Synthesis of a versatile multifunctional building block for the construction of polyketide natural products containing ethyl side-chains†

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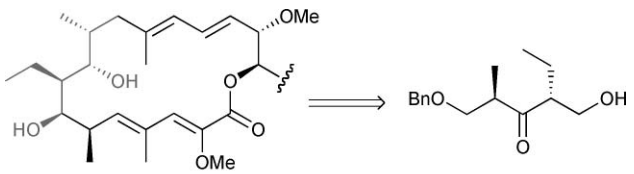
The synthesis of a multifunctional building block for polyketide construction and several subsequent reactions are presented.

Polyketides are a major class of natural products that are biosynthetically produced by sequential linkage of malonyl-CoA subunits. Some life forms of mainly marine origin also incorporate butyryl units in the form of ethylmalonyl-CoA into the growing chains, which leads to ethyl side-groups in the natural product.[1] Thus, stereoselective syntheses of building blocks for the construction of pharmacologically interesting compounds such as concanamycin A (**1**),[2] salinomycin,[3] lasalocid A[4] and others are highly significant. In this manuscript, we report the synthesis of a multifunctional building block for the synthesis of compounds such as **1** (Scheme 1).

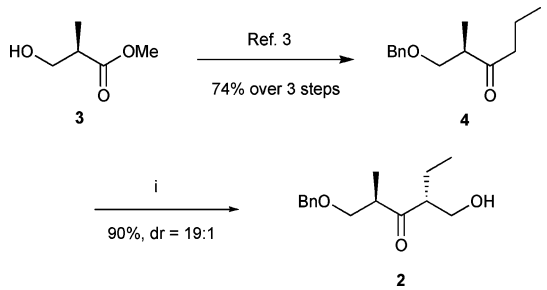


1 **2**

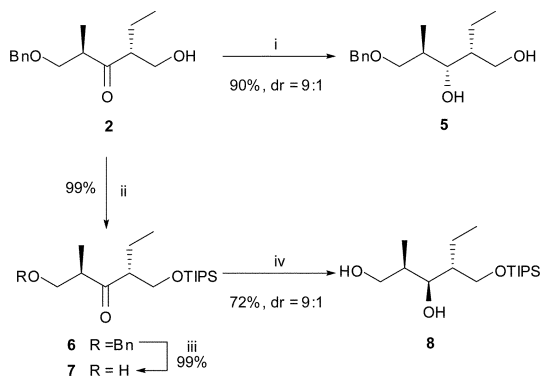
Scheme 1 Core structure of concanamycin A (**1**) and multifunctional building block **2**.

Our synthetic efforts started from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**3**), which was transformed to ketone **4** utilising a strategy originally developed by Paterson.[5] This intermediate was then reacted with gaseous formaldehyde in an *anti*-selective aldol reaction[6] using a commercially available hexane solution of chlorodicyclohexylborane. Upon oxidative workup using hydrogen peroxide in MeOH, we were able to obtain multifunctional building block **2** in an overall yield of 90% with a diastereoselectivity of 19 : 1 in favour of the *anti* isomer (Scheme 2).

This useful building block can easily be transformed to the corresponding triols. The stereochemistry of the newly formed alcohol function can be controlled by variation of the order of protecting group manipulations and reduction steps (Scheme 3). Direct chelation-controlled reduction of **2** using sodium triacetoxyborohydride[7] leads to clean reduction in a yield of 90% with a 9 : 1 diastereoselectivity in favour of the diastereomer with a *syn* relationship between the alcohol and ethyl groups. When **2** is first protected as a TIPS-derivative under standard conditions, debenzylated and then subjected to reduction, isomer **8**, with an *anti* relationship between the alcohol and ethyl groups, can be obtained in a yield of 72%. Thus, alcohols with opposite stereochemistry at C-3 can be synthesized using a similar methodology in comparable yields and stereoisomeric purities.



Scheme 2 *Reagents and conditions*: (i) a) (*c*-Hex)$_2$BCl (1.5 equiv.), NEt$_3$ (1.8 equiv.), Et$_2$O, −78 °C, then 0 °C, 2 h; b) formaldehyde (4.0 equiv.), −78 °C, 2 h, then −26 °C, 14 h; c) H_2O_2, MeOH–pH7 buffer, 90%, dr = 19 : 1.



