

Synthesis of the C1-C9 Fragment of the Potent Antitumor Agent Dictyostatin

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Descrevemos neste trabalho uma síntese curta e eficiente para o fragmento C1-C9 do potente agente antitumoral dictyostatina. Esta abordagem sintética inclui uma reação de epoxidação assimétrica de Sharpless seguida da abertura de epóxido nas condições de Myashita para introduzir os centros estereogênicos em C6 e C7 e uma reação de olefinação tipo Horner-Wadsworth-Emmons nas condições de Ando para construir a ligação com geometria *Z*/do dieno 1,3-*Z*/*E*.

We describe herein a short and efficient synthesis of the C1-C9 fragment of the potent antitumor agent dictyostatin. Notable features of this approach include a Sharpless asymmetric epoxidation followed by epoxide opening under Myashita's conditions to introduce the stereogenic centers at C6 and C7, and a Horner-Wadsworth-Emmons type reaction under Ando's conditions to construct the *Z*-double bond of the 1,3-*(Z,E)*-diene system.

Keywords: total synthesis, dictyostatin, Sharpless asymmetric epoxidation, macrolactone

Introduction

The marine-derived macrolactone dictyostatin (**1**) was isolated by Pettit and co-workers¹ from the marine sponge *Spongia sp.* as well as by Wright and co-workers² from *Corallistidae* sponges. Dictyostatin is a potent antitumor agent, with microtubule stabilization activity (Figure 1).^{3,4}

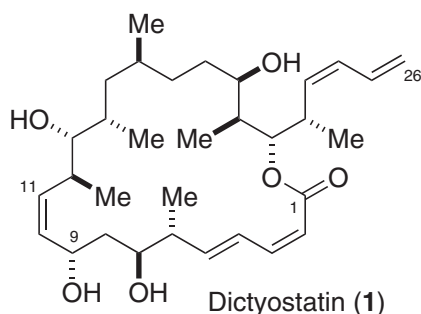


Figure 1. Structure of dictyostatin (**1**).

The structure of dictyostatin was deduced by Pettit and co-workers,¹ and the stereochemical assignments were made on the basis of the total syntheses described by the research groups of Paterson and Curran.^{5,6}

Due to its potent antitumor activity, a number of research groups have described the total synthesis of dictyostatin.^{5,6} Our research group also initiated a project

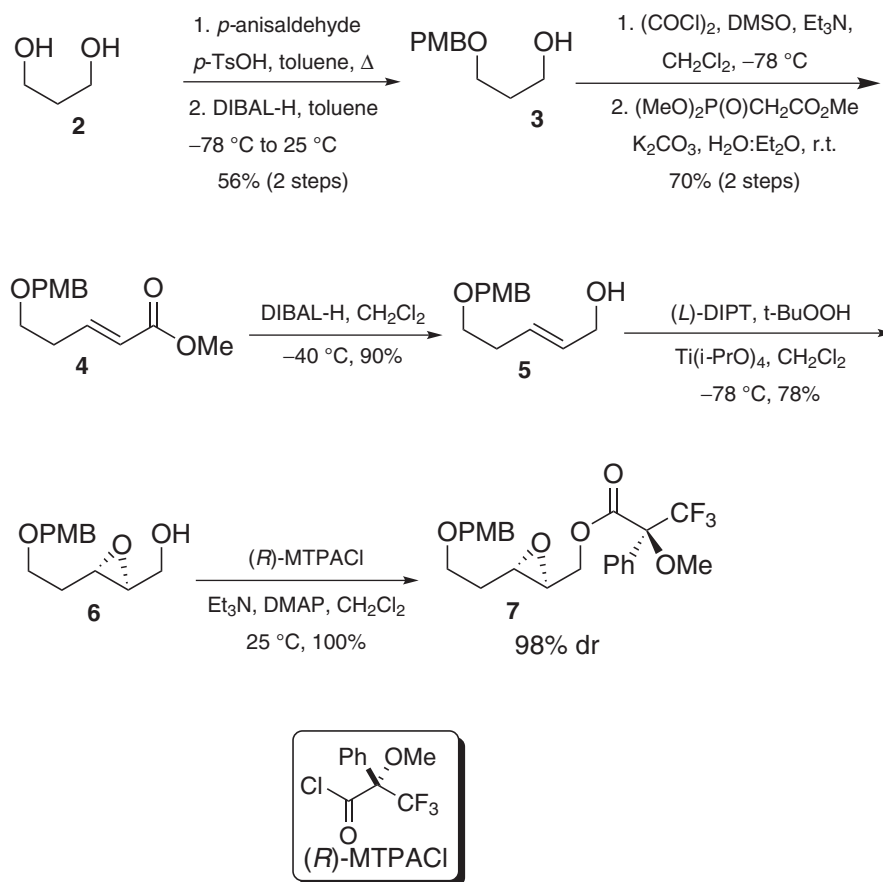
toward the total synthesis of dictyostatin, which resulted in the synthesis of the C11-C23 fragment.⁷ In this work we wish to describe a practical synthesis of the C1-C9 fragment of this potent antitumor agent.

