81 (t, 2H, J = 5.5 Hz), 2.90 (t, 2H, J = 6.6 Hz), 3.11 (s, 2H), 3.50-3.65 (m, 10H), 3.78 (t, 2H, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$) δ −3.2, 37.6, 47.5, 48.5, 65.3, 70.3, 70.5, 74.6, 123.1, 133.7, 132.1, 168.3; HRMS (FAB) *m/z* 409.2163 (M+1, $C_{20}H_{33}N_2O_5Si$ requires 409.2159).

15: ^{1}H-NMR ($CDCl_3$) δ 0.00 (s, 9H), 2.80 (t, 2H, J = 5.5 Hz), 2.90 (t, 2H, J = 6.6 Hz), 3.11 (s, 2H), 3.50-3.63 (m, 14H), 3.78 (t, 2H, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ −3.6, 37.0, 46.9, 47.9, 64.6, 69.7, 69.8, 69.9, 70.3, 69.9, 70.0, 74.0, 122.5, 133.3, 131.5, 167.6; HRMS (FAB) *m/z* 453.2418 (M+1, $C_{22}H_{37}N_2O_6Si$ requires 453.2421).

Preparation of *N*-[*N'*-*t*-Boc-*N''*-((ω-trimethylsilylmethoxy)polyethyleneoxy)amino]ethylphthalimides 1 and 2. To each of two solutions of THF (100 mL) containing *N*-aminoethylphthalimide (1.4 g, 5 mmol for **13**; 2.0 g, 5 mmol for **14**) and triethylamine (6.5 g, 6 mmol for **13** and **14**) was added di-*t*-butyldicarbonate (1.4 g, 6 mmol for **13** and **14**). The resulting solutions were stirred at 80 °C for 17 h and concentrated *in vacuo* giving residues, which were diluted with EtOAc and washed with 10% HCl solution. The organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to afford residues, which were subjected to column chromatography (1:3 EtOAc:*n*-hexane for **13**, 1:5 EtOAc:*n*-hexane for **14**) to yield **1** (1.2 g, 65%) and **2** (1.5 g, 60%).

1 (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ −0.02 (s, 9H), 1.19 (s, 9H), 3.05 and 3.07 (rotameric s, 2H), 3.29-3.56 (m, 6H), 3.78-3.83 (m, 2H), 7.61-7.69, 7.76-7.82 (rotameric m, 4H); ^{13}C-NMR ($CDCl_3$) δ −3.2, 28.0 and 28.4 (rotamer), 35.9 and 36.0 (rotamer), 45.7, 46.0, 46.4 and 47.1 (rotamer), 65.1 and 65.4 (rotamer), 74.0 and 74.4 (rotamer), 79.4 and 79.6 (rotamer), 123.0 and 123.2 (rotamer), 132.2 and 132.3 (rotamer), 133.5 and 139.0

(rotamer), 155.1 and 155.6 (rotamer), 168.0, 168.3; HRMS (FAB) *m/z* 421.2162 (M+1, $C_{21}H_{33}N_2O_5Si$ requires 421.2159).

2 (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 0.00 (s, 9H), 1.21 and 1.31 (rotameric s, 9H), 3.11 (s, 2H), 3.22-3.43, 3.54-3.59 (m, 14H), 3.79-3.85 (m, 2H), 7.62-7.70, 7.78-7.84 (rotameric m, 4H); ^{13}C-NMR ($CDCl_3$) δ −3.1, 28.1 and 28.2 (rotamer), 36.1 and 36.2 (rotamer), 38.0, 46.0 and 46.1 (rotamer), 46.3, 46.8, 47.3, 65.4, 69.8, 70.1, 70.4, 70.6, 74.7, 79.7, 123.1 and 123.2 (rotamer), 132.1 and 132.2 (rotamer), 133.6 and 133.9 (rotamer), 168.1 and 168.4 (rotamer); HRMS (EI) *m/z* 580.2600 (M^+, $C_{25}H_{40}N_2O_7Si$ requires 580.2605).

Preparation of *N*-[*N*′-((*t*-Boc)-L-alanyl)-*N*″-((ω-trimethylsilylmethoxy)polyethyleneoxy)amino]ethylphthalimides 3 and 4. To each of two solutions of CH_2Cl_2 (100 mL) containing *N*-aminoethylphthalimides (2.2 g, 5 mmol of **14**; 4.0 g, 10 mmol of **15**) were added 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (2.0 g, 8 mmol for **14**; 3.6 g, 15 mmol for **15**) and *t*Boc-L-alanine (1.5 g, 8 mmol for **14**; 2.8 g, 15 mmol for **15**). The solutions were stirred at 50 °C for 8 h and concentrated *in vacuo* giving residues, which were diluted with CH_2Cl_2 and washed with 10% HCl solution. The organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give residues, which were subjected to column chromatography (1:3 EtOAc:*n*-hexane) to yield **3** (1.4 g, 46%) and **4** (2.3 g, 41%).

