Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3451–3453

TETRAHEDRON LETTERS

Synthesis of dihydroxylated polyamines from an erythronolactone

Myriam Le Roch, Jacques Renault, Kristell Penlaë and Philippe Uriac*

UPRES 2234: Synthèse et Extraction de Molécules à Visée Thérapeutique, Université de Rennes I, Faculté des Sciences Biologiques et Médicales, 2, Avenue du Pr. Léon Bernard, 35043 Rennes, France

Received 14 February 2003; revised 12 March 2003; accepted 13 March 2003

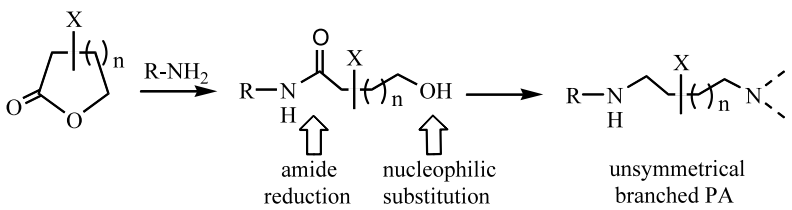
Abstract—The opening of protected erythronolactone by an amine or a diamine furnished hydroxy-amides. Their multistep functional conversion led to either selectively protected or free dihydroxy-polyamines.

Synthetic analogues and derivatives of polyamines (PA) are potential therapeutic agents in various biological disorders and attract considerable attention in organic chemistry.[1] Despite promising biological properties, the neurotoxicity of PA derivatives, due probably to their high affinity for receptors involved in neurotransmission, is a major limitation to their development as therapeutics. However, recent studies[2] have demonstrated that the hydroxylation of PA structures may be a means of decreasing their toxicity. Few routes for the preparation of hydroxylated PA have been described. They mostly require the preparation and the opening of chiral epoxides.[2]

To our knowledge, lactones have not been used as building blocks for the synthesis of PA compounds. However, their simple aminolysis may lead to amido-alcohols whose functional groups can be independently converted to amines. This approach could take advantage of their natural and synthetic diversity. Scheme 1 shows the general route to this type of 'unsymmetrical branched PA precursor'. In this general example, the diversity may come from R (amines or diamines), X substituents including chiral groups and the number of methylenes *n*.

In accordance with this idea, we report here the synthesis of di-hydroxylated putrescine, spermidine and spermine from an erythronolactone (X represents two protected hydroxyl groups, $n=1$, Scheme 1). Our purpose was not only to prepare di-hydroxylated natural PA but also to access unsymmetrical protected intermediates likely to undergo classical functionalisation.

The synthesis of our hydroxylated putrescine analogues (Scheme 2) started with the easy opening of the commercially available lactone **1** with benzylamine. Initially, we planned to modify the hydroxyl group of **2** prior to reducing its amide function. The amide would hence play the role of a protected amine until the end of the synthesis. Unfortunately, when submitted to mesylation, the amido-alcohol **2** furnished incomplete and complicated reactions. The undesired cyclisation to lactam is a possible reason for this failure. Therefore, the amide function of the synthon **2** was first reduced[3] leading to a secondary amine. This chemical step was carefully optimised. Borane (BH_3/THF) was used initially but always led to unexploitable mixtures. Lithium aluminium hydride was then chosen. The classical acidic work up was replaced by the use of concentrated sodium hydroxide to avoid hydroxyl groups deprotec-

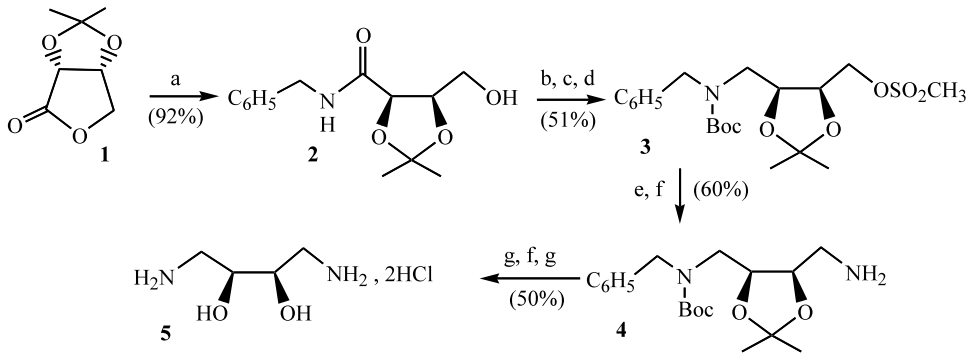


Scheme 1.

