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Synthesis of discodermolide intermediates from engineered polyketides

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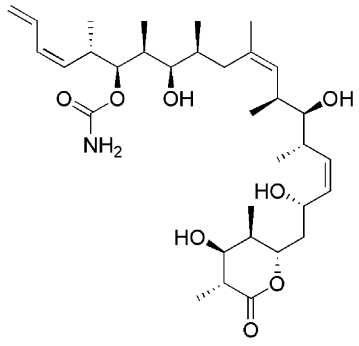
Abstract—Key intermediates used in Smith's total synthesis of discodermolide were synthesized from an engineered polyketide made via precursor feeding to genetically modified polyketide producing bacteria.

(+)-Discodermolide **1** (Fig. 1), a polyketide natural product isolated from the marine sponge *Discodermia dissoluta*,[1] has potent growth inhibitory activity against human tumor cell lines.[2,3] The mode of action, similar to that of paclitaxel, involves the assembly and stabilization of microtubules, leading to mitotic arrest and ultimately cell death.[3] Attempts to acquire practically useful quantities of (+)-discodermolide, either by cultivation of the producing sponge, or via harvesting of the organism in the wild have thus far failed. Therefore totally synthetic (+)-**1** was necessary to permit human clinical trials.[4] Any methods that would reduce the difficulty and cost of the synthetic effort would be of great value to such endeavors.



Discodermolide
(1)

Figure 1. Structures of 6-dEB and discodermolide.

Production of modified polyketides via genetic manipulation of the organisms that synthesize these natural products has been well documented,[5] most notably in the case of modified erythronolides and erythromycins.[6] Recently, a series of 'unnatural' polyketides were produced in *E. coli* via a de novo design and rearrangement of modular polyketide synthase genes.[7] By these methodologies it is now possible to obtain engineered polyketides, which may then be modified and assembled into otherwise unavailable complex natural products and their analogues. We report in this letter the implementation of this technology, by which the marine natural product discodermolide may be assembled using synthons derived from an engineered polyketide fragment.

There are many published syntheses of discodermolide,[8] however the modular nature of Smith's total synthesis,[8h] using a common precursor (CP) **3** to synthesize the three major substructures of discodermolide was perfectly suited to demonstrate this methodology (Fig. 2). An economical synthesis of a number of racemic 'diketide thioesters' including (±)-**10** has been previously reported,[9] as well as the efficient conversion of these synthetic diketides via fermentation, using bacteria with modified 6-dEB PKS genes, to produce 'vinyl TKL', (3R,4S,5R,6R)-tetrahydro-4-hydroxy-3,5-dimethyl-6-vinylpyran-2-one[10] **11** (Fig. 3).

An inspection of the intermediate polyketide backbone of **11** prior to cyclization shows the significant structural similarity to CP (Fig. 3). The vinyl group was chosen to start the polyketide chain as it provides significant flexibility for chemical manipulation. Two routes were explored to affect the conversion of **11** into

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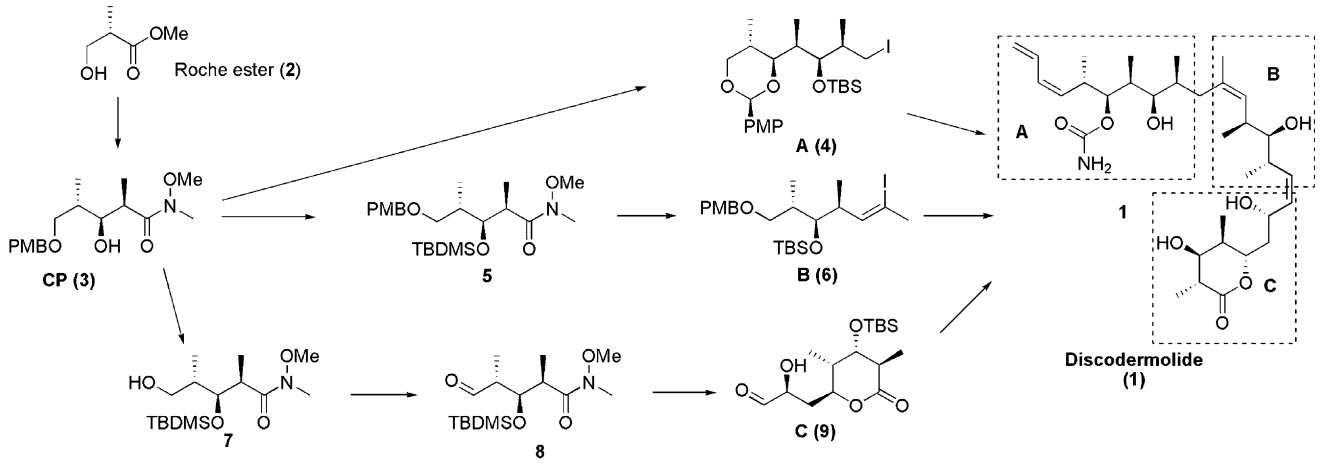


Figure 2. Smith's synthesis of discodermolide.

