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Synthesis of a Laterally Branched Polyamine from α-Methylene-γ-butyrolactone

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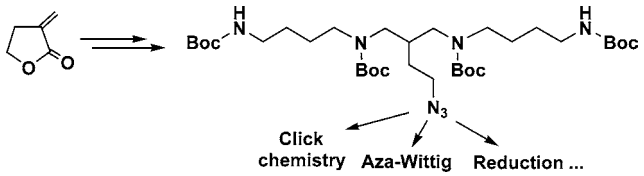
ABSTRACT



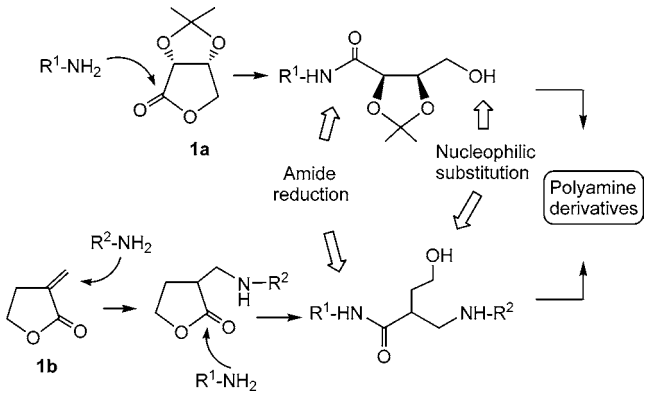
A polyamine derivative was prepared from α-methylene-γ-butyrolactone. This method used Michael addition and lactone aminolysis followed by the nucleophilic substitution of the hydroxyl group by an azido group. The coupling of a lipophilic alkyne led to a polyamine that will be probed as a gene transfer agent.

Synthetic polyamines, whose access through either classical or solid-phase chemistry has been widely described, are very diverse structures with various biological properties.[1] In a recent paper,[2] we have proposed a new type of access to these compounds from an erythronolactone **1a**. The synthesis involved the aminolysis of the lactone ring leading to a hydroxyamide whose amide reduction and hydroxyl group nucleophilic displacement resulted in a dihydroxylated polyamine (Scheme 1).

In accordance with this idea, we considered the synthesis of a laterally branched polyamine from α-methylene-γ-butyrolactone **1b** as described in Scheme 1. In addition to the aminolysis and nucleophilic substitution, this method would take advantage of Michael addition, allowing for a wide range of chemical diversity.

In this work, this type of synthesis was used to make a symmetrical tetramine bearing a lateral alkyl chain functionalized by an azido group. This versatile group is suitable for click chemistry and provides a compound designed for its interest as a transfer agent in gene therapy.

Scheme 1



The synthesis started with the reaction of the α-methylene-γ-butyrolactone with 1.1 equiv of mono-Boc-putrescine

(1) (a) Karigiannis, G.; Papaioannou, D. *Eur. J. Org. Chem.* **2000**, *10*, 1841−1863. (b) Kuksa, V.; Buchan, R. *Synthesis* **2000**, *9*, 1189−1207 and references therein.

(2) Le Roch, M.; Renault, J.; Penlaë, K.; Uriac, P. *Tetrahedron Lett.* **2003**, *44*, 3451−3453.