Keywords: polyamines; hydroxylated polyamines; erythronolactone.

* Corresponding author. E-mail: philippe.uriac@univ-rennes1.fr

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00693-2



Scheme 2. *Reagents and conditions*: (a) $C_6H_5CH_2NH_2$, THF, Δ, 22 h; (b) H_4LiAl, THF, Δ, 22 h; (c) $(Boc)_2O$, CH_2Cl_2, 20 h; (d) CH_3SO_2Cl, TEA, CH_2Cl_2, 0°C, 2 h; (e) $C_6H_5CH_2NH_2$, Δ, 72 h; (f) H_2 3 bars, $Pd(OH)_2$, CH_3OH, 24 h; (g) HCl/EtOH 3N.

tion. The choice of the solvent (THF or diethyl ether) took into account amide solubility and heating necessity. In the best experimental conditions, the yield of this sole reduction step reached 65%.

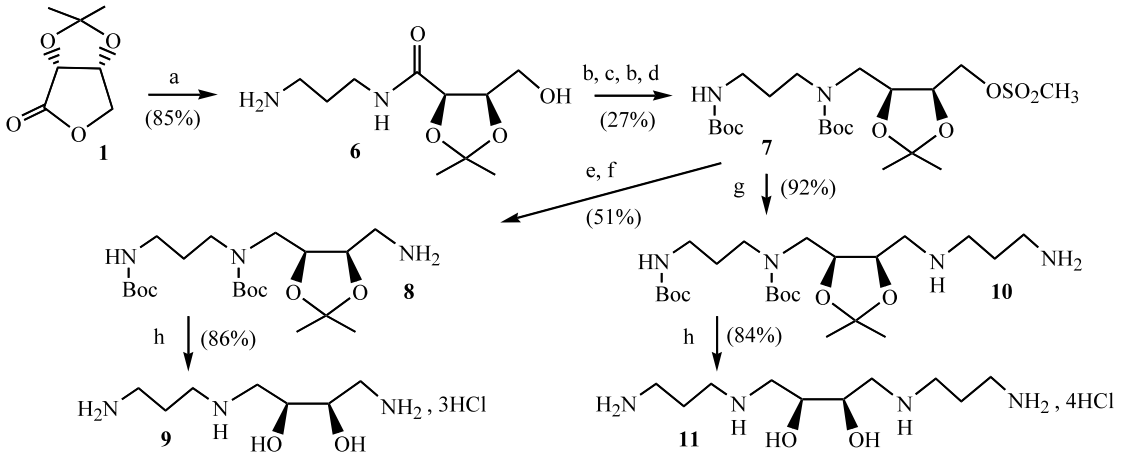
After Boc protection of the secondary amine, the hydroxyl group underwent a simple reaction with methanesulfonyl chloride leading to compound **3**.[4]

The mesyl group of **3** may undergo nucleophilic displacement[5] by various amines in order to obtain diverse *N*-substituted putrescines. For this work, due to the incomplete reaction with ammonia, we used benzylamine as a nucleophile, then proceeded to debenzylation.[6] Contrary to what could be expected,[7] our experimental conditions only led to mono-debenzylation, providing the potentially useful synthon **4**. In spite of our efforts, the second catalytic debenzylation remained unsuccessful as long as the Boc group was present. This finding led us to treat the compound **4** as follows: deprotection of amino and hydroxyl groups in acidic medium, alkaline treatment then catalytic debenzylation, finally acidic treatment to isolate **5** as the hydrochloride salt.[8] The overall yield of this sequence reached 14%.

Concurrently to this first route we carried out a similar preparation of di-hydroxylated spermidine and spermine (Scheme 3).