Results and Discussion

Our approach began with monoprotection of diol **2** as the *p*-methoxybenzyl ether (Scheme 1). We have applied the strategy of creating a ketal group, followed by opening of this ketal with DIBAL-H in toluene to give the monoprotected alcohol **3** in 56% overall yield over two steps.⁸ Alcohol **3** was converted to the corresponding aldehyde using the Swern oxidation protocol, and the crude aldehyde was directly subjected to a Horner-Wadsworth-Emmons reaction to give (*E*)- α,β -unsaturated ester **4** in 70% yield (*E:Z* > 95:5) over two steps (Scheme 1).⁹

The ester **4** was reduced to the allylic alcohol **5** upon treatment with DIBAL-H in CH_2Cl_2 at -40°C in 90% yield. Overall, alcohol **5** was prepared in 35% yield after 5 steps starting from diol **2**. Then, alcohol **5** was submitted to a Sharpless asymmetric epoxidation using (–)-DIPT to afford the desired epoxy alcohol **6** in 78% yield and 98% *ee*. The absolute configuration of epoxy alcohol **6** was confirmed by comparison of the value of the optical rotation described in the literature (observed: $[\alpha]_{\text{D}} +25$, *c* 1.15; CHCl_3 ; literature: $[\alpha]_{\text{D}} -25.3$ *c* 1.09, CHCl_3 , for antipode epoxy alcohol **6**).^{9,10} The enantiomeric excess

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Scheme 1. Preparation of epoxy alcohol **6**.

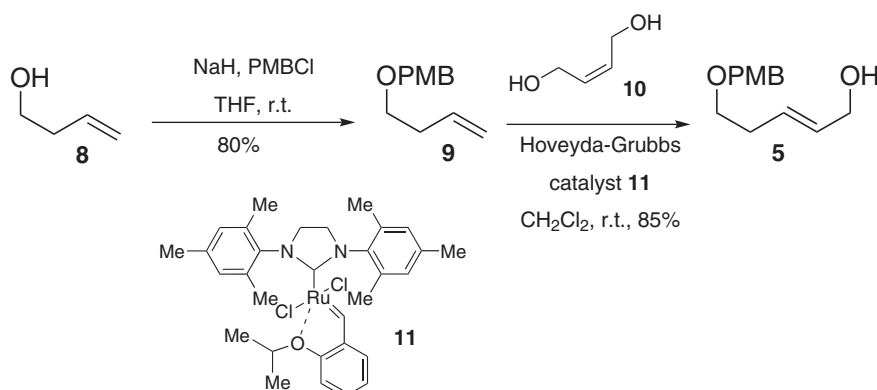
was determined using the Mosher ester method, as shown in Scheme 1.¹¹

In addition, we have prepared allylic alcohol **5** by a shorter synthetic route (Scheme 2).¹² Homoallylic alcohol **8** was converted to the corresponding *p*-methoxybenzyl ether **9** in 80% yield. A cross metathesis reaction of **9** with *cis*-2-buten-1,4-diol (**10**) in the presence of Hoveyda-Grubbs second generation catalyst **11** afforded allylic alcohol **5** in 85% yield.

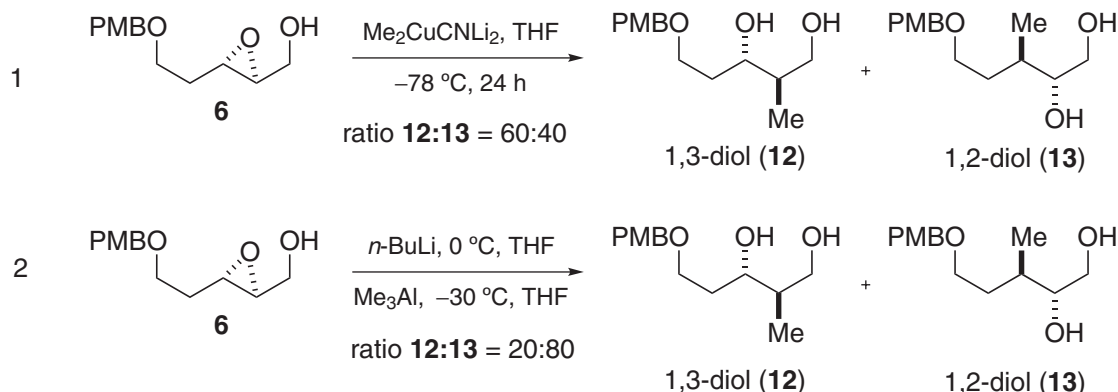
Based on literature precedent it seemed feasible that the regioselective nucleophilic addition of an

organocuprate could be used to install the desired methyl group at the 2 position of 2,3-epoxyalkanes.¹³ Unfortunately, we observed poor regioselectivity, and mixtures of 1,3-diol (**12**) and 1,2-diol (**13**) were obtained (Scheme 3). In addition, the use of *n*-BuLi/ Me_3Al led to a 20:80 mixture of **12** and **13**.

