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Chemoenzymatic Synthesis of the C10–C23 Segment of Dictyostatin

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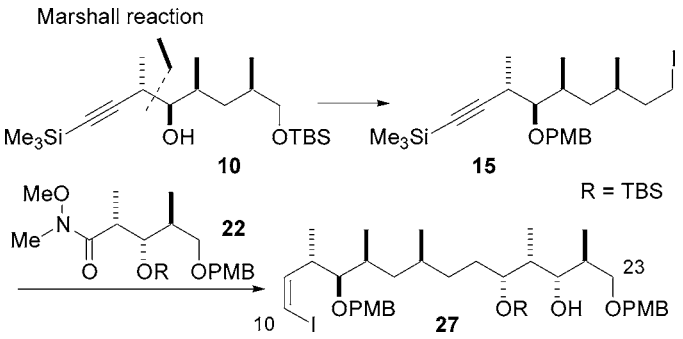
ABSTRACT



Employing enzymatic desymmetrization and resolution, respectively, the two aldehydes 8 and 20 were prepared. The precursor to aldehyde 8, *meso*-2,4-dimethylglutaric anhydride 3, could be obtained by base treatment of the diastereomeric mixture. Aldehyde 8 was extended to alkyne 10 by a Marshall reaction introducing four carbon atoms. Lithiation of the derived iodide 15 and trapping of the anion with amide 22 gave ketone 23. This compound led to the C10–C23 fragment 27 of dictyostatin.

A range of cytotoxic natural products confer their biological activity through stabilization of the microtubule during cell division. The taxol and epothilone cases show that this mode of action can be of enormous clinical relevance.[1] Nevertheless, undesired toxicity or sensitivity toward the P-glycoprotein efflux pump can render compounds unsuitable for further clinical development. The polyketide dictyostatin (**1**) also turned out to be an inducer of tubulin polymerization (Figure 1). Most interestingly, it retains this activity in cells expressing the P-glycoprotein pump.[2] The 22-membered macrolide was originally isolated by Pettit and co-workers.[3] Later, Wright et al. found the same compound in a different sponge.[2] Although the constitution was known, the stereochemistry was reported only recently by Wright and Paterson.[4] A striking feature of dictyostatin is its structural similarity to discodermolide. In fact, the 10 stereocenters in the overlapping regions all have the same configuration. This similarity was first recognized and exploited by Curran for the synthesis of discodermolide/dictyostatin hybrids.[5] So far, total syntheses of dictyostatin have been achieved by the

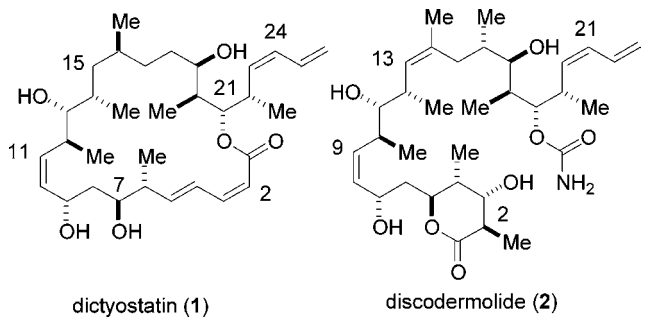


Figure 1. Structures of dictyostatin (**1**) and discodermolide (**2**).

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groups of Curran[6] and Paterson.[7] In addition, the synthesis of the C9−C19 subunit was described by Philipps.[8] Biological studies are consistent with the hypothesis that the macrocyclic structure of dictyostatin resembles the bioactive conformation of the more flexible discodermolide.[9] Most recently, an analogue, 16-normethyldictyostatin, turned out to have an activity profile toward several cell lines different from that of dictyostatin.[10]

The macrolactone of dictyostatin features a dienoate, a dienyl side chain, and several clusters of stereocenters that are commonly found in polyketides.[11,12] Proven strategies to reach the stereotriads of discodermolide are based on aldol reactions with the Roche aldehyde[13−16] or with methacrolein followed by hydroboration.[17] To combine the various subunits, the Paterson group employed Wittig−Horner reactions. The Curran synthesis features an acetylide addition to a Weinreb amide and a Wittig−Horner coupling as key steps for connecting the subunits.

We devised a strategy to dictyostatin on the basis of an intramolecular Nozaki−Hiyama−Kishi reaction (Figure 2, structure **A**).[18−20] Building block **B** containing a Z-vinyl iodide can be traced back to the 2,4-pentane diol **C** which is available from the corresponding diol by enzymatic symmetry breaking.[21] As an alternative, building block **D** could also be considered. Finally, we wanted to circumvent the use of the Roche ester because of its prohibitive costs. In this paper, we illustrate the realization of these goals.