Firstly the propane-1,3-diamine reacted with **1** to lead very easily to the hydroxy amide **6**. This intermediate was poorly soluble either in diethyl ether or in THF. Moreover its reduction would furnish a diamino alcohol whose hydrophilicity could cause problematic work-up. For these reasons, we first protected its primary amine, then reduced the amido group to a secondary amine that was Boc-protected. The hydroxyl group was next converted to mesyloxy group to give **7**. Despite our efforts to optimise the experimental procedure, the reduction step never exceeded 45% with the result of a moderate overall yield from **6** to **7**.

The synthon **7** was divided in two parts: the first underwent reaction with benzylamine then catalytic debenzylation. For the second, an excess of propane-1,3-diamine was used. These nucleophilic displacements furnished the protected hydroxy PA **8** and **10**. Their final treatment in acidic medium led respectively to **9** and **11** in good yield.[8]



Scheme 3. *Reagents and conditions*: (a) propane-1,3-diamine, THF, Δ, 22 h; (b) $(Boc)_2O$, CH_2Cl_2:CH_3OH (75:25), 20 h; (c) H_4LiAl, Et_2O, Δ, 22 h; (d) CH_3SO_2Cl, TEA, CH_2Cl_2, 0°C, 2 h; (e) $C_6H_5CH_2NH_2$, Δ, 72 h; (f) H_2 3 bars, $Pd(OH)_2$, CH_3OH, 24 h; (g) propane-1,3-diamine, Δ, 48 h; (h) HCl/EtOH 3N.

In conclusion, we have presented an efficient method for the synthesis of the dihydroxylated PA **5**, **9** and **11** whose biological investigations are in progress The protected intermediates **3**, **4**, **7**, **8** and **10** (bearing amino or mesyloxy groups) were easily produced in a 0.5–1 g scale. They represent potentially useful synthons for the preparation of diverse di-hydroxylated PA conjugates whose biological activity deserves interest. The extension of this method to other types of lactones should be of interest for the synthesis of diverse branched PA.

Acknowledgements

We gratefully acknowledge the Association de Recherche sur le Cancer (ARC), The Ligue Nationale Contre le Cancer (LNCC, Comité d'Ille et Vilaine) for financial support, and to Margaret Uriac, Jean-Guy Delcros, David Cuperly and Jean-François Cupif for technical assistance to this work.

