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Polymer backbone disassembly: polymerisable templates and vanishing supports in high loading parallel synthesis

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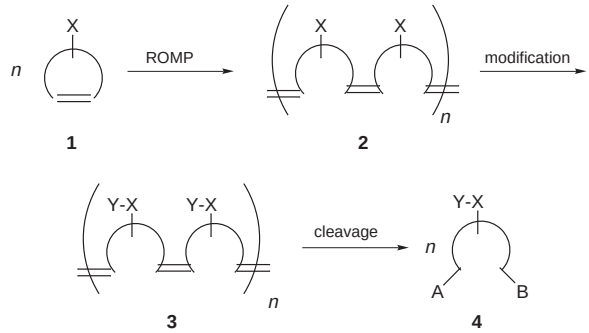
In the synthesis of a library of *N*-alkyl-3-aza-8-oxabicyclo[3.2.1]octane-6,7-dimethanol derivatives, prepared from an 7-oxabicyclo[2.2.1]hept-2-ene-5,6-dimethanol derivative *via* ring opening metathesis polymerisation using $Cl_2(Cy_3P)_2Ru{=}CHPh$, selective alkylation, ozonolytic scission of the polymer backbone and reductive alkylation, purification was facilitated by the differential solubility of the polymer intermediates.

The emergence of combinatorial methodologies and parallel syntheses have dramatically accelerated synthetic chemistry and the quest for novel pharmaceuticals and other specialty chemicals.[1] Many state-of-the-art parallel syntheses rely upon polymer-supported procedures in which the substrate is attached to a support throughout a synthetic sequence. Assay is either carried out on the support or following late release. Such supported syntheses are aided by the 'polymer advantage' which allows (i) solid phase reactions to be driven to completion by the addition of excess solution phase reagents which are simply removed by filtration techniques and (ii) the separation of reaction products from the polymer post-cleavage. There is clear merit in maximising substrate loading so that for any given synthesis, sufficient substrate is produced at a minimum resin weight such that compound authentication, bioassay and compound archiving are facilitated. As such there is need to maximise the loadings yet to also facilitate on-support analysis. The use of PEG supports clearly addresses the need for easy solution-based analyses but these supports are not ideal in terms of loadings. On the other hand, the preparation of polymer supported dendritic materials[2] leads to improved loadings yet does not greatly facilitate analysis. The use of insoluble polymers often necessitates the utilisation of time-consuming, non-standard analytical techniques, *e.g.* solid state NMR spectroscopy, in order to determine the character of the polymer-bound substrates.

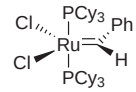
Herein, we report the concept of polymer backbone disassembly for the preparation of synthetic libraries. In this approach the substrate is also the monomer building block for the polymer. As such the polymer loading should ideally approach quantitative. The polymerisation of an appropriate monomer (starting material) to form an insoluble (or differentially soluble) polymeric material is followed by substrate modification for the introduction of chemical diversity. Finally oxidative disassembly generates the modified monomers which are in fact the small molecules of interest. Polymers derived from ring opening metathesis polymerisation (ROMP)[3] fulfil these criteria and were chosen for initial evaluation in the strategy outlined in Scheme 1. ROMP polymers are, unlike cross-linked polystyrene resins, generally soluble in a range of organic solvents yet insoluble in others. Thus, chemical modifications may be carried out in a homogenous environment thereby avoiding poor solvation which often inhibits reactions carried out with insoluble solid supports. Moreover, reactions may be probed using standard solution phase spectroscopic techniques and the ability to rapidly determine the nature of the attached substrate offers a significant advantage over standard solid-phase organic synthesis. Following synthesis, the ROMP



Scheme 1

polymers may be precipitated by the correct choice of solvent to afford solids which can be washed to remove excess reagents. In this respect ROMP polymers show similar behaviour to the PEG polymers recently further developed by Janda *et al*.,[4] after the pioneering work by Bayer, Mutter and Shemyakin.[5]

Norbornene, 7-oxanorbornene and cyclobutene ROMP monomers containing functional groups which are either hydrophilic or hydrophobic in nature are readily available and many offer the opportunity for post-polymerisation chemical modification required for library generation. 7-Oxanorbornene **6** was chosen for initial study as depicted in Scheme 2. The monomer **6** is readily prepared from diol **5** *via* mono-silylation followed by tetrahydropyranyl protection. The use of orthogonal protecting groups[6] allows for a stepwise hydroxy group modification strategy to be utilised in library synthesis. Polymerisation of **6** using the Grubbs catalyst **13**[7] and chain