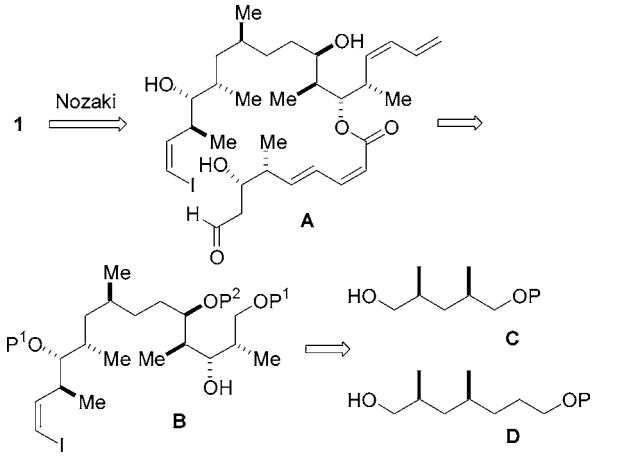

Figure 2. Retrosynthetic cuts for dictyostatin (**1**).

The *meso*-diol **4** is available by reduction of the anhydride *meso*-**3** (Scheme 1). Unfortunately, the synthesis produces a mixture of diastereomeric anhydrides that has to be separated by repeated recrystallization leading to a low yield for *meso*-**3**.[22] However, we found that the diastereomeric mixture of *meso*-**3**/*dl*-**3** could be converted more or less completely to *meso*-**3** by stirring the mixture with Hünig's base in ethyl acetate. One crystallization provided the *meso*-anhydride in excellent yield. The derived diol **4** was then converted to the acetate **5** using lipase Amano AK in the presence of vinyl acetate.[23] This reaction could be run on a multigram scale in high ee (98%). Silylation and basic cleavage of the acetate gave alcohol **7**.[24] This operation could be performed without chromatography. Oxidation[25] of alcohol **7** with bis(acetoxy)iodobenzene in the presence of catalytic amounts of tetramethyl-1-piperidinyloxyl (TEMPO)

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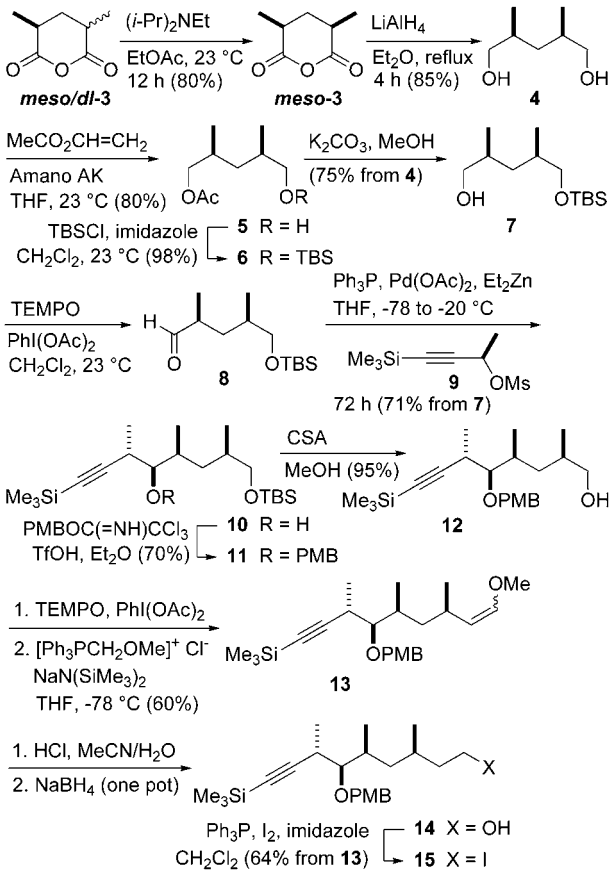
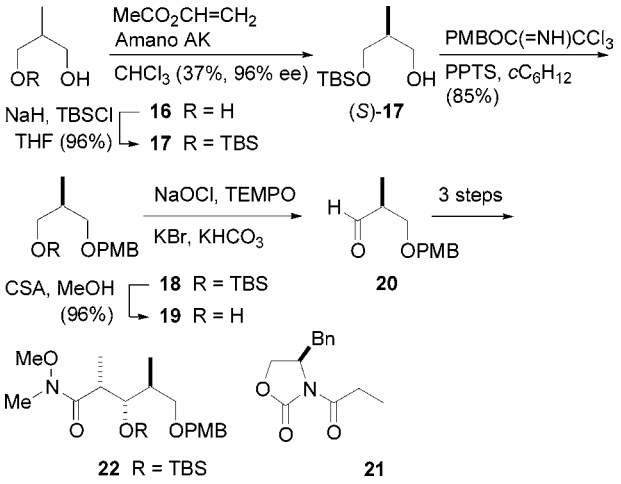
Scheme 1. Synthesis of the C10−C18 Fragment of Dictyostatin



