

# Iterative approach to polyketide-type structures: stereoselective synthesis of 1,3-polyols utilizing the catalytic asymmetric Overman esterification†

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An iterative systematic approach to the 1,3-polyol motif has been developed to provide access to all possible stereoisomers by utilizing the catalytic asymmetric Overman esterification for the construction of all stereogenic centres.

Polyketide-derived natural products often combine a specific biological activity with both complexity and broad skeletal diversity. As a synthetic challenge, they have stimulated the development of numerous methods for their stereoselective synthesis, many of which resulted in *de-novo* syntheses.<sup>1,2</sup> However, nature has evolved an iterative and flexible approach for the synthesis of polyketides utilizing only a few building blocks.<sup>3</sup> By mimicking this processive mechanism, a conceptually related strategy towards polyketide-type structures was envisioned in which repetition of a simple sequence provides the desired structural units through chain extension, with each iteration attaching a C<sub>2</sub>-building block. We initiated the research described in this communication with the premise that a general and synthetic approach to polyketides will be well suited for efforts aimed at the construction of natural products and polyketide libraries. As a start, herein we report an iterative approach to the synthesis of 1,3-polyols<sup>4</sup> that makes all possible stereoisomers freely accessible.

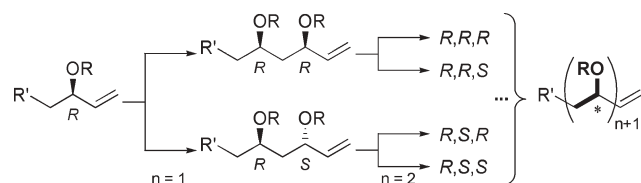
Within this context, allylic alcohols were identified as a potentially useful class of substrates. It was envisaged that the existing allylic alcohol group is extended by a C<sub>2</sub>-unit through each chain extension cycle (Scheme 1). Since the chirality of the already established 1,3-polyol chain makes the stereoselective chain elongation a challenging process,<sup>5</sup> a versatile synthetic method that addresses the flexible construction of all possible stereoisomers is required. Despite numerous strategies for accessing the 1,3-diol

motif through substrate controlled asymmetric induction,<sup>6,7</sup> the most widely used methods to prepare 1,3-polyols in an iterative fashion are by allyl addition sequences utilizing stoichiometric amounts of chiral boron<sup>8</sup> or titanium<sup>9</sup> reagents. An alternative and catalytic approach involves sequential construction of carbon–oxygen bonds through asymmetric epoxidation,<sup>10</sup> although these approaches are somewhat limited due to stereochemical restrictions.<sup>5</sup>

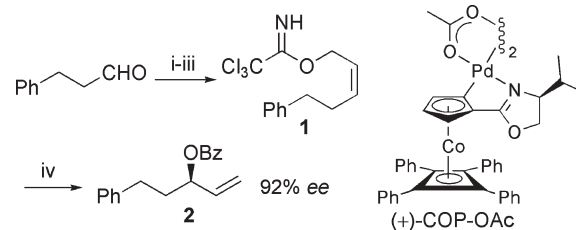
In 2005, Overman and Kirsch reported that prochiral (*Z*)-allylic trichloroacetimidates react with carboxylic acids to give branched allylic esters using chiral palladium(II) catalysts. When the palladium(II) catalyst is COP-OAc, achiral substrates were efficiently transformed into chiral products of high enantiopurity.<sup>11</sup> Our preliminary experiments indicated that the asymmetric Overman esterification is also a powerful method for the reaction of chiral substrates. In these cases, asymmetric induction is completely controlled by the chiral catalyst affording a predictable creation of new stereogenic centres. In this communication, we utilize the Overman esterification for the construction of both the first and all further stereogenic centres in a 1,3-polyol chain.

The first stereogenic center was introduced by reaction of trichloroacetimidate **1** with benzoic acid in the presence of palladacyclic (+)-COP-OAc (1 mol%).<sup>13</sup> The conversion in CH<sub>2</sub>Cl<sub>2</sub> at 23 °C provided (*R*)-allylic ester **2** in 93% yield and 92% ee after 16 h (Scheme 2).

Starting from allylic ester **2**, the projected C<sub>2</sub> extension was conveniently achieved using a multistep sequence (1<sup>OH</sup>→3<sup>OH</sup>), which resulted in the formation of (*R,R*)-diol **5** in 53% overall yield (Scheme 3). A series of transformations consisting of transesterification,<sup>14</sup> ring-closing metathesis,<sup>15</sup> and base-catalyzed double-bond isomerization<sup>8a,16</sup> led to the formation of α,β-unsaturated δ-lactone **3**.<sup>17</sup> The lactone ring was opened with NaBH<sub>4</sub>/



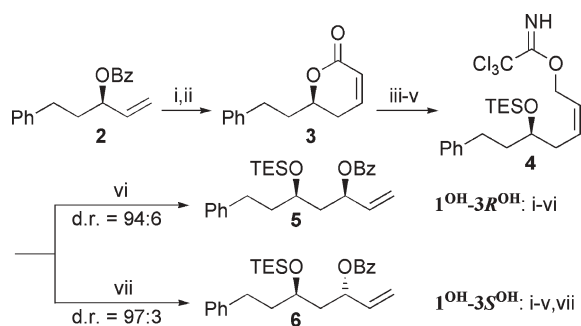
**Scheme 1** Iterative strategy for the synthesis of 1,3-polyols.