Scheme 3 *Reagents and conditions*: (i) NaBH(OAc)$_3$ (3.0 equiv.), THF–AcOH, 0 °C, 18 h, 90%, dr = 9 : 1; (ii) TIPSCl (1.1 equiv.), imidazole (2.5 equiv.), DMAP (cat.), CH_2Cl_2, rt, 22 h, 99%; (iii), H_2, 10% Pd/C, MeOH, rt, 4 h, 99%; (iv) repeat of step (i), 72%, dr = 9 : 1.

To emphasize the utility of our approach, we developed two routes that could be useful in the application of these building blocks to the synthesis of complex natural products. As the Wittig reaction is a useful approach for fragment union, we transformed alcohol **8** using the sequence detailed in Scheme 4. We were able to obtain Wittig salt **10** in a overall yield of 47% starting from **8** using

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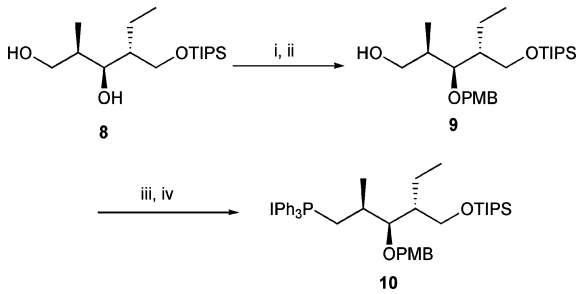
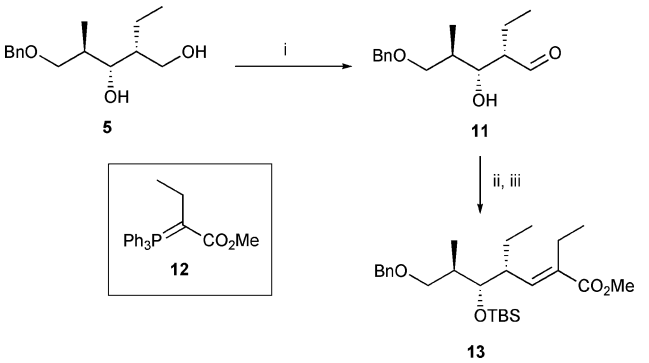


Scheme 4 *Reagents and conditions*: (i) $PMPCH(OMe)_2$ (5.0 equiv.), *p*-TsOH (0.1 equiv.), $CHCl_3$, rt, 5 h, 95%; (ii) DIBAL-H (5.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 68%; (iii) PPh_3 (2.0 equiv.), imidazole (2.2 equiv.), I_2 (2.0 equiv.), CH_2Cl_2, rt, 1 h, 99%; (iv) PPh_3 (10.0 equiv.), 95 °C, 20 h, 84%.

a sequence of acetalisation, regioselective opening, iodination and salt formation. The Wittig salt could then be used as building block in subsequent reaction steps.

We finally elaborated a second reaction series for the homologation of derivative **5**. These efforts are summarised in Scheme 5. Monoprotected diol **5** can be transformed to aldehyde **11** upon oxidation using TEMPO with iodobenzene diacetate as a stoichiometric oxidant.[8] Wittig reaction with stabilized ylide **12**[9] proceeded uneventfully, though it was crucial to introduce the TBS protection afterwards for reasonable yields in the olefination reaction. Final protection provided us with homologated compound **13** in an overall yield of 64%.

In conclusion, we have detailed the synthesis of a multifunctional building block for polyketide synthesis. We have shown that this building block can easily be transformed to a number of more advanced intermediates that can be useful for the synthesis of complex natural products.



Scheme 5 *Reagents and conditions*: (i) TEMPO (0.2 equiv.), iodobenzene diacetate (1.2 equiv.), CH_2Cl_2, rt, 10 h; (ii) **12**, benzene, reflux, 10 h, 80% over 2 steps, $E/Z = 9:1$; (iii) TBSOTf (1.1 equiv.), 2,6-lutidine (2.0 equiv.), CH_2Cl_2, 0 °C, 1 h, then rt, 20 h, 80%.

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