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Synthesis of the C11–C23 Fragment of the Potent Antitumor Agent Dictyostatin

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We wish to report here our initial efforts toward the total synthesis of the potent antitumor agent dictyostatin, describing a short and efficient synthesis of the C11–C23 fragment.

Introduction

The marine-derived macrolactone dictyostatin is a potent antitumor agent, which acts by microtubule stabilization (Figure 1). Dictyostatin was first isolated in small amounts by Pettit and coworkers[1] from the marine sponge *Spongia sp.* and more recently by Wright and coworkers[2] from *Corallistidae* sponges.[3,4]

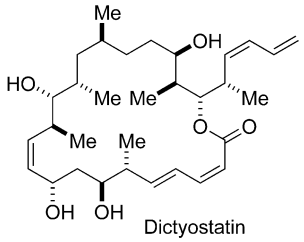

Figure 1. Structure of dictyostatin.

The structure of dictyostatin, an unsaturated 22-membered macrolactone containing 11 stereocenters, a *Z*-alkene, and two diene systems, was deduced by Pettit and coworkers. The stereochemical assignments were made on the basis of the elegant total synthesis described by the research groups of Paterson and Curran.[5,6]

As the natural supply is extremely restricted and attracted by its impressive anticancer activity, we initiated a project directed toward the total synthesis of dictyostatin.[7,8] An efficient and flexible synthesis is essential to provide material for more-extensive biological studies, along with access to novel analogs. In this work we describe an efficient synthesis of the C11–C23 fragment, an important intermediate in a planned total synthesis of dictyostatin.[9] This fragment contains 8 of the 11 stereocenters of dictyostatin.

Results and Discussion

Our approach began with an asymmetric aldol addition of the boron enolate derived from oxazolidinone (*R*)-**1** with aldehyde **2** to give aldol adduct **3** in 75% yield, exhibiting excellent diastereoselectivity (*dr* >95:5) (Scheme 1).[10,11] Exchange of the oxazolidinone auxiliary in *syn*-aldol **3** with *N*,*O*-dimethylhydroxylamine generated the Weinreb amide, whose purification was performed by isolation of the recyclable oxazolidinone chiral auxiliary (92%) by efficient crystallization from the reaction mixture.[12] Protection of the OH function as its TBS ether cleanly provided Weinreb amide **4** in 90% yield (over two steps, transamidation and TBS protection). This amide was smoothly reduced to the aldehyde upon treatment with diisobutylaluminum hydride in toluene at –78 °C (Scheme 1). This unpurified aldehyde was directly subjected to a Horner–Wadsworth–Emmons homologation with required phosphonate reagent **5**, under Ando's conditions, to give α,β-unsaturated ester **6** in 90% isolated yield (*Z*/*E*, 90:10) over the two-step sequence.[13] This corresponds to the C11–C17 fragment.

Subsequent efficient removal of the TBS protecting group positioned at C13 with concomitant lactonization was achieved upon treatment of **6** with a catalytic amount of CSA in MeOH to give α,β-unsaturated lactone **7** in 80% isolated yield, after purification by silica-gel column chromatography (Scheme 2). Selective hydrogenation[14] of the double bond proceeded smoothly leaving the PMB group intact to give the corresponding saturated lactone **8**,[15] which after treatment with $LiAlH_4$ in THF followed

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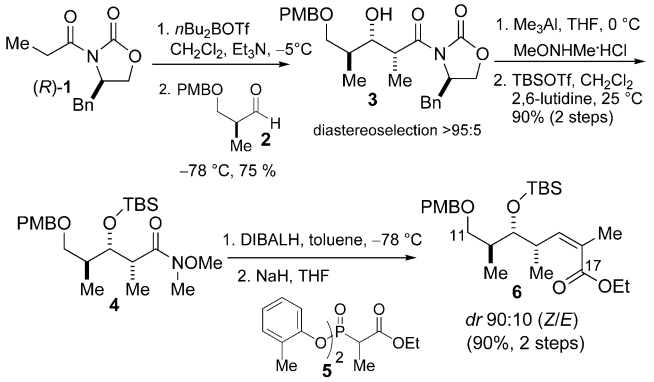
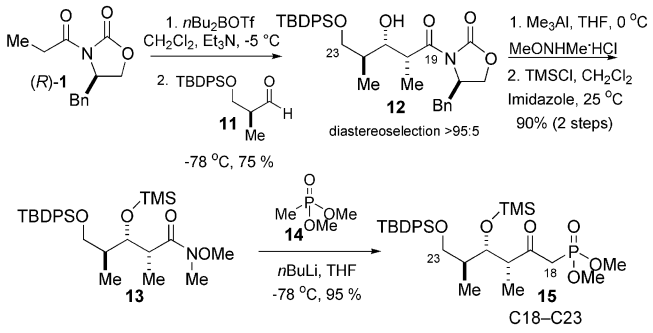
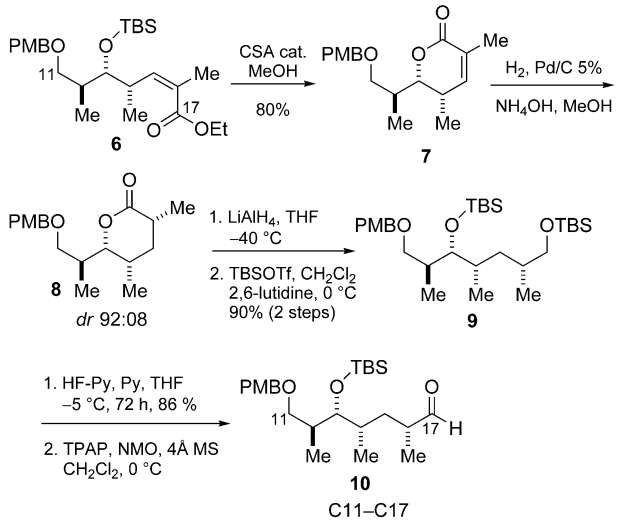