led to aldehyde **8**. For the introduction of the stereocenters at C-12 and C-13, an *anti*-aldol reaction or an equivalent thereof was required. Although chain extension turned out to be possible with the Abiko reagent,[26] the subsequent functional group manipulations to introduce an alkyne were too elaborate. We therefore turned to the Marshall reaction which is characterized by addition of a chiral allenyl metal to an aldehyde.[27] The corresponding starting material, 4-trimethylsilyl-3-butyn-2-ol, is available by lipase-catalyzed resolution. In the event, reaction of the allenyl zinc reagent derived from mesylate[28] **9** introduced the necessary stereocenters and all required four carbon atoms. The diastereoselectivity of the reaction was greater than 90:10. Although the reaction is rather slow, its great advantage is that four carbons are introduced in one operation. After protection of the secondary hydroxyl function as its *p*-methoxybenzyl ether,[29] the primary silicon ether was cleaved. Through the classical sequence of oxidation, Wittig reaction with (methoxymethylene)(triphenyl)phosphorane to give the enol ethers **13**, hydrolysis, and reduction, the homologated alcohol **14** was obtained. Instead of extension of **14** via aldol or related technologies in a linear approach, we opted for a coupling with a more elaborate right-hand fragment. For this purpose, alcohol **14** was converted to iodide **15** using I_2 and Ph_3P.[30]

As a suitable right-hand building block, we initially chose the known Weinreb amide **22**.[13a] However, aldehyde **20** was not prepared from the Roche ester but rather from diol **16** (Scheme 2). Because an enzymatic desymmetrization is not

Scheme 2. Synthesis of the Weinreb Amide **22** from the Diol **16**



very efficient with this diol, resolution of the racemic mono-*tert*-butyldimethylsilyl ether *rac*-**17** was performed.[31] Via a lipase-mediated acetylation followed by chromatographic separation of alcohol and acetate, the alcohol **17** could be obtained in 37% yield and 96% ee. Two further steps, namely, etherification with the PMB imidiate followed by cleavage of the silyl ether under acidic conditions using camphorsulfonic acid (CSA), delivered alcohol **19**. As was checked by Mosher analysis, these protecting group manipulations proceeded without loss of optical purity. After oxidation of **19**, the derived aldehyde **20** was extended by an Evans aldol reaction[32] using the propionyl oxazolidinone **21** as described in the literature, leading to building block **22**.[13a]

The combination of iodide **15** and Weinreb amide **22** could be achieved in an efficient manner via lithiation of iodide **15** with *t*-BuLi (2 equiv) followed by addition of amide **22** to produce ketone **23** (Scheme 3). At this point, the trimethylsilyl-protected alkyne was converted to the (*Z*)-vinyl iodide by treatment of **23** with *N*-iodosuccinimide (NIS) followed by diimide reduction of the resulting iodoalkyne.[33] This way, vinyl iodide **24** could be secured in excellent yield.

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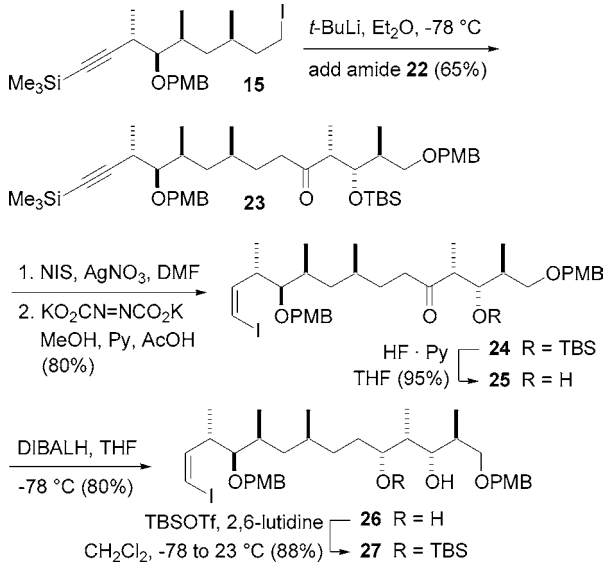
Scheme 3. Combination of the Iodide **15** and the Weinreb Amide **22** and Transformation of the Resulting Ketone **23** to the C10−C23 Building Block **27**



Subsequently, the silyl ether was cleaved using the HF·pyridine complex.[34] Treatment of the hydroxy ketone **25** with DIBALH in THF induced a *syn*-selective reduction furnishing the 1,3-diol **26**.[35] Among the two hydroxyl groups of **26**, the left one (OH-19) is less hindered, and in fact, a selective silylation was easily possible,[7] completing the synthesis of the C10−C23 segment **27**.

In summary, we could illustrate the use of *meso*-diol **4** for the synthesis of an important dictyostatin subunit. This diol is now easily available by equilibration of the diastereomeric dimethylglutaric anhydride. After enzymatic resolution of **4**, the derived aldehyde **8** was extended in one step to alkyne **10** via a Marshall reaction. Subsequently, homologation of **12** and coupling of the derived iodide **15** with Weinreb amide **22** led to ketone **23**. A *syn*-selective reduction on hydroxyketone **25** and a selective silylation completed the synthesis of the C10−C23 dictyostatin fragment **27**. Out of the eight stereocenters, five were ultimately derived by chemoenzymatic methods.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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