Versatile process for the stereodiverse construction of 1,3-polyols: iterative chain elongation with chiral building blocks†

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A versatile process for the construction of 1,3-polyols, a key structural element of polyketide-type natural products, is presented. The modular synthesis strategy involves the iterative chain elongation with novel four-carbon building blocks to access all possible stereoisomers of a growing 1,3-polyol chain. These chiral building blocks are designed to install four carbon atoms with two sterogenic centres by performing only four experimentally simple steps per elongation cycle, thus making these building blocks attractive for the realization of a universal platform from which to access a diverse range of polyketidic molecules.

Polyketide-type natural products are a class of molecules with astonishing structural diversity. Their highly complex structures constitute a rich source of bioactive compounds, with many possessing therapeutic relevance as antibiotics and cardiovascular and antitumor agents, and thus are of particular interest from a pharmacological point of view.1 It is remarkable that the carbon skeletons underlying the vast range of polyketidic structures in Nature derive from a common biosynthetic origin where the chemical total synthesis of polyketide-type sequences,14 our strategy focused on the use of olefination reactions to attach the chiral building blocks without generating stereogenic centres by use of a carbonyl oxides 1 as building blocks for the stereospecific introduction of 1,3-diols in the synthesis of polyketidic structures; (R)-1 and (S)-1 were accessible on a multigram scale through a facile and high-yielding sequence of six and seven linear steps, respectively.13 In this work, we expanded on that principle by using these four-carbon building blocks, which already carry preinstalled stereo-chemical information, in a repetitive chain elongation process as shown in Scheme 1. While, for example, Paterson et al. used boron-mediated aldol reactions for the synthesis of polyketide-type sequences,14 our strategy focused on the use of olefination reactions to attach the chiral building block 1 at the terminal aldehyde functionality A′−A″ in an iterative way. The attachment of the building blocks occurs without generating stereogenic centres by use of a carbonyl olefination followed by hydrolysis (→B).15,16 In consequence, by the selection of the chiral building block at each stage of the iterative sequence, the stereogenic centre that is part of the building block is unambiguously fixed.17 Regarding all the further reactions of the chain-extending sequence, we decided

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Scheme 1 General strategy for the synthesis of 1,3-polyols by use of four-carbon building block 1.

only to rely on well-established and easy-to-perform reactions: substrate-controlled directed reduction of hydroxyl ketones (→ C), hydroxyl protection (→ D), and oxidative aldehyde formation.

The potential of this strategy to easily access any given 1,3-polyol chain in an enantioenriched manner was first put to the test starting from aldehyde 2. As outlined in Scheme 2, the initial elongation started with (R)-1: by use of a short two-step sequence, the diols 4 and 5 were formed in high overall yields (77% for 4; 76% for 5). In the course of this sequence, the aldehyde 2 was converted first into the olefination product through reaction with the lithiated building block (R)-1.18 The resulting mixture of double bond isomers was not isolated; instead, the enol acetonide rapidly and quantitatively hydrolysed during the acidic work-up to provide ketone 3.19 Regarding the substrate-controlled reduction of the newly formed carbonyl group, we firstly relied on Evans’ well-established method of directed anti-reduction to obtain the desired anti-diol 4 in 93% yield (dr 90:10).20 Secondly, syn-diol 5 was accessed in 91% yield by use of Et₂BOMe/NaBH₄.21 The enantiomeric purity of the diols 4 and 5 was shown to be higher than 99% ee. Subsequent protection of the diols as acetonides followed by ozonolysis of the terminal olefin then gave the aldehydes 8 (anti) and 9 (syn) that represent the chain growth products of the iteration.22,23 In brief, the overall chain elongation sequences with building block 1 comprise of only four synthetic steps and allow for the attachment of a four-carbon unit and the stereo-controlled installation of two stereoegenic centres.24

To illustrate the ease of synthesising 1,3-polyols in this way, aldehydes 8 and 9 were subjected to further iterations of the four-step sequences to selectively prepare all eight possible diastereomers (10–17) of a tetraol skeleton in enantiopure form (Scheme 3). Although the average yields for the second iteration were, in particular when starting with anti-aldehyde 8, somewhat lowered (i.e., between 67% and 82% average yield per step), all target compounds were produced as expected, without any attempts to readjust experimental details or further optimise conditions.

Having thus demonstrated the stereochemical diversity of products accessible by this method, we next sought to apply it to the synthesis of a specific and more complex target. We decided on (protected) hexaol 19 as the desired product, which corresponds to the hexaol skeleton of (+)-cryptocaryol A (22) (Scheme 4). Due to its highly valuable biological properties (i.e. the stabilization of tumour suppressor protein Pdcd4),25,26 this natural product has attracted considerable interest, and its synthetic access has already been thoroughly investigated by several research groups.27–30 As a result, cryptocaryol A is analytically well documented, which would present us with the opportunity to confirm the structure and stereochemistry of desired hexaol 19 by further converting it into (+)-cryptocaryol A and comparing the NMR spectroscopic data with the literature. At the same time, its linear synthesis would underline the applicability of our method in natural product synthesis.

As detailed in Scheme 4, the iterative chain growth toward hexaol 19 using our method started from commercially available aldehyde 18. We were pleased to find that the synthesis via three iterations of the elongation cycle (the last of which was shortened by the ozonolysis step to stop at the terminal olefin) proceeded as smoothly and efficiently as hoped: a stereospecific elongation by thirteeen carbon atoms and six stereogenic centres was achieved in eleven steps, with an average yield of 84% per step for all three iterations, to furnish hexaol 19 under full stereocontrol. Including the six-step synthesis of building block (R)-1,13 the longest linear sequence toward hexaol 19 consists of 17 steps.

Regarding reaction conditions of the iteration steps, minor changes (specifically of solvents and reaction temperature) were required here in some instances due to solubility issues arising from the long aliphatic chain (see ESI†). Lastly, to confirm structure and stereochemistry of the synthesised polyol chain
small amounts were subjected to a short series of manipulations to obtain a sample of (+)-cryptocaryol A: first, hydroboration of the olefin gave primary alcohol, which was then oxidised with TPAP followed by Ando olefination to yield conjugated ester. The natural product was accessed through universal deprotection and cyclization under acidic conditions; while the conversion of with TFA effectively cleaved the acetonide protecting groups, further treatment with p-TSA was necessary to complete the final cyclization step. Thus, sufficient amounts of cryptocaryol A were obtained to positively match NMR spectroscopic data with those previously reported, which gave us verification that the desired hexaol was indeed synthesised as planned.

Comparison with the previous strategies for the synthesis of cryptocaryol A shows that our method with linear steps (16 from aldehyde) is competitive regarding the step count (O’Doherty: 23, Cossy: 20, Dias: 17 linear steps for ); however, our building block approach ensures full flexibility with respect to stereochemical variants of the target molecule.

In conclusion, a versatile process for the construction of 1,3-polyols, a key structural element of polyketide-type natural products, is described. Our modular synthesis strategy involves the iterative chain elongation with chiral four-carbon building blocks. All possible stereoisomers of a growing 1,3-polyol chain are accessible in a fully controlled manner, thus making these building blocks attractive for the realization of a universal platform from which to access a diverse range of polyketidic molecules. In our follow-up works, we will introduce several related building blocks that enable the incorporation of structural motifs other than pure 1,3-diols into synthetic polyketides.

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Notes and references

For recent examples, see inter alia: (a) T. J. Harrison, S. Ho and J. L. Leighto