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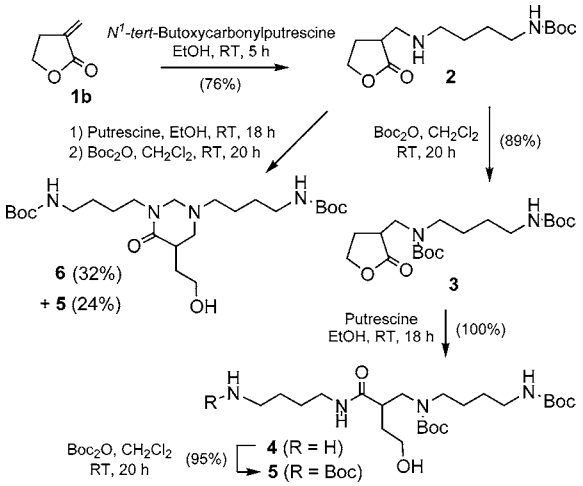
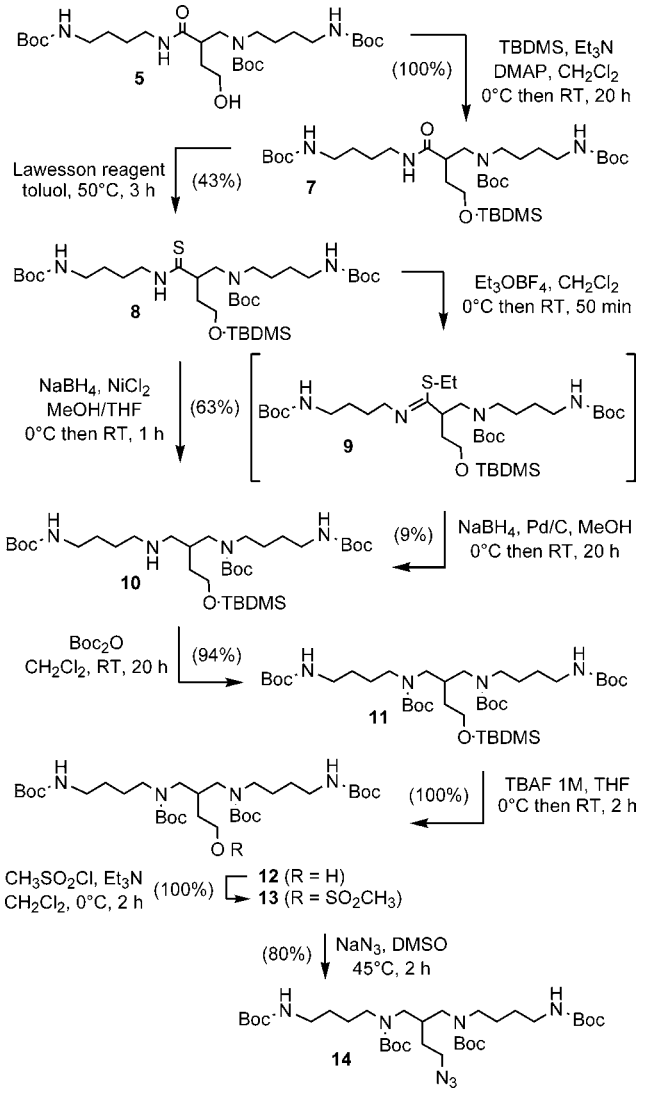
Scheme 2



Scheme 3



(Scheme 2), which was used to avoid 1,4-diamide formation and to facilitate purification.

Our main concern during this first step referred to the possible priority of one of the reactions: aminolysis on one hand, Michael addition to the exocyclic double bond on the other hand. According to the litterature,[3] the use of 1.1 equiv of monoprotected diamine resulted in a unique Michael addition leading to **2**. Even with an excess of 5 equiv, we observed the priority of this reaction.

The second step of the synthesis aimed at the aminolysis of the aminolactone **2**. As previously reported,[2,4] only the use of a large excess of putrescine (10 equiv) at room temperature was successful. After removal of excess diamine, the reaction mixture was Boc protected. Its purification revealed an unexpected result: in addition to a poor yield of hydroxyamide **5** (24%), we observed formation of a tetrahydropyrimidinone derivative **6**.[5] To avoid this unwanted formation, we decided to protect the amino group of **2** leading to **3**. Its treatment with an excess of putrescine followed by introduction of a terminal Boc protective group led to the polyamine precursor **5** in good yield (Scheme 2). It is noteworthy that, when submitted to an acidic medium, the compound **5** tended to give rise to the lactone **3** and putrescine, attesting to the reversibility of the lactone opening.

The amide reduction of compound **5** was then carried out (Scheme 3). The main procedures for this purpose classically consist of the use of lithium aluminum hydride ($LiAlH_4$) or borane. In a previous work, we had used $LiAlH_4$ to reduce a similar amide to an amine.[2]

We started our attempts using this reagent (2.5 equiv) at room temperature for 16 h in anhydrous diethyl oxide. Unfortunately, these conditions left the amide group unchanged. To prevent any harmful influence of the hydroxyl group on $LiAlH_4$, we protected **5** using *tert*-butyldimethylsilyl chloride,[6] but a second reduction attempt under similar conditions remained ineffective.

The borane−tetrahydrofuran complex[7] (BH_3−THF, 3.5 equiv in THF) was then employed under various conditions but remained unsuccessful from either compound **5** or **7**. Ineffective amide reduction was observed (16% from **7**) even after increasing the reducing agent to 20 equiv.

Because of these various problems, we decided to convert the amide group into the corresponding thioamide and to proceed with a desulfuration (Scheme 3). The compound **7** was submitted to Lawesson's reagent under classical conditions,[8] leading to **8** in moderate yield. From the latter, a reaction with triethyloxonium tetrafluoroborate (Et_3OBF_4) followed by a reduction with sodium borohydride[9] ($NaBH_4$) led to the expected compound **10** but with a poor yield (9%).

