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An iterative approach to novel polyamines *via* nucleophilic ring-opening of aziridinium ions with β-amino alcohols†

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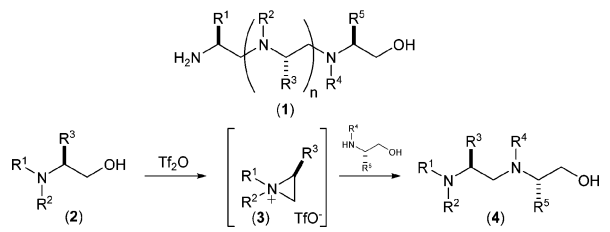
An iterative procedure for the synthesis of a novel class of synthetic polyamines has been developed, utilising the regioselective ring-opening of aziridinium ion intermediates; facile *N*-allyl deprotection of intermediate polyamines allows the rapid construction of high molecular weight, stereochemically defined compounds in a convergent manner.

Polymethylene polyamines, their analogues and conjugates occur naturally and show interesting biological activities. The distribution of these compounds ranges from simple bacteria to plants, insects, mammals and marine organisms, and in the last two decades, many cellular functions have been shown to be polyamine dependent.[1] Research on polyamines has resulted in numerous reports detailing the preparation of a vast array of synthetic polyamine analogues and conjugates.[2,3]

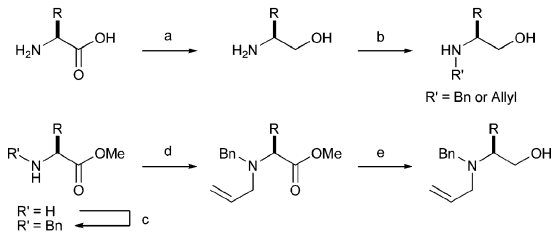
Herein, we present an initial report on the results of our efforts towards the synthesis of a novel class of α-substituted polymethylene polyamines using an iterative aziridinium ion formation–ring opening protocol. Previous work by our group,[4] and others,[5] has demonstrated the synthetic utility of aziridinium ion intermediates for the synthesis of highly functionalised 1,2-amino alcohols and 1,2-diamines. We reasoned that if attacked by a β-amino alcohol nucleophile containing a secondary amine, this would lead to formation of the corresponding tertiary amine, which would allow the iterative strategy to proceed. Repetition of this sequence could ultimately be used to construct α-substituted polymethylene polyamines **1** (Scheme 1) with overall structure and substitution patterns similar to those in a small peptide, but lacking the amide carbonyl group.[6] As such, we believe these stereochemically defined polymers will have application in many different areas (*vide infra*).

The β-amino alcohols required as starting materials could be synthesised in high yield from the corresponding amino acids or amino acid methyl esters *via* a combination of simple alkylation and reduction reactions[7] (Scheme 2). Initial studies focussed on the regioselectivity of the ring-opening reaction when the aziridinium ion was attacked by morpholine (entries 1, 2, 6 and 7, Table 1). With both allyl- and benzyl-protected amino alcohols, the reaction yielded a mixture of regioisomers. This behaviour has been noted previously.[8] Using secondary amino alcohols as nucleophiles however (entries 3–5 and 8–10), we found that the aziridinium ion intermediate was attacked with complete regioselectivity in good to excellent yields, and with exclusive *N*-alkylation of the aminoalcohol nucleophile.



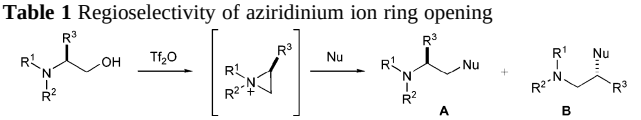
Scheme 1

We then used this work as a basis for developing the amino alcohol homologation as a route to polyamine compounds (Scheme 3). Treatment of *N*-allyl-*N*-benzyl alaninol **5** with trifluromethanesulfonic anhydride at low temperature facilitated formation of the intermediate aziridinium triflate **7**. This was treated *in situ* with the



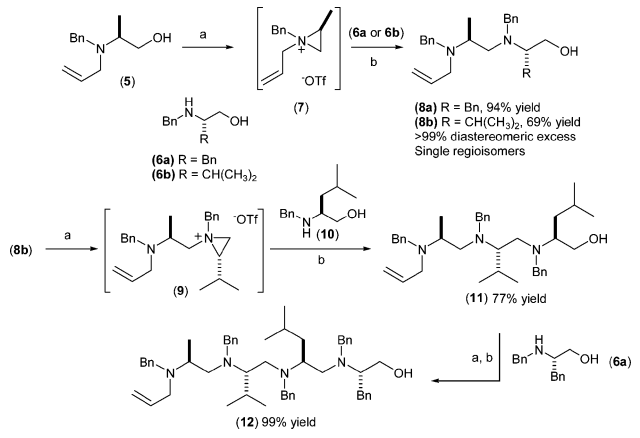
Scheme 2 *Reagents and conditions:* (a) 2.5 eq. $NaBH_4$, 1.0 eq. I_2, THF, reflux 18 h; (b) 0.5 eq. R′Br, neat or in MeCN; (c) (i) 1.0 eq. PhCHO, 1.0 eq. NEt_3, MeOH, rt; (ii) 2.0 eq. $NaBH_4$, MeOH, 0 °C → rt; (d) 1.2 eq. allyl bromide, 1.1 eq. NEt_3, DMF, 65 °C, 48 h; (e) 2.5 eq. $LiAlH_4$, THF, 0 °C → rt.