References

1. For recent reviews on polyamine synthesis and biological activity see: (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 cited therein.
2. (a) Bergeron, R. J.; Müller, R.; Huang, G.; McManis, J. S.; Algee, S. E.; Yao, H.; Weimar, W. R.; Wiegand, J. *J. Med. Chem.* **2001**, *44*, 2451–2459; (b) Bergeron, R. J.; Müller, R.; Bussenius, J.; McManis, J. S.; Merriman, R. L.; Smith, R. E.; Yao, H.; Weimar, W. R. J. *J. Med. Chem.* **2000**, *43*, 224–235; (c) Bergeron, R. J.; Bussenius, J.; Müller, R.; McCosar, B. H.; McManis, J. S. *Tetrahedron: Asymmetry* **1999**, *10*, 4285–4294.
3. Vassis, S.; Karigiannis, G.; Balayannis, G.; Militsopoulou, M.; Mamos, P.; Francis, G. W.; Papaioannou, D. *Tetrahedron Lett.* **2001**, *42*, 1579–1582.
4. Initially, the opening of the lactone **1** was undertaken by ammonia leading to a primary amide that was subjected to a similar sequence (b, c, d, Scheme 2) but resulted in the intramolecular cyclisation to give the corresponding substituted *N*-Boc-protected pyrrolidine.
5. For applications to the PA synthesis, see: (a) Wang, C.; Abboud, K. A.; Phanstiel, O. *J. Org. Chem.* **2002**, *67*, 7865–7868; (b) Nagamani, D.; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 103–106; (c) Rajeev, K. G.; Sanjavan, G. J.; Ganesh, K. N. *J. Org. Chem.* **1997**, *62*, 5169–5173; (d) Renault, J.; Lebranchu, M.; Lecat, A.; Uriac, P. *Tetrahedron Lett.* **2001**, *42*, 6655–6658.
6. Boyle, P. H.; Davis, A. P.; Dempsey, K. J.; Hosken, G. D. *Tetrahedron: Asymmetry* **1995**, *6*, 2819–2828.
7. Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1997**, *53*, 1411–1416.
8. Analytical data (NMR spectra were recorded on a Bruker DMX 500 WB apparatus at 500 MHz. IR spectra were recorded on a Perkin–Elmer 16PC FTIR apparatus by diffuse reflectance. The sample were diluted in a KBr matrix. Mass spectra were recorded on a Varian MAT 311 apparatus).
***meso*-2,3-Dihydroxyputrescine 5**: ^{1}H NMR (D_2O) δ (ppm): 3.05 (dd, $J=9.22$ Hz, $J=13.03$ Hz, 2H, H-1, H-4), 3.37 (m, 2H, H-1, H-4), 3.86 (m, 2H, H-2, H-3). ^{13}C NMR (D_2O) δ (ppm): 42.00 (C-1, C-4), 69.38 (C-2, C-3). MS (Electrospray): $(M+H)^+$ theor.: 121.0977, found: 121.0974. $R_f=0.43$ (CH_3OH:NH_4OH, 50:50). FTIR ν (cm^{-1}): 3262 (OH), 3213, 3049, 2988, 2907 (NH_3^+). $[\alpha]_D^{21.5}=0°$ (c 2.1×10^{-3}, H_2O).
(6*S*,7*R*)-6,7-Dihydroxyspermidine hydrochloride 9: ^{1}H NMR (D_2O) δ (ppm): 2.15 (m, 2H, H-2), 3.04* (dd, $J=9.60$ Hz, $J=13.20$ Hz, 1H, H-8), 3.13 (m, 2H, H-1), 3.15* (m, 1H, H-5), 3.24 (t, $J=8.05$ Hz, 2H, H-3), 3.36* (dd, $J=2.97$ Hz, $J=13.20$ Hz, 1H, H-8), 3.42* (dd, $J=2.81$ Hz, $J=12.94$ Hz, 1H, H-5), 3.85* (m, 1H, H-7), 3.92* (m, 1H, H-6). ^{13}C NMR (D_2O) δ (ppm): 24.01 (C-2), 36.98 (C-1), 41.92 (C-8), 45.21 (C-3), 50.02 (C-5), 68.63* (C-6), 69.38* (C-7). MS (LSIMS): $(M+H)^+$ theor.: 178.1556, found: 178.1551. $R_f=0.25$ (CH_3OH:NH_4OH, 50:50). FTIR ν (cm^{-1}): 3373 (OH), 3020, 2892, 2818, 2410 (NH_3^+, NH_2^+). $[\alpha]_D^{21.5}=-5.1°$ (c 3.34×10^{-3}, H_2O).
***meso*-6,7-Dihydroxyspermine hydrochloride 11**: ^{1}H NMR (D_2O) δ (ppm): 2.15 (m, 4H, H-2, H-11), 3.14 (t, $J=7.80$ Hz, 4H, H-1, H-12), 3.17 (m, 2H, H-5, H-8), 3.25 (t, $J=7.97$ Hz, 4H, H-3, H-10), 3.42 (d, $J=12.92$ Hz, 2H, H-5, H-8), 3.93 (m, 2H, H-6, H-7). ^{13}C NMR (D_2O) δ (ppm): 23.57 (C-2, C-11), 36.54 (C-1, C-12), 44.78 (C-3, C-10), 49.46 (C-5, C-8), 68.16 (C-6, C-7). MS (Electrospray): $(M+H)^+$ theor.: 235.2134, found: 235.2134. $R_f=0.13$ (CH_3OH:NH_4OH, 50:50). FTIR ν (cm^{-1}): 3387 (OH), 2969, 2901, 2807, 2516, 2422 (NH_3^+, NH_2^+). $[\alpha]_D^{21.5}=0°$ (c 4.42×10^{-3}, H_2O).