Scheme 1. Synthesis of the C11–C17 fragment.



Scheme 3. Preparation of ketophosphonate **15**.

by full protection of the corresponding diol, gave PMB ether **9** in 90% yield for the two-step sequence. Selective removal of the primary TBS group was accomplished by treatment of **9** with HF-Py in pyridine/THF as solvent to give a primary alcohol that was treated with TPAP/NMO[16] in CH_2Cl_2 to give aldehyde **10**, corresponding to the C11–C17 fragment of dictyostatin.

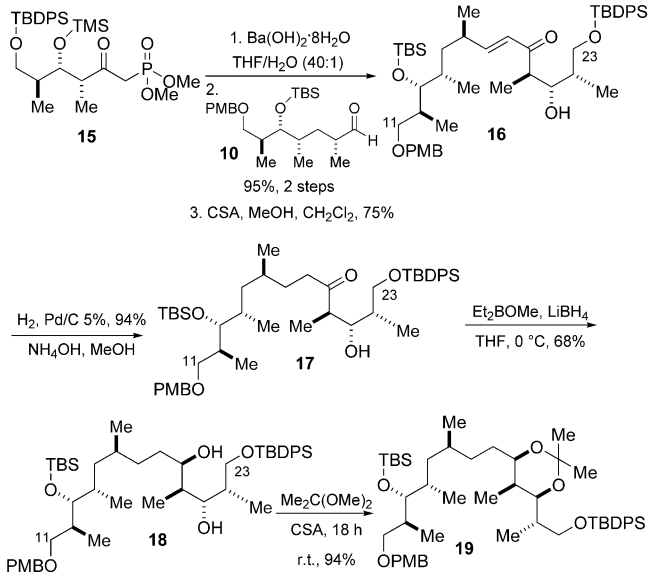


Scheme 2. Preparation of aldehyde **10**.

We next moved to the preparation of ketophosphonate **15**, corresponding to the C18–C23 fragment, necessary to couple with fragment C11–C17 (Scheme 3). Weinreb amide **13** was prepared by using the same strategy as that applied to the synthesis of **4** (Scheme 1).

The aldol reaction of **1** with aldehyde **11** gave **12** in 75% yield and >95:05 diastereoselectivity (Scheme 3).[10,11] Transamidation followed by protection of the hydroxy function as its TMS ether gave amide **13** (90% yield, two steps).[12] The optimal conditions involved treatment of Weinreb amide **13** with the lithium anion of methylphosphonate **14** to give ketophosphonate **15** in 95% yield.[17]

With fragments C11–C17 and C18–C23 (**10** and **15**, respectively) in hand, their coupling was undertaken (Scheme 4). This was accomplished by a Horner–Wadsworth–Emmons homologation of aldehyde **10** with ketophosphonate **15** that proceeded smoothly to give the corresponding α,β-unsaturated ketone **16** after treatment with a catalytic amount of CSA in MeOH ($E/Z > 95:05$) in 71% yield (three steps).[18] Double-bond hydrogenation[15] provided **17**, which was followed by selective 1,3-*syn* reduction[19] of the carbonyl function to give diol **18** in 95% overall yield (two steps).



Scheme 4. Synthesis of the C11–C23 fragment.

The stereochemistry of the secondary alcohols at C19 and C21 in **18** was determined on the basis of ^{13}C NMR spectroscopic analysis of the corresponding 1,3-acetonide **19**, prepared in 94% yield from diol **18** (Scheme 4). ^{13}C NMR resonances at δ = 19.7, 26.9, and 98.7 ppm are characteristic of a *syn* acetonide.[20]

Conclusions

We have described here an efficient asymmetric synthesis of the C11–C23 fragment of dictyostatin. Notable features of this approach include selective hydrogenation of an α,β-unsaturated lactone and a very efficient Horner–Wads-

worth–Emmons homologation to couple fragments C11–C17 and C18–C23. The synthesis required 15 steps from (*R*)-**1** (longest linear sequence) and produced the C11–C23 fragment of dictyostatin in good overall yield. This approach is amenable to a gram scale-up and is, in principle, readily applicable for the preparation of dictyostatin as well as to additional analogs.[21] Extension of this work toward completion of the synthesis of dictyostatin is underway and the results will be described in due course.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for the prepared compounds.

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