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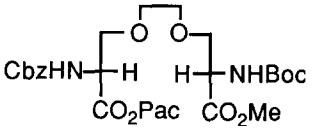
SYNTHESIS OF AN ETHYLENE GLYCOL CROSS-LINKED AMINO ACID[1]

Mengfei Ho*, Weiheng Wang, Maria Douvlos, Thuha Pham, Timothy Klock
Department of Medicinal Chemistry, School of Pharmacy
State University of New York at Buffalo, Buffalo, NY 14260

Abstract: *Synthesis of an ethylene glycol-containing amino acid, (2R,9S)-N^2-Cbz-N^9-Boc-2,9-diamino-4,7-dioxadecanedioic acid 1-phenacyl 10-methyl diester* ***1****, was studied through direct alkylation of N-Boc-L-serine and through BF_3-catalyzed ring opening of N-acylaziridinecarboxylates.*

In our modeling studies on conformationally constrained peptide analogs, we found that the ethylene glycol unit could provide certain structural features currently unavailable in peptide models containing disulfide cross-links. The favorable gauche placement for the *O-C-C-O* bond and anti placement for the *C-O-C-C* bond in oligoethylene glycols and crown ethers[2,3] would allow the ethylene glycol unit to serve as a covalent link which is longer than a disulfide bond, but which is less flexible and more hydrophilic than other carbon chain linkers. In order to test the effectiveness of such a cross-link in stabilizing peptide conformations, we have designed an ethylene glycol cross-linked amino acid **1**. We have included four different protecting groups in this design to allow the possibility of manipulating two chiral centers when this cross-linked amino acid is incorporated into peptide analogs. These stereochemical and multifunctional considerations make the synthesis of **1** quite challenging. We report here our studies toward the synthesis of **1**.



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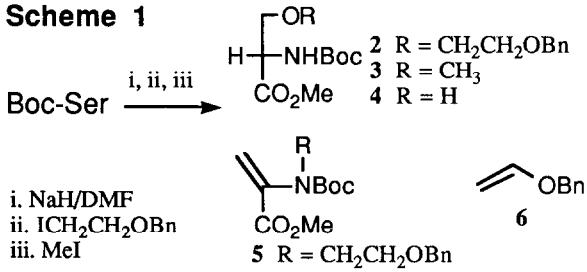
Ether-containing amino acids such as 4-oxalysine[4] and 5-oxahomolysine[5] have been prepared from alkylation of phthalimidomalonate. This method is incompatible with our objective to incorporate an ether-cross-linked amino acid into peptide analogs through conventional peptide synthesis, wherein the integrity of chiral centers and the application of orthogonally labile protecting groups are frequently emphasized. Direct *O*-alkylation of *N*-Boc-serine dianion prepared with NaH in DMF has been reported for the preparation of *N*-Boc-*O*-benzyl-L-serine (57%).[6] The alkylation appeared to be specific for ether formation and virtually no racemization was detected in the product. This procedure has also been reported for the preparation of *O*-allylserine derivatives.[7] We have similarly found that *O*-

methylserine derivatives can easily be obtained with methyl iodide. Even though we observed no *O*-alkylation products with ethylene dibromide or ethylene diiodide under similar conditions, we were, however, able to obtain *N*-Boc-*O*-(2-benzyloxyethyl)-L-serine through direct alkylation with 2-benzyloxyethyl mesylate (15%) at room temperature.[8]