3 (mixture of rotamer): ^{1}H-NMR ($CDCl_3$) δ −0.03, −0.01 (s, 9H), 1.08, 1.25 (d, 3H, *J* = 6.9Hz, *J* = 6.6 Hz), 1.29, 1.35 (s, 9H), 3.08, 3.10 (s, 2H), 3.31-3.38 (m, 2H), 3.43-3.64 (m, 12H), 3.76-3.94, 4.02-4.13 (m, 2H), 4.45-4.55, 4.59-4.64 (m, 1H), 5.20 (d, 1H, *J* = 5.3 Hz), 7.65-7.69, 7.77-7.82 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ −3.3, 18.7, 28.1, 28.1, 35.2, 36.0, 44.6, 45.9, 47.2, 65.2, 69.3, 70.1, 70.2, 70.3, 70.6, 74.5, 79.0, 123.0, 123.2, 133.7, 131.9, 154.7, 168.0, 173.8; HRMS (ES) *m/z* 580.3077 (M+1, $C_{28}H_{46}N_3O_8Si$ requires 580.3054).

4 (mixture of rotamer): ^{1}H-NMR ($CDCl_3$) δ 0.01 (s, 9H), 1.09, 1.27 (d, 3H, *J* = 6.6 Hz, *J* = 6.9 Hz), 1.30, 1.36 (s, 9H), 3.10, 3.11 (s, 2H), 3.33-3.39 (m, 2H), 3.49-3.70 (m, 16H), 3.82-3.90, 4.05-4.13 (m, 2H), 4.36-4.65 (m), 5.21 (d, 1H, *J* = 10.0 Hz), 7.66-7.69, 7.77-7.83 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ −3.4, 18.5, 28.0, 35.1, 44.4, 45.8, 46.1, 47.1, 65.0, 68.5, 69.1, 70.0, 70.1, 70.3, 70.4, 74.3, 78.9, 122.8, 123.1, 133.6, 131.8, 154.6, 167.7, 167.9, 173.6; HRMS (ES) *m/z* 646.3143 (M+Na, $C_{30}H_{49}N_3O_9NaSi$ requires 646.3136).

Preparation of *N*-[*N*′-Acetyl-L-leucinyl)-*N*″-((ω-trimethylsilylmethoxy)ethyleneoxy)amino]ethylphthalimides 5 and 6. To each of two solutions of CH_2Cl_2 (100 mL) containing *N*-aminoethylphthalimide (1.9 g, 6 mmol of **13**; 2.5 g, 6 mmol of **14**) were added EEDQ (2.0 g, 8 mmol for **13** and **14**) and *N*-acetyl-L-leucine (1.4 g, 8 mmol for **13** and **14**). The solutions were stirred at room temperature for 15 h and concentrated *in vacuo* giving residues, which were diluted with CH_2Cl_2 and washed with 10% HCl solution. The organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give residues, which were subjected to column chromatography (6:1 EtOAc:*n*-hexane) to yield **5** (1.1 g, 39%) and **6** (1.2 g, 41%).

5 (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ −0.02, −0.01 (s, 9H), 0.81 and 0.89, 0.87 and 0.98 (rotameric d of d, *J* = 6.6 Hz), 1.10-1.30 (m, 2H), 1.47-1.54 (m, 1H), 1.82 and 1.89 (rotameric s, 3H), 3.09 (s, 2H), 3.25-4.12 (m, 8H), 4.79-4.87 and 4.94-5.21 (rotameric m, 1H), 6.15 and 6.26 (rotameric s, 1H), 7.66-7.70, 7.78-7.81 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ −3.2 and −3.1 (rotamer), 21.5 and 21.8 (rotamer), 22.8 and 23.0 (rotamer), 23.4, 24.5 and 24.7 (rotamer), 35.7 and 36.1 (rotamer), 44.7, 47.3 and 47.4 (rotamer), 47.5, 65.5 and 65.9 (rotamer), 73.3 and 74.0 (rotamer), 123.2 and 123.5 (rotamer), 131.9 and 132.1 (rotamer), 133.8 and 134.0 (rotamer), 167.9 and 168.2 (rotamer), 169.7, 173.3; HRMS (FAB) *m/z* 476.2579 (M+1), $C_{24}H_{38}N_3O_5Si$ requires 476.2581).

