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Polyketide Library Synthesis: Iterative Assembly of Extended Polypropionates Using (*R*)- and (*S*)-1-(Benzyloxy)-2-methylpentan-3-one.

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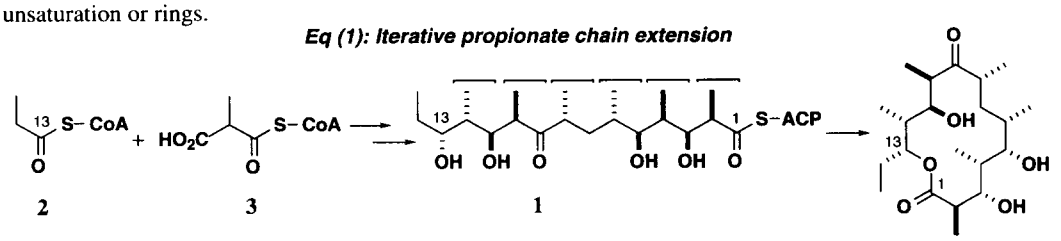
Abstract: The heptapropionates **5** and **20** were synthesised by iterative application of the boron-mediated aldol reaction of ethyl ketone (*R*)-**4** and subsequent reduction. Polyketide library diversification was realised by varying the ketone configuration and substitution in the aldol bond constructions. © 1997 Elsevier Science Ltd.

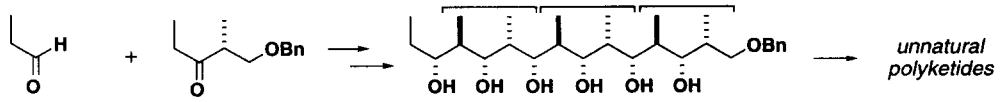
The polyketides represent an important reservoir of natural product diversity, which is associated with a wide range of biological activity (typically antibiotic, antitumour, antifungal, or immunosuppressant action). For polyketide metabolites of bacterial origin, a processive mechanism of biosynthesis is considered to operate, where each chain extension unit introduced is correctly functionalised prior to addition of the next.[1] In the case of erythromycin (Eq (1), **Scheme 1**),[2] the primary heptapropionate framework in **1** is assembled by the polyketide synthase from a propionate starter unit **2** and six methyl malonyl extender units **3**, where the nascent chain remains bound to the acyl carrier protein (ACP). By mimicking this chain growth synthetically, the assembly of libraries of diverse *unnatural* polyketides can be envisaged through variation in the building blocks, the number of chain extensions, the stereochemical information, oxidation state, and the introduction of unsaturation or rings.