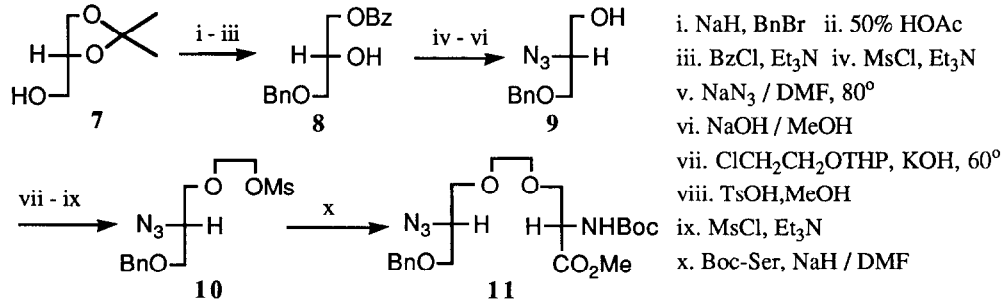
When benzyloxyethyl iodide (BEI) was used for *O*-alkylation (19 hr, r.t.) and was followed by methyl iodide workup, the ester of the desired product **2** (21.5%), the ester of recovered *N*-Boc-L-serine **4** (26%), methyl ether **3** (1.5%), β-elimination products **5** (< 2%) and **6** (yield undetermined) were obtained (Scheme 1).[9] The occurrence of **3** indicated that the alkylating agent was prematurely consumed. Further investigation showed that the yield of the alkylation product **2** could be increased substantially (up to 41%) with excess NaH and BEI (See table below). It is important to note that BEI apparently caused very little esterification even when 3 equivalents were used.

Scheme 1



No.	NaH eq.	BEI eq.	**2** (% Yield)
1	3.0	3.0	41
2	3.9	2.3	35
3	2.2	2.2	26
4	2.2	1.0	21
5	2.0	1.0	18

Scheme 2

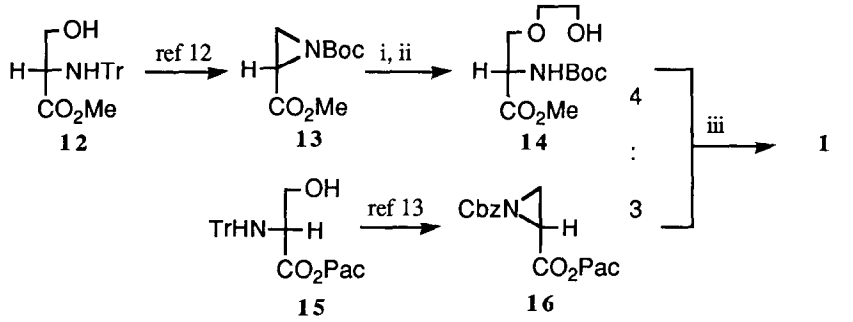


Attempts to carry out the synthesis of **1** via direct alkylation of Boc-serine is outlined in Scheme 2. Mesylate **10** was prepared from chirogenic glycerol acetonide through the series of transformations shown, including an S_N2 step to introduce the nitrogen at the α-position. Most of these steps can be carried out in excellent yield (close to or greater than 90%) with step vii (61%) as the only exception. This critical step was carried out by heating alcohol **9** with $ClCH_2CH_2OTHP$ (2.5 eq.) and KOH (2.5 eq.) at 60° (**Caution:** Heating a mixture of **9** and KOH had resulted in an explosion in our laboratory). Ethylene glycol ether **11** was

obtained from **10** in 22% yield with two-fold excess of Boc-serine dianion and in 12% yield with one equivalent of the dianion. Longer reaction times (up to 3 days) with one equivalent of Boc-serine dianion did not improve the yield. Although most unreacted **10** can be recovered and the efficiency of this cross-linking alkylation may be improved with a large excess of Boc-serine dianion, the lengthy synthesis of **11** made this approach less appealing. Thus, we turned to a more practical alternative.

Nakajima et al.[10] have reported a convenient synthesis of optically active β-alkoxy-α-amino acids via Lewis acid catalyzed ring opening of 2-aziridinecarboxylates (Azy). *N*-Acyl-Azy derivatives have also been shown to undergo ring opening by attack with other nucleophiles such as carboxylates, thiols and enolates.[11] Lanthionine and other thioether cross-linked amino acid derivatives have also been prepared through this route.[14] Although >90% yields could be achieved for alcoholysis of *N*-acyl-Azy derivatives using excess alcohol as co-solvent,[10] the synthesis of thioether cross-linked amino acids using only an equivalent of thiol nucleophile gave poor yields (up to 37%) and required unusually long reaction times (up to 5 days).[14] Despite the apparent need for a large excess of alcohol, we were able to obtain **1** from a 4:3 ratio of **14** and **16** in 64% yield.