6 (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ −0.01, 0.00 (rotameric s, 9H), 0.81 and 0.89, 0.88 and 0.99 (rotameric d of d, *J* = 6.6 Hz), 1.10-1.30 (m, 2H), 1.46-1.56 (m, 1H), 1.83 and 1.88 (rotameric s, 3H), 3.09 and 3.10 (rotameric s, 2H), 3.34-4.09 (m, 14H), 4.81-4.89 and 4.92-5.04 (rotameric m, 1H), 6.03 and 6.15 (rotameric d, 1H, *J* = 9 Hz), 7.66-7.70, 7.76-7.80 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ -3.1, 21.6 and 21.7 (rotamer), 22.6 and 23.0 (rotamer), 23.4, 24.5 and 24.7 (rotamer), 29.6 and 30.0 (rotamer), 35.3 (rotamer), 42.0, 42.8 (rotamer), 44.8, 47.3 and 47.5 (rotamer), 65.4, 69.1 and 69.6 (rotamer), 70.3 and 70.5 (rotamer), 70.8, 74.7, 123.2 and 123.5 (rotamer), 131.9 and 132.1 (rotamer), 133.8 and 134.0 (rotamer), 167.9 and 168.2 (rotamer), 169.7, 173.2 and 173.5 (rotamer); HRMS (FAB) *m/z* 564.3107 (M+1, $C_{28}H_{46}N_3O_7Si$ requires 564.3105).

Irradiation of *N*-[*N*′-*t*-Boc-*N*″-((ω-trimethylsilylmethoxy)polyethyleneoxy)amino]ethylphthalimides 1 and 2. Formation of crown ethers 20 and 21. Each of two nitrogen pursed solutions of MeOH (150 mL) containing phthalimide (240 mg, 0.6 mmol of **1**; 500 mg, 1.0 mmol of **2**) was irradiated with Pyrex glass filtered light (2.5 h for **1**; 3 h for **2**). Concentration of each solution *in vacuo* gave a residue, which was subjected to column chromatography (5:2 EtOAc:*n*-hexane for **1**; 8:1 for **2**) to yield **20** (60% conversion, 113 mg, 95%) and of **21** (70% conversion, 283 mg, 93%).

20 (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 1.29 and 1.43 (rotameric s, 9H), 2.67-2.75, 2.94-3.08, 3.20-3.29, 3.38-3.78 (rotameric m, 8H), 3.64 and 3.94, 3.70 and 4.16 (rotameric two d, 2H, *J* = 10.2 Hz, 10.8 Hz), 4.70 and 4.84 (rotameric s, 1H), 7.37-7.56 (rotameric m, 4H); ^{13}C-NMR ($CDCl_3$) δ 28.2 and 28.4 (rotamer), 29.6, 39.2 and 39.4 (rotamer), 49.6, 50.9, 52.4, 53.7, 67.9, 69.2, 73.5, 75.5, 80.1and 80.2 (rotamer), 89.1 and 89.4 (rotamer), 121.7 and 121.9 (rotamer), 123.0 (rotamer), 129.6 and 129.8 (rotamer), 131.1 and 131.3 (rotamer), 132.3, 145.1 and 145.7 (rotamer), 155.0 and 155.1 (rotamer), 168.2 and 168.7 (rotamer); HRMS (FAB) *m/z* 349.1761 (M+1, $C_{18}H_{25}N_2O_5$ requires 349.1763).

21 (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 1.44 and 1.48 (rotameric s, 9H), 3.24-3.88 (m, 16H), 3.83 and 3.99 (two d, 2H, *J* = 10.5 Hz), 4.89 (rotameric s, 1H), 7.40-7.60 (m, 3H), 7.71 (d, 1H, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 28.4, 38.1, 48.1, 49.6, 70.2, 70.5, 71.6, 75.4, 80.0, 89.1, 122.6, 123.0, 129.5, 131.7, 131.8, 145.6, 155.8, 167.4; HRMS (EI) *m/z* 436.2208 (M^+, $C_{22}H_{32}N_2O_7$ requires 436.2210).