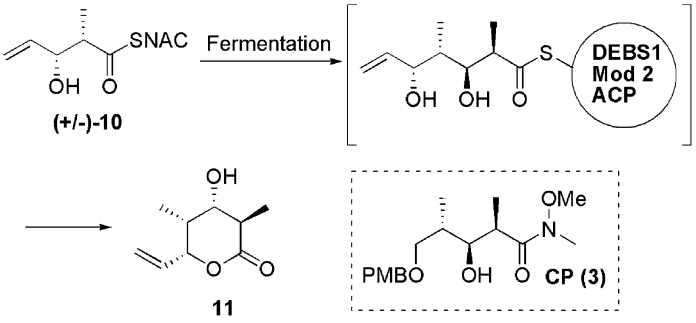
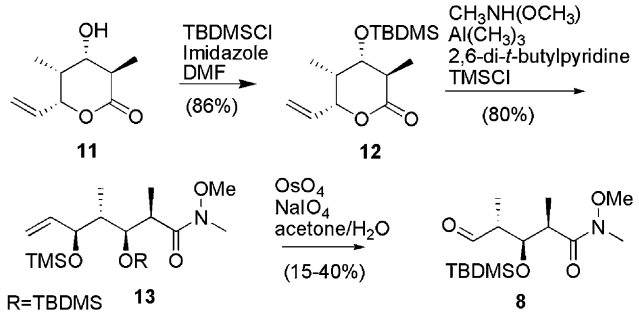
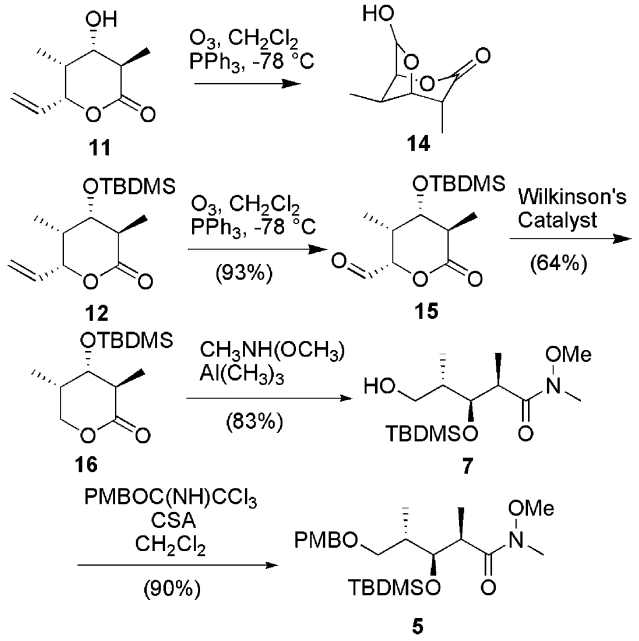


Figure 3. Fermentation of SNAC diketide to produce 'vinyl TKL'.



Scheme 1. Oxidative cleavage route.



Scheme 2. Decarbonylation route.

intermediates used in the Smith synthesis: (a) the conversion of the olefin to the aldehyde followed by decarbonylation, and (b) an essentially 'one pot iterative oxidative cleavage (Schemes 1 and 2). The latter method allowed quick access to an advanced intermediate in the synthetic manifold of the 'C' fragment. Protection of the secondary alcohol of **11** according to the conditions of Corey and Venkateswarlu[11] gave the silyl ether **12** in good yield. However, ring opening to the Weinreb amide required forcing conditions and the reaction could not be driven to completion. This was exacerbated upon work-up as the product readily recyclized. The problem was overcome by the addition of trimethylsilyl chloride and 2,6-dimethylpyridine to the reaction mixture, trapping the aluminum alkoxide as the TMS ether, preventing recyclization. This provided the desired amide in very good yield. Concomitant removal of the

silyl group and iterative oxidative cleavage of the vinyl group gave the aldehyde **8**, an advanced intermediate used to make fragment C (**9**) in Smith's discodermolide synthesis. This route using 'vinyl TKL' is three steps as compared to seven steps starting from the Roche ester (**2**). The last step is currently being optimized to improve the overall yield and reproducibility.

To probe the decarbonylation route, ozonolysis was employed to oxidize the olefin of **11** (Scheme 2). This gave the desired aldehyde that spontaneously formed the bicyclic acetal **14**. Decarbonylation using Wilkinson's catalyst[12] was ineffective, as was reduction by sodium borohydride, suggesting that the compound exists exclusively in the acetal form. Ozonolysis of the silyl ether **12** at −78 °C, followed by reduction of the ozonide with triphenylphosphine provided the aldehyde **15** in excellent yield. Decarbonylation using Wilkinson's catalyst furnished the desired lactone **16**. This lactone has been used in the syntheses of a number of natural products including a synthetic approach to dictyostatin by Curran and co-workers,[13] as well as alternative syntheses of discodermolide and analogues.[14] Interestingly, ring opening proceeded smoothly, and careful work-up avoided the previous recyclization issues yielding Weinreb amide **7**, which can be used to make fragment C (**9**). Protection of the primary alcohol as the parmethoxybenzyl ether[15] gave the desired intermediate **5** used in the synthesis of fragment B (**6**), thus providing two late stage entry points into Smith's synthesis of discodermolide.

This letter demonstrates the utility and potential of engineered polyketide fragments derived from well known, readily available polyketides such as 6-dEB, through genetic manipulation and expression of the modified PKS genes in the appropriate production organisms, and the use of these custom polyketides to construct other complex polyketide natural products.

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