**Scheme 2** Synthesis of allylic ester **2**. Reagents and conditions: (i) 1. (PhO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, NaH, 0 °C, THF; 2. 3-phenylpropionaldehyde, −78 °C, 85%, dr > 95 : 5; (ii) DIBAL-H, −78 °C, CH<sub>2</sub>Cl<sub>2</sub>, 80%; (iii) Cl<sub>3</sub>CCN, DBU (10 mol%), 23 °C, CH<sub>2</sub>Cl<sub>2</sub>, 94%; (iv) PhCOOH (3 equiv.), (+)-COP-OAc (1 mol%), 23 °C, CH<sub>2</sub>Cl<sub>2</sub>, 93%, 92% ee.

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† Electronic supplementary information (ESI) available: Representative experimental procedures, and copies of <sup>1</sup>H and <sup>13</sup>C NMR of **2**, **3**, **5–11**, **14** and **15**. Copies of HPLC traces used to determine enantiopurity for **2** and **14**. See DOI: 10.1039/b708248g



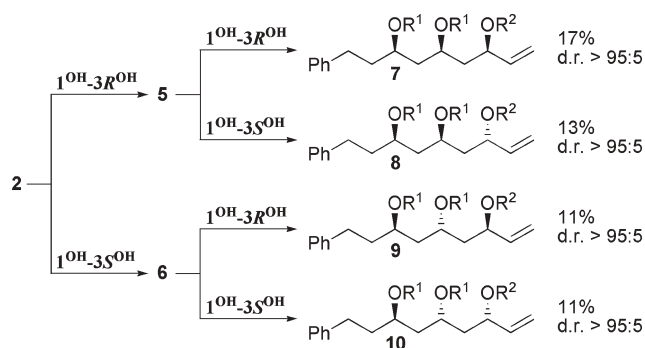
**Scheme 3** Synthesis of (*R,R*)-diol **5** (via  $1^{\text{OH}}\text{-}3R^{\text{OH}}$ ) and (*R,S*)-diol **6** (via  $1^{\text{OH}}\text{-}3S^{\text{OH}}$ ). **Reagents and conditions:** (i) 1. DIBAL-H,  $-78^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ ; 2.  $\text{CH}_2=\text{CHCH}_2\text{CO}_2\text{H}$ , DCC, DMAP (15 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 88%; (ii) 1. Grubbs II (1 mol%),  $38^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ ; 2. DBU (10 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 82%; (iii)  $\text{NaBH}_4$ ,  $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$ ,  $0^\circ\text{C}$ , MeOH, 91%; (iv) 1. TESOTf, lutidine,  $0^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ ; 2.  $\text{K}_2\text{CO}_3$ ,  $0^\circ\text{C}$ , MeOH, 90%; (v)  $\text{Cl}_3\text{CCN}$ , DBU (10 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 94%; (vi)  $\text{PhCOOH}$  (3 equiv), (+)-COP-OAc (1 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 95%, dr = 94 : 6; (vii)  $\text{PhCOOH}$  (3 equiv), (–)-COP-OAc (1 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 94%, dr = 97 : 3.

$\text{CeCl}_3\cdot 7\text{H}_2\text{O}$  followed by the formation of the corresponding bisilyl ether. The protecting group on the primary alcohol was removed selectively, and then the *Z*-configured allylic alcohol was converted into trichloroacetimidate **4**. The imidate was subsequently reacted with benzoic acid in the presence of (+)-COP-OAc (1 mol%) to create the next stereogenic center. Under catalyst control, *syn*-1,3-diol **5** was produced in high diastereoselectivity (dr = 94 : 6). It was also possible to conduct the sequence with (–)-COP-OAc ( $1^{\text{OH}}\text{-}3S^{\text{OH}}$ ), a modification that resulted in the formation of *anti*-1,3-diol **6** in excellent yield and diastereoselectivity (dr = 97 : 3).

This sequence for the stereoselective synthesis of 1,3-diols is particularly attractive since a catalytic amount of the chiral reagent is sufficient to install all possible stereogenic centres with a predictable stereoinduction. Without diminishing yield and diastereoselectivity, the reaction can be run at lower catalyst loadings (up to 0.1 mol% of COP-OAc), although a significantly longer period of time is required for the reaction to reach completion. In addition, COP-OAc is commercially available in both enantiomeric forms. The overall chain extension cycle proceeds under mild reaction conditions in reproducibly high yields, thus reducing the fundamental drawback of this protocol that is due to the high number of synthetic steps per iteration.<sup>18</sup> Of primary importance, this concept might be a step towards a general approach to polyketide-type structures, primarily since straightforward modifications of the synthetic intermediates enable the construction of other structural elements of polyketides. For example, lactone **3** and allylic alcohol derivatives **5** and **6** are suitable substrates for further functionalizations.