Scheme 3



i. $BnOCH_2CH_2OH$ / $BF_3{\cdot}Et_2O$ ii. Pd-C / H_2 iii. $BF_3{\cdot}Et_2O$

As outlined in Scheme 3, Boc-L-Azy-OMe **13** and Cbz-D-Azy-OPac **15** were prepared from L-serine and D-serine via their N-trityl derivatives following published procedures.[12,13] Alcoholysis of **13** by 2-benzyloxyethanol gave **2** and subsequent hydrogenolysis yielded **14**. The final coupling step was carried out as follows:

To a stirred solution of alcohol **14** (4.4 mmol) and aziridinecarboxylate **16** (3.3 mmol) in 5 mL of dry chloroform (distilled over P_2O_5) under N_2 at r.t., 0.5 mL of 10% BF_3 etherate (prepared in dry chloroform) was added. Three hours later, the reaction mixture was loaded on a silica gel column and purified by chromatography. Ethylene glycol cross-linked product (*2R,9S*)-N^2-Cbz-N^9-Boc-2,9-diamino-4,7-dioxadecanedioic acid 1-phenacyl 10-methyl diester **1** was obtained as an oil (1.28 g, 2.12 mmol; 64%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.40(9H, s), 3.40(4H, s), 3.68 (3H, s), 3.7-4.0(4H, m), 4.42(1H, m), 4.68(1H, m),

5.15(2H, s), 5.20, 5.23(2H, ABq, J=16.8 Hz), 5.64(1H, d, J=8.4 Hz), 6.0(1H, d, J=7.8 Hz), 7.35(5H, s) 7.4-7.6(3H, m), 7.92(2H, m); IR ν_{max}(neat) 965, 1062, 1167, 1367, 1450, 1511, 1709, 1749 2850-3050, 3300-3400 cm^{-1}; $[\alpha]^D$ = +4.9 (c=7; EtOAc).[15]

In summary, direct alkylation of Boc-serine dianion with excess alkylating agent is an effective method for introducing an ethylene glycol unit into an amino acid side chain, but is less satisfactory for cross-linking two amino acid moieties. Lewis acid catalyzed ring opening of *N*-acyl aziridinecarboxylates with ethylene glycol-containing amino acid derivatives is a more practical method for preparation of ethylene-glycol cross-linked amino acids.

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References and Notes

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8. The yield was based on the free acid purified by flash chromatography on silica gel (CH_2Cl_2:MeOH/4:1). If the reaction mixture was treated with methyl iodide before workup, the ester product was obtained after chromatography (EtOAc:Hexanes/1:4) in 20% yield.
9. Methyl *N* - Boc-*N* - (2-Benzyloxyethyl)-2-aminoacrylate **5**: ^1H NMR ($CDCl_3$) δ 1.41(9H, s), 3.67 (4H, s), 3.75(3H, s), 4.52(2H, s), 5.63(1H, s), 5.94(1H, s), 7.32(5H, s). Benzyl vinyl ether **6**: ^1H NMR ($CDCl_3$) δ 4.03(1H, dd, J=6.7 Hz, 2.0 Hz), 4.25(1H, dd, J=14.1 Hz, 2.0 Hz), 4.69(2H, s), 6.50(1H, dd, J=14.1 Hz, 6.7 Hz), 7.27(5H, s).
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15. Compound **1** is not distinguishable from its (*2S,9S*)-diastereomer by TLC or NMR. However, derivatives of D- and L-Azy-OMe with Gerlach reagent (Gerlach, H.; Zagalak, B. *J.C.S. Chem. Comm.* **1973**, 274.) showed that in our preparations both were enatiomerically pure within the limit of 400 MHz NMR instrument.

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