Irradiation of *N*-[*N*′-((*t*-Boc)-L-alanyl)-*N*″-((ω-trimethylsilylmethoxy)polyethyleneoxy)amino]ethylphthalimides 3 and 4. Formation of crown ether 23a and 23b, and 24a and 24b. Each of two nitrogen purged solutions of MeOH (160 mL) containing phthalimides (0.5 g, 0.8 mmol of **3**; 0.5 g, 0.8 mmol of **4**) was irradiated with Pyrex glass filtered light (3 h for **3** and

4). Concentration of each solution *in vacuo* gave a residue, which was subjected to column chromatography (EtOAc) to afford diastereomers **23a** (conversion 89%, 90 mg, 23%) and **23b** (180 mg, 47%), and **24a** (conversion 83%, 100 mg, 27%) and **24b** (210 mg, 57%).

23a (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 7.2 Hz), 1.37, 1.41 (s, 9H), 3.25-3.96, (m, 16H), 3.80 and 4.11 (two d, 2H, J = 9.6 Hz), 4.71-4.80, 4.91-5.00, (m, 1H), 5.30, 5.60 (d, 1H, J = 8.4 Hz), 7.41-7.47, 7.50-7.57, 7.70-7.74 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 19.5, 28.4, 38.7, 46.8, 47.8, 48.8, 49.2, 49.7, 68.9, 70.3, 70.5, 70.6, 71.2, 74.9, 75.2, 79.3, 88.9, 89.0, 121.8, 122.3, 123.2, 129.8, 131.8, 132.0, 131.6, 145.1, 145.4, 154.9, 155.1, 167.8, 173.9, 174.7; HRMS (ES) *m/z* 530.2486 (M+Na, $C_{25}H_{37}N_3O_8Na$ requires 530.2478).

23b (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, J = 6.6 Hz), 1.34, 1.40 (s, 9H), 3.24-3.89 (m, 16H), 3.85 and 4.05 (two d, 2H, J = 9.6 Hz), 4.64-4.78, 4.93-4.99 (m, 1H), 5.25, 5.59 (d, 1H, J = 8.1Hz), 7.41-7.47, 7.51-7.55, 7.71-7.73 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 19.4, 28.3, 38.5, 46.4, 46.6, 47.7, 48.2, 48.8, 49.0, 49.5, 69.2, 69.6, 69.9, 70.2, 70.3, 70.5, 70.8, 70.9, 73.8, 74.0, 79.5, 79.8, 88.9, 89.0, 121.8, 121.9, 123.1, 129.5, 131.7, 145.5, 145.6, 154.9, 155.1, 167.8, 167.8, 173.7, 173.8; HRMS (ES) *m/z* 530.2474 (M+Na, $C_{25}H_{37}N_3O_8Na$ requires 530.2478).

24a (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 1.09, 1.27 (d, 3H, J = 6.6 Hz), 1.15, 1.36 (s, 9H), 3.35-3.79 (m, 20H), 3.70, 4.05 (two d, 2H, J = 10.5 Hz), 4.30-4.45, 4.46-4.56 (m, 1H), 5.25, 5.32 (d, 1H, J = 9.1 Hz), 7.39-7.44, 7.51-7.56, 7.63-7.71 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 18.9, 19.6, 28.0, 28.3, 37.9, 44.7, 45.6, 46.4, 47.3, 47.4, 48.5, 69.9, 70.2, 70.3, 70.4, 70.6, 71.0, 73.7, 74.3, 79.3, 79.8, 89.3, 89.6, 121.8, 122.7, 123.1, 129.3, 129.5, 131.9, 132.0, 131.5, 145.3, 146.1, 154.8, 155.4, 167.6, 168.1, 173.1, 174.1; HRMS (ES) *m/z* 574.2750 (M+Na, $C_{27}H_{41}N_3O_9Na$ requires 574.2741).

24b (mixture of rotamers): ^{1}H-NMR ($CDCl_3$) δ 1.21 (d, 3H, J = 7.2Hz), 1.25, 1.39 (s, 9H), 3.34-3.80 (m, 20H), 3.81 and 3.98 (two d, 2H, J = 9.9Hz), 4.26-4.34, 4.46-4.57 (m, 1H), 5.13, 5.29 (d, 1H, J = 7.9 Hz), 7.39-7.45, 7.50-7.53, 7.67-7.72 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 18.8, 28.2, 28.3, 37.8, 46.5, 47.3, 47.9, 48.2, 48.7, 69.8, 70.0, 70.4, 70.5, 71.0, 71.1, 71.3, 73.4, 79.2, 79.7, 89.4, 89.5, 121.8, 122.7, 122.8, 129.3, 131.8, 131.4, 145.6, 146.0, 154.8, 155.3, 167.8, 167.4, 173.2, 173.7; HRMS (ES) *m/z* 574.2741 (M+Na, $C_{27}H_{41}N_3O_9Na$ requires 574.2741).