To illustrate the feasibility of synthesizing 1,3-polyols in this way, the sequences  $1^{\text{OH}}\text{-}3R^{\text{OH}}$  and  $1^{\text{OH}}\text{-}3S^{\text{OH}}$  were employed to selectively prepare the four stereoisomers **7**, **8**, **9** and **10** (Scheme 4). While the average yields for the second cycle were somewhat lowered, the stereoselective syntheses of the target compounds were realized as expected.

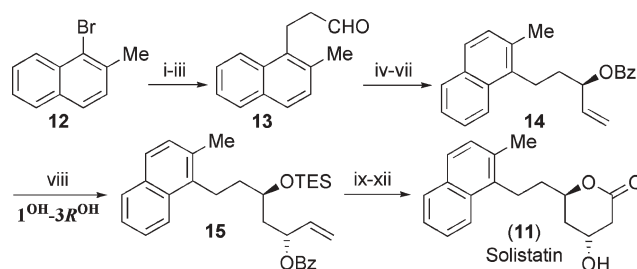
The utility of this sequence for the formation of polyketide-type structures was realized in an expedient total synthesis of (+)-solistatin (**11**). Isolated from *Penicillium solitum*, solistatin is an



**Scheme 4** Stereoselective synthesis of triol derivatives **7**, **8**, **9** and **10**.  $R^1 = \text{Et}_3\text{Si}$ ,  $R^2 = \text{Bz}$ .

aromatic compactin analogue presumably with a related biosynthetic origin.<sup>19</sup> To this end, Heck reaction<sup>20</sup> of 1-bromo-2-methylnaphthalene (**12**) with ethyl acrylate and subsequent reductions provided aldehyde **13** (Scheme 5). Olefination of this product under Ando conditions<sup>21</sup> followed by reduction with DIBAL-H and reaction with trichloroacetimidate yielded the *Z*-configured trichloroacetimidate, which upon esterification<sup>11</sup> with benzoic acid catalyzed by (+)-COP-OAc gave allylic ester **14** (94% ee). The extended allylic ester **15** was then formed in 40% overall yield and excellent diastereoselectivity (dr = 94 : 6) by employing the  $1^{\text{OH}}\text{-}3R^{\text{OH}}$  sequence. Hydroboration gave the primary alcohol, which was subjected to oxidation and acid mediated deprotection to provide (+)-solistatin (**11**) ( $[\alpha]_{\text{D}}^{20} = +32.5$  [ $c = 0.8$ , EtOH]; natural product:<sup>19</sup>  $[\alpha]_{\text{D}}^{20} = +32.0$  [ $c = 0.251$ , EtOH]).

In conclusion, an iterative sequence for the stereoselective construction of 1,3-polyols is described. Within each iteration, the creation of the stereogenic center proceeds with catalyst-controlled stereoinduction. Further modifications of this sequence to introduce structural elements such as C=C-double bonds and carbonyls are in progress. Applications to the synthesis of more complex polyketides will be reported in due course.



**Scheme 5** Synthesis of (+)-Solistatin (**11**). **Reagents and conditions:** (i)  $\text{CH}_2=\text{CHCO}_2\text{Et}$ ,  $\text{Pd}(\text{OAc})_2$  (10 mol%),  $\text{PPh}_3$  (15 mol%),  $100^\circ\text{C}$ ,  $\text{NEt}_3$ , 86%; (ii)  $\text{H}_2$ , Pd-C (5 mol%),  $23^\circ\text{C}$ , EtOH, 91%; (iii) DIBAL-H,  $-78^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 67%; (iv) 1.  $(\text{PhO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$ , NaH,  $0^\circ\text{C}$ , THF; 2. **13**,  $-78^\circ\text{C}$ , 80%, dr > 95 : 5; (v) DIBAL-H,  $-78^\circ\text{C}$ , THF, 96%; (vi)  $\text{Cl}_3\text{CCN}$ , DBU (10 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 87%; (vii)  $\text{PhCOOH}$  (3 equiv.), (+)-COP-OAc (1 mol%),  $23^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , 92%, 94% ee; (viii)  $1^{\text{OH}}\text{-}3R^{\text{OH}}$  (see Scheme 3), 40%, dr = 94 : 6; (ix) 1. DIBAL-H,  $-78^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ ; 2. TESOTf, im,  $23^\circ\text{C}$ , DMF, 72%; (x) 1. 9-BBN-H,  $0^\circ\text{C}$ , THF; 2. NaOH,  $\text{H}_2\text{O}_2$ ,  $0^\circ\text{C}$ , 79%; (xi) IBX,  $23^\circ\text{C}$ , DMSO, 66%; (xii) 1.  $\text{NaClO}_2$ , 2-methyl-2-butene,  $\text{NaH}_2\text{PO}_4$ ,  $23^\circ\text{C}$ ,  $t\text{BuOH-H}_2\text{O}$ ; 2.  $p\text{TsOH}$ ,  $23^\circ\text{C}$ , EtOH, 85%.

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