Eq (1): Iterative propionate chain extension



2 **3** **1** *6-deoxyerythronolide B*

Eq (2): Iterative dipropionate chain extension

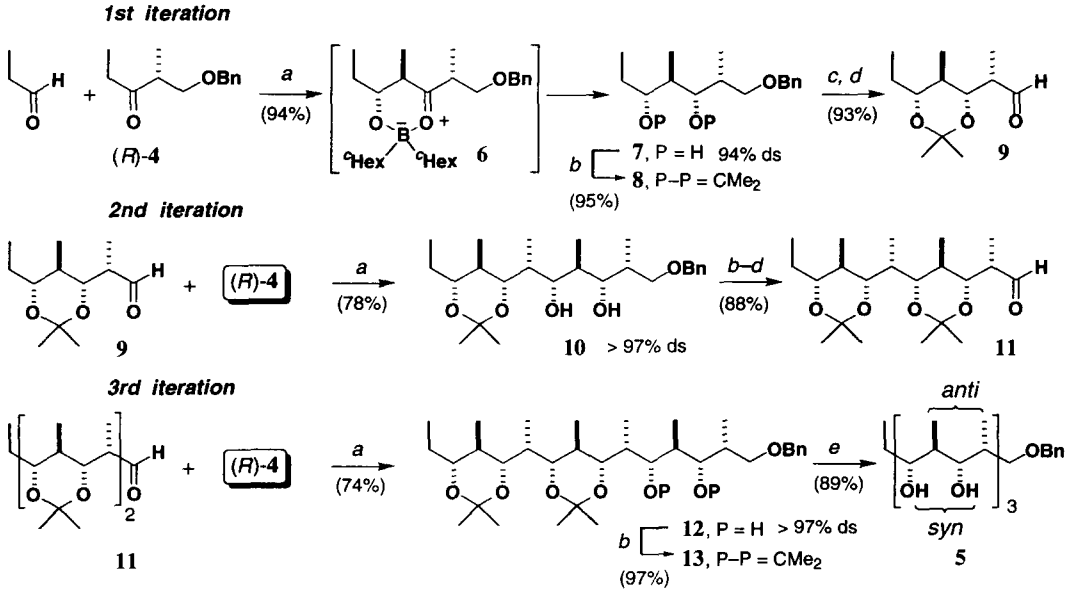


(*R*)-**4** **5**

Scheme 1

In initiating our studies in such polyketide library synthesis, we now report on the iterative construction of extended polypropionates using (*R*)- and (*S*)-1-(benzyloxy)-2-methylpentan-3-one (**4**) as dipropionate reagents for chain growth, *i.e.* as synthetic equivalents of **3**. This is illustrated by the synthesis of the heptapropionate **5**, shown in Eq (2) (**Scheme 1**), using the ketone (*R*)-**4** for three iterations. In this process, structural diversification may be achieved by varying the aldol bond construction step and ketone reduction sequences. Despite their acyclic and flexible nature, many of the resulting 1,3-polyol systems are expected to exhibit distinct conformational preferences, as discussed in the accompanying paper.[3]

The development of a reliable iterative protocol for the synthesis of stereotetrad units was first required. We had previously shown that selective generation of the (*E*)-enol dicyclohexylborinate of the ethyl ketones (*R*)- and (*S*)-**4** and aldol addition[4,5] to a variety of aldehydes, followed by reduction[6] *in situ*, proceeds with excellent diastereoselectivity. Using our standard enolisation procedure (**Scheme 2**),[5] *anti* aldol addition of (*R*)-**4** to propionaldehyde gave the intermediate aldolate **6**, which was reduced *in situ* with $LiBH_4$ to give the 1,3-*syn* diol **7** in 94% yield with 94% ds.[7] Protection as its acetonide **8** (95%) enabled the stereochemistry of the aldol bond construction and reduction to be confirmed.[8] With the required stereotetrad set up, the iterative protocol was completed by hydrogenolysis of the benzyl ether and Swern oxidation to give the aldehyde **9** (93%). In this way, the tripropionate building block **9** was obtained in four steps from (*R*)-**4** in 83% yield with 94% ds.

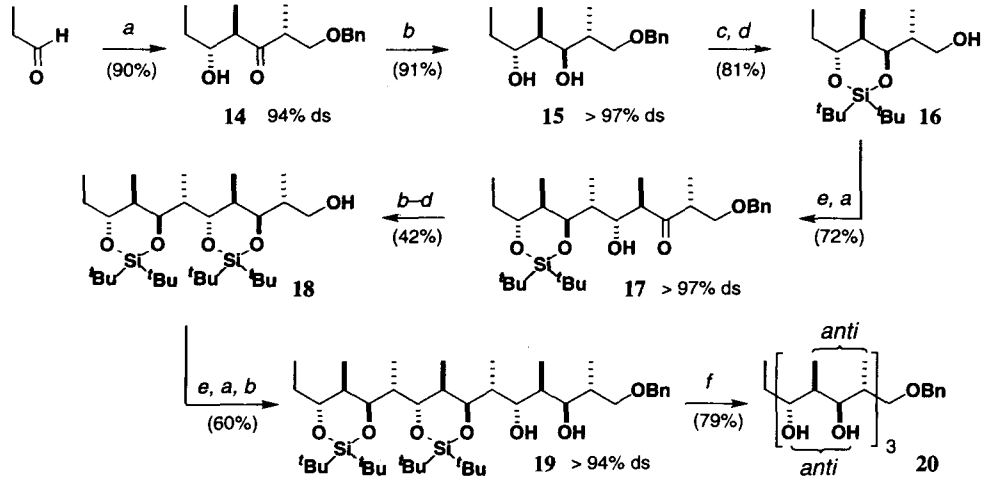


Scheme 2: (*a*) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C, 1.5 h; RCHO, −78 → −15 °C, 3.5 h; $LiBH_4$, −78 °C, 2 h; H_2O_2, 10% NaOH, MeOH, 2 h; (*b*) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 5 – 18 h; (*c*) $Pd(OH)_2$ / C, H_2, EtOH, 1 – 4 h; (*d*) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min; Et_3N, −78 → − 40 °C, 15 min; (e) Dowex-50, MeOH / H_2O (9:1), Δ, 4 h.

With these optimum reaction conditions, we applied this *syn*-reduction iterative sequence twice successively. The boron aldol reaction of aldehyde **9** with the (*E*)-enolate of (*R*)-**4**, followed by reduction *in situ* by $LiBH_4$, gave the 1,3-*syn* diol **10** in 78% yield with >97% ds. In this second iteration, the enhanced stereochemical fidelity is ascribed to matched asymmetric induction from the reaction partners in the aldol bond construction.[4,9] Using the standard 3-step sequence (*cf.* **7** → **9**), this was elaborated into aldehyde **11** (88%) in readiness for a further chain extension. The third iteration again proceeded with matched induction to give the diol **12** (74%, >97% ds). Protection of **12** as its triacetonide **13** (97%) led to diagnostic ^{13}C NMR acetal resonances at 97.2, 97.1 and 96.8 ppm.[8] Overall, the protected 1,3-polyol **13** was obtained in 41% overall yield (10 steps) from the starting ketone (*R*)-(**4**), with >88% ds for introduction of the 12 contiguous stereogenic centres. Finally, acetonide hydrolysis using activated Dowex-50 resin gave the hexol **5** (89%) in which the hydroxyls have an all-*syn* arrangement, combined with 1,3-*anti* methylation along the hydrocarbon backbone.[3]