Irradiation of *N*-[*N'*-acetyl-L-leucinyl)-*N''*-((ω-trimethylsilylmethoxy)ethyleneoxy)amino]ethylphthalimides 5 and 6. Formation of crown ether 26a and 26b, and 27a and 27b. Each of two nitrogen purged solutions of MeOH (160 mL) containing phthalimides (0.4 g, 0.6 mmol of **5**; 0.2 g, 0.4 mmol of **6**) was irradiated with Pyrex glass filtered light (1 h for **5**; 2.5 h for **6**). Concentration of each solution *in vacuo* gave a residue, which was subjected to column chromatography (6:1 EtOAc:*n*-hexane for **5**; 8:1 for **6**) to afford inseparable mixtures of diastereomers **26a** (conversion 98%, 45 mg, 19%) and **26b** (168 mg, 71%), and **27a** (conversion 96%, 20 mg, 12%) and **27b** (122 mg, 74%).

26a+26b (1:4 diasteromeric mixture): ^{1}H-NMR ($CDCl_3$) δ 0.89, 0.91, 0.94, 0.95, 1.08 (diastereomeric d, 6H, J = 6.6 Hz), 1.23-1.33 (m, 1H), 1.48-1.70 (m, 2H), 1.76, 2.02 and 2.04 (s, 3H), 2.91-2.99, 3.08-3.36, 3.48-4.00, 4.04-4.28 (m, 8H), 4.06, 4.16, 4.26 (diastereomeric two d, 2H, J = 9.6 Hz), 4.61-4.90 (m, 1H), 5.75-5.79, 6.08-6.19 (m, 1H), 7.43-7.60, 7.67-7.70, 7.74-7.77 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 21.8, 22.4, 22.7, 22.9 (diastereomer), 24.0, 24.1, (diastereomer) 25.6, 25.7, 25.8 (diastereomer), 39.8, 40.8, 41.2, 41.5, 41.8, 42.4 (diastereomer), 49.0, 49.5, 49.7 (diastereomer), 50.7, 51.4, 53.5, 51.4, 53.5, 54.2, 54.7, 55.4, 55.8 (diastereomer), 69.0, 69.5, 70.0, 70.2 (diastereomer), 74.3, 75.3, 76.5 (diastereomer), 89.9, 90.1, 90.6 (diastereomer), 123.2, 123.3, 123.4, 123.6 (diastereomer), 130.2, 130.3 (diastereomer), 132.8, 132.9, 133.0, 133.3, 133.4, 133.5, (diastereomer) 147.4, 147.7, 147.8 (diastereomer), 168.5, 169.0, 170.3, 170.9, 171.4 (diastereomer), 174.7, 174.8, 174.9 (diastereomer); HRMS (FAB) *m/z* 404.2188 (M+1, $C_{21}H_{30}N_3O_5$ requires 404.2185).

27a+27b (1:6 diasteromeric mixture): ^{1}H-NMR ($CDCl_3$) δ 0.84-0.90 (m, 3H), 0.94, 0.95, 1.02 (diastereomeric d, 3H, J = 6.3 Hz), 1.35-1.71 (m, 3H), 1.93, 1.95, 1.97, 1.98 (diasteromeric s, 3H), 3.15-3.24, 3.37-4.06, 4.12-4.22 (m, 16H), 3.82 and 3.93, 3.70 and 4.04 (diasteromeric two d, 2H, J = 10.2 Hz, 9.6 Hz), 5.00-5.07, 5.10-5.20 (m, 1H), 5.92, 6.08 (s, 1H) 6.19, 6.31-6.40 (m, 1H), 7.04-7.57, 7.69-7.73 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 21.6, 22.0, 22.1 (diasteromer), 23.2, 23.3, 23.5 (diastereomer), 24.6, 24.7, 24.9 (diastereomer), 38.2, 38.4 (diastereomer), 42.4, 42.9 (diastereomer), 47.8, 48.2, 48.8, 49.0, 49.7 (diastereomer), 69.2, 69.3, 70.3, 70.4, 70.9, 71.1 (diastereomer), 74.5, 74.8 (diastereomer), 78.2, 89.0, 89.3 (diastereomer), 121.7, 121.9, 122.1 (diastereomer), 122.8, 123.1, 123.2 (diastereomer), 129.5, 131.6, 131.8, 132.0 (diastereomer), 145.3, 145.7 (diastereomer), 167.6, 168.5, 169.3, 169.9, 170.4 (diastereomer), 173.0, 174.1; HRMS (FAB) *m/z* 492.2707 (M+1, $C_{25}H_{38}N_3O_7$ requires 492.2710).

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