Table 1 Regioselectivity of aziridinium ion ring opening



Entry	R^1	R^2	R^3	Nu	Yield (%)	Ratio A : B
1	allyl	allyl	Bn	morpholine	80	88 : 12
2	Bn	Bn	Bn	morpholine	69	95 : 5
3	allyl	allyl	Bn	*N*-allyl Phe–OH	84	> 95 : 5[a]
4	Bn	Bn	Bn	*N*-allyl Phe–OH	67	> 95 : 5[a]
5	Bn	allyl	Bn	*N*-allyl Phe–OH	89	> 95 : 5[a]
6	allyl	allyl	Me	morpholine	74	68 : 32
7	Bn	Bn	Me	morpholine	79	71 : 29
8	Bn	Bn	Me	*N*-allyl Val–OH	30	> 95 : 5[a]
9	Bn	allyl	Me	**6a**	69	> 95 : 5[a]
10	Bn	allyl	Me	**6b**	94	> 95 : 5[a]

[a] None of alternative regioisomer detected.



Scheme 3 *Reagents and conditions*: (a) 1.3 eq. Tf_2O, 1.5 eq. NEt_3, DCM, −78 °C → rt; (b) 1.1 eq. amino alcohol, rt, 2 h.

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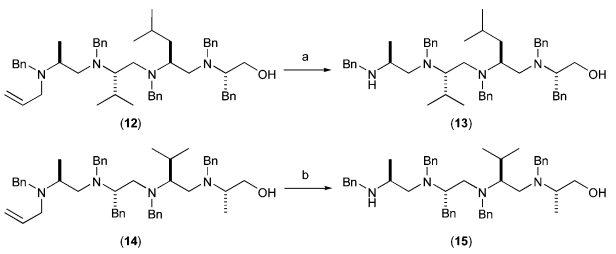
secondary β-amino alcohols **6a** or **6b** which attacked the aziridinium ion at the methylene carbon, opening the ring to form the diamines **8a** or **8b** in 94% and 69% yield, respectively.[9] Diamine **8b** could then be reactivated under the same conditions to form the aziridinium ion moiety **9**, which was reacted with the secondary β-amino alcohol **10**, derived from L-leucine, to form the triamine **11**. In an iterative manner, the triamine could then be treated with triflic anhydride under the same conditions to form an aziridinium intermediate that reacted with the L-phenylalanine derived β-amino alcohol **6a** to form the tetramine **12**.

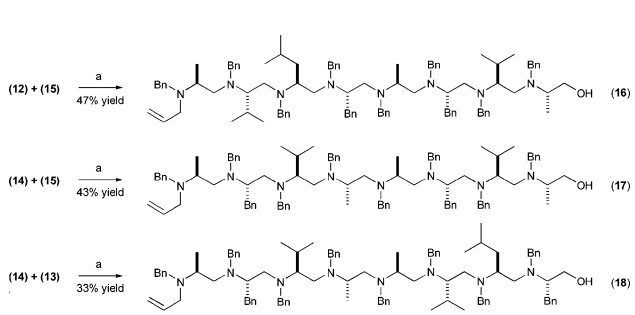
At this point further extension of the polyamine chain became difficult, and there was some evidence to suggest that as the molecules grew larger, the aziridinium ion formed became less reactive. Exploring alternative methods of elongating the polyamine chain, we decided that a convergent synthesis would be desirable. Deprotecting the terminal nitrogen atom of a tetramine such as **12** would unmask a nucleophilic secondary amine moiety that could be used to attack an aziridinium ion formed from another tetramine leading to our initial octamine targets. The removal of an allyl group from nitrogen was easily accomplished *via* a metal-catalysed rearrangement/enamine hydrolysis[4a] and we found that this strategy worked well in the deprotection of polyamines. Initial efforts using palladium on activated charcoal gave a poor recovery of the polyamines from the catalyst. The use of Grubbs' metathesis catalysts[10] was equally unsuccessful, but this was unsurprising in light of recent literature reports.[11] Efficient *N*-deprotection was eventually achieved using $ClRh(PPh_3)_3$ in acetonitrile/water or, more simply, tetrakis(triphenylphosphine)palladium(0) in dichloromethane with 1,3-dimethylbarbituric acid as an allyl group scavenger (Scheme 4).[12] After filtering the crude material through a plug of silica, the deprotected polyamine **13** was isolated in over 90% yield when Wilkinson's catalyst was used, and **15** could be obtained in quantitative yield after reaction with the palladium-based catalyst.

Polyamines **13** and **15** with *N*-terminal secondary amines could then be coupled to tetramine-derived aziridinium ions to form the octamines **16–18** in modest yields (Scheme 5). The octamines were analysed by QTof MSMS, and showed characteristic fragmentations dependent on the sequence of the amino alcohol residues.[13]

We have recently demonstrated that these polyamines bind to DNA using Surface Plasmon Resonance (SPR), and are currently investigating this and other potential applications of these new complex polyamines in areas such as asymmetric catalysis and molecular recognition,[14] the results of which shall be reported in due course.



Scheme 4 *Reagents and conditions*: (a) 10–20 mol% $(PPh_3)_3RhCl$, 84 : 16 $MeCN/H_2O$, reflux (90%); (b) 1 mol% $Pd(PPh_3)_4$, 3.0 eq. 1,3-dimethylbarbituric acid, DCM, rt, 12 h (99%).



Scheme 5 *Reagents and conditions*: (a) (i) 1.1 eq. Tf_2O, 1.3 eq. NEt_3, DCM, −78 °C → rt; (ii) 1.1 eq. amino alcohol, rt, 12 h.

In conclusion, we have developed a novel method of aziridinium ion mediated coupling of β-amino alcohols, and utilised efficient protocols for the selective deprotection of polyamines, leading to a convergent synthesis of complex stereochemically defined octameric polyamines, which we believe will have widespread use in a diverse range of applications.

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