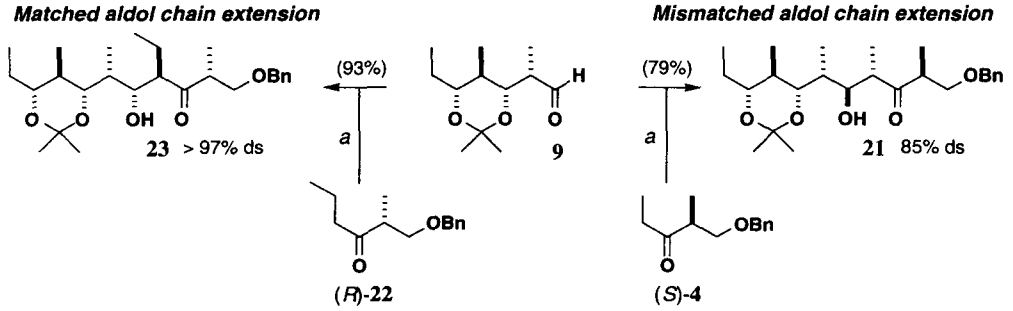
Having established an iterative protocol for dipropionate chain extension, we next sought to introduce structural diversity through stereochemical changes. First, the ketone reduction stereochemistry was reversed, as shown in **Scheme 3**. Using $Me_4NBH(OAc)_3$ for hydroxyl-directed reduction[10] of **14** gave the 1,3-*anti* diol

15 (91%, >97% ds). Silylene protection of this diol and debenzylation then provided the new tripropionate building block **16** (81%). After Swern oxidation, a second chain extension with (*R*)-**4** was performed to give the ketone **17** (72%, >97% ds). Application of the standard 3-step sequence (*cf.* **14** → **16**) then gave **18**, in readiness for a third dipropionate extension.[11] As before, the *anti* aldol reaction of (*R*)-**4** with the aldehyde derived from **18** was followed by *anti* reduction, leading to diol **19** (60%). At this stage, silylene deprotection was carried out (HF•py) to give the hexol **20** (79%). This isomeric heptapropionate has the same 1,3-*anti* methylation as in **5** but now the hydroxyls have a stereoregular 1,3-*anti* arrangement.[3]



Scheme 3: (*a*) (*R*)-**4**, *c*-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1.5 h; RCHO, –78 → –15 °C, 3.5 h; H$_2$O$_2$, pH 7, MeOH, 2 h; (*b*) Me$_4$NBH(OAc)$_3$, AcOH / MeCN, –20 °C, 13 – 44 h; (*c*) (*t*-Bu)$_2$Si(OTf)$_2$, 2,6-lutidine, CH$_2$Cl$_2$, 20 °C, 21 – 44 h; (*d*) 10% Pd / C, H$_2$, EtOH, 1.5 – 3 h; (*e*) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, –78 °C, 30 min; Et$_3$N, –78 → – 40 °C, 15 min; (*f*) HF•py, pyridine, THF, 14 h, 20 °C.

We now sought further library diversification by variation of the ketone building block with regard to the substitution and absolute configuration (**Scheme 4**). For example, an *anti* aldol reaction of the aldehyde **9** with the enantiomeric ketone (*S*)-**4** gave adduct **21** (79%) as the major isomer with 85% ds. In this more demanding mismatched case,[4,9] the high level of π-face selectivity from the (*E*)-enolate overrides any Felkin-Anh type influence from the aldehyde. Selecting (*R*)-**22**[6a] in the aldol reaction with **9** gave ketone **23** with high diastereoselectivity (>97% ds), as expected from a matched situation, demonstrating the potential for introducing substituents other than methyl in these extended polyketide systems.



Scheme 4: (*a*) *c*-Hex$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1.5 h; **9**, –78 → –15 °C, 3.5 h; H$_2$O$_2$, pH 7, MeOH, 2 h.

In summary, the ketones (*R*)- and (*S*)-**4** are demonstrated to be powerful dipropionate reagents,[12] enabling access to a library of stereodefined aliphatic polyketides. Further structural diversification should be possible by variation of the ketone substituent[13] and the stereochemistry of the aldol bond construction (*syn vs anti*).[14] Altogether, this work should provide a diverse range of novel polyoxygenated molecules with a hydrocarbon backbone, in contrast to the more conventional peptidic and peptidomimetic libraries currently available. Moreover, this synthetic approach to unnatural polyketides complements that provided by combinatorial biosynthesis.[2,15] Block coupling reactions of primary polyketide library members and applications to solid phase synthesis are now underway.

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