(3) (a) Matsuda, H.; Kageura, T.; Inoue, Y.; Morikawa, T.; Yoshikawa, M. *Tetrahedron* **2000**, *56*, 7763−7777. (b) Lawrence, N. J.; McGown, A. T.; Nduka, J.; Hadfield, J. A.; Pritchard, R. G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 429−431.

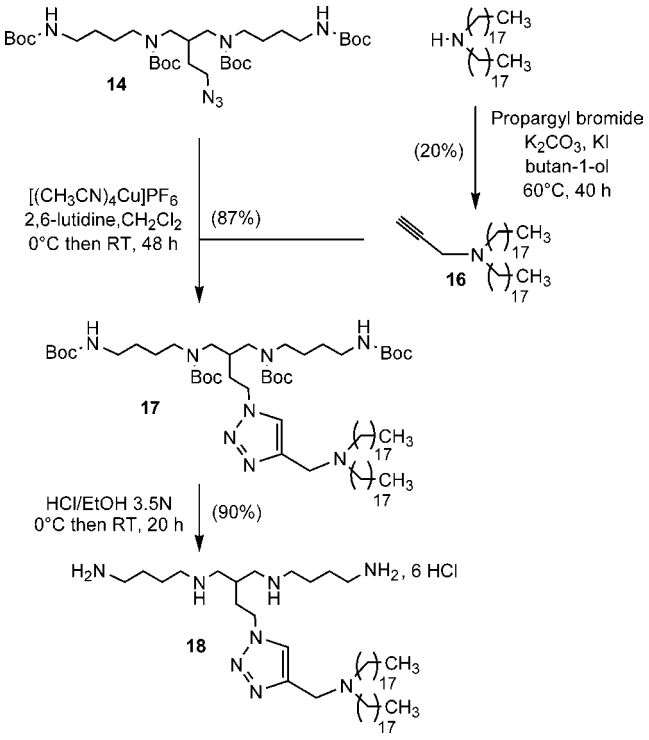
(4) (a) Huang, P. Q.; Zheng, X.; Deng, X. M. *Tetrahedron Lett.* **2001**, *42*, 9039−9041. (b) Meyers, C. L. F.; Borch, R. F. *Org. Lett.* **2001**, *3*, 3765−3768.

(5) Formation of **6**, similar to the protected polyamines described by Ganem, can be explained by the reaction of **4** with **2** acting as a methylene donor: (a) Chantrapromma, K.; McManis, J. S.; Ganem, B. *Tetrahedron Lett.* **1980**, *21*, 2475−2476. (b) Murta, M. M.; de Azevedo, B. M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7537−7541.

The optimal desulfuration procedure we have found consisted of the use of a large excess of $NaBH_4$ in the presence of nickel chloride[10] ($NiCl_2$) that led to **10**. We could then easily carry out the protection of the last amino group to obtain **11** in good yield. The synthesis ended with classical methods: removal of a *tert*-butyldimethylsilyl group using a fluoride salt and mesylation, which allowed for a nucleophilic substitution with sodium azide to obtain **14**.[11]

We provide here (Scheme 4) an example synthesis using the polyamine platform **14** in the preparation of gene transfer agent **18**.[12]

Scheme 4



For this synthesis, we reacted propargyl bromide with the dioctadecylamine leading to **16**. The coupling of **16** with **14**, according to click chemistry, was realized in CH_2Cl_2 in the presence of lutidine and a soluble complex of copper(I)[13] to give **17** with a good yield. The final deprotection of **17** gave rise to **18** in good yield.

We have thus obtained the laterally substituted polyamine **18** that will undergo biological assays as a gene transfer agent. Our method takes advantage of the independent Michael addition, lactone aminolysis, and hydroxyl functionalization to design flexible unsymmetrical amino compounds.

Acknowledgment. We gratefully acknowledge M. Uriac, J. C. Corbel, R. Gillet, P. Jéhan, S. Sinbandhit, and J. F. Cupif for technical assistance with this work.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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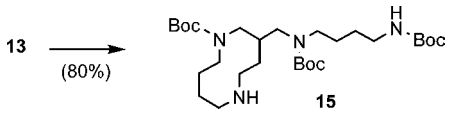
(7) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912−916.

(8) Clausen, K.; Thorsen, M.; Lawesson, S. O. *Tetrahedron* **1981**, *37*, 3635−3639.

(9) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061−4064.

(10) Frank, S. G., Jr.; Wasmund, L. M. *Tetrahedron Lett.* **1990**, *31*, 23−26.

(11) We have observed that the storage, at 4°C under argon, of the mesylated intermediate **13** resulted in the unwanted formation of the cyclized compound **15** as follows:



(12) Behr, J. P.; Demeneix, B.; Loeffler, J. P.; Perez-Mutul, J. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 6982−6986.

(13) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.