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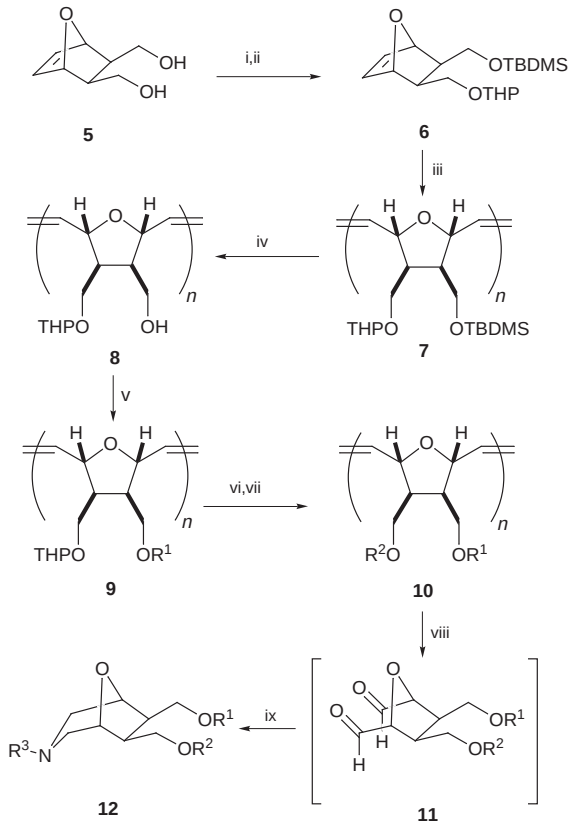
termination with ethyl vinyl ether[8] gave polymer **7** as an off-white foam which was most conveniently isolated (90%) following repeated precipitation from 1,2-dichloroethane solution with MeOH. Both ^{1}H and ^{13}C NMR spectra were consistent with polymer **7** having a 1:1 *trans*:*cis* stereochemistry.[8] Selective desilylation of polymer **7** gave the corresponding polyol **8** as a THF-insoluble precipitate which was washed with THF and Et_2O and dried *in vacuo*, whereupon ^{1}H and ^{13}C NMR spectra (acetone-d_6) indicated complete removal of the *tert*-butyldimethylsilyl residues. Alkylation of polymer **8** using MeI or 4-bromobenzyl bromide (R^1X) in the presence of NaH in THF gave the corresponding THF-soluble polymeric ethers **9** which were precipitated from MeOH. In turn, cleavage of the tetrahydropyranyl ether of **9** using TsOH in a MeOH–THF–CH_2Cl_2 (1:2:1) mixture and precipitation from THF followed by further alkylation with MeI or 4-bromobenzyl bromide (R^2X) afforded the polyethers **10** which were isolated in the same way as **9**. All polymers were isolated cleanly and with high recovery.



Scheme 2 *Reagents and conditions*: i, NaH, THF, TBDMSCl, 78%; ii, dihydropyran, cat. PPTS, CH_2Cl_2, 92%; iii, **13**, $ClCH_2CH_2Cl$, then $EtOCH{=}CH_2$ quench, 90%; iv, Bu_4NF, THF; v, NaH, THF, R^1X; vi, TsOH, MeOH–THF–CH_2Cl_2 (1:2:1); vii, NaH, THF, R^2X; viii, O_3, CH_2Cl_2, −78 °C, then EtOH, Me_2S; ix, $NaBH(OAc)_3$, R^3NH_2.

The three functionalised polymers **10** were disassembled by ozonolysis with a Me_2S work-up to reveal the corresponding dialdehydes **11** which were not isolated. Direct *in situ* reductive amination[9] with $BnNH_2$, $BuNH_2$ and (cyclohexylmethyl)amine gave the corresponding 3-aza-8-oxabicyclo[3.2.1]octanes **12** in overall yields of around 30% from the starting polymer **7**. The same nine 3-aza-8-oxabicyclo[3.2.1]octane derivatives **12** were prepared from monomer **6** by sequential double deprotection and monoalkylation, ozonolysis and reductive amination. Overall yields in these reactions were comparable (30–40%).

We have demonstrated the utility and advantage of polymer backbone disassembly for the rapid generation of small molecule targets using polymer **7**. Advantages include ease of intermediate purification and facile reaction monitoring. The modification of polymer **7** for library construction with different chemistry is ongoing and will be reported in due course.

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Notes and references

† All new compounds were fully characterised by spectroscopic data and microanalysis and/or high resolution mass spectrometry.

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