To overcome this problem we decided to use Myashita's methodology for nucleophilic substitution of γ,δ -epoxy acrylates.¹⁴ This strategy seemed promising, because nucleophilic substitution into (*E*)- γ,δ -epoxy acrylate would



Scheme 2. Alternative preparation of allylic alcohol **5**.



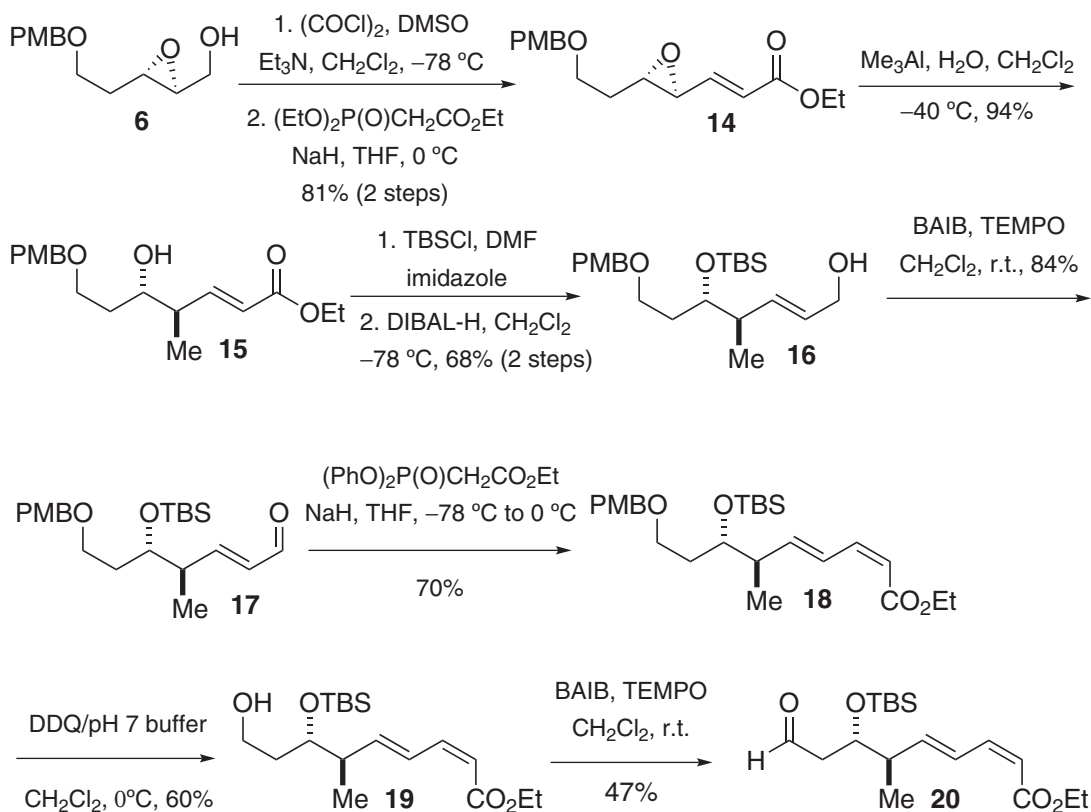
Scheme 3. Attempts to synthesize the 1,3-diol.

stereospecifically provide the two stereogenic centers at C6 and C7, in an *anti* relationship. Moreover, the *E* olefin of dictyostatin would already be present.

To synthesize the (*E*)- γ,δ -epoxy acrylate **14**, the epoxy alcohol **6** was submitted to the Swern oxidation conditions, cleanly providing the corresponding aldehyde (Scheme 4). This aldehyde was used in the next step without purification to form **14** by a Horner-Wadsworth-Emmons reaction in 81% yield for the two-step sequence (*E:Z* > 95:5). Next, the (*E*)- γ,δ -epoxy acrylate **14** was treated with Me_3Al and H_2O in dichloromethane at -40°C , following the protocol

described by Myashita and co-workers,¹⁴ which provided ester **15** in 94% yield as the only observed product.¹⁵

Subsequently, the protection of ester **15** was accomplished using TBSCl and imidazole in DMF, followed by treatment with DIBAL-H in dichloromethane at -78°C to give allylic alcohol **16** in 68% yield over two steps. Oxidation of this alcohol with (bis-acetoxyiodo) benzene (BAIB) and TEMPO provided the desired aldehyde in 84% yield (Scheme 4). To prepare the C1-C9 fragment of dictyostatin, we had to construct the *2Z,4E*-diene at C1-C5.¹⁶ To carry out this transformation we prepared the

Scheme 4. Preparation of aldehyde **20**.

phosphonate ester according a method reported by Ando and co-workers.¹⁶ This phosphonate ester was deprotonated with NaH and the intermediate aldehyde **17** was added at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 18 h at $0\text{ }^{\circ}\text{C}$ to provide ester **18** in 70% yield (*Z:E* > 95:5). Oxidative removal of the PMB ether with DDQ in $\text{CH}_2\text{Cl}_2/\text{pH 7 buffer}$ (9:1) gave alcohol **19** in 60% yield. Oxidation of the hydroxyl group with BAIB and TEMPO provided the desired aldehyde **20** in 47% unoptimized yield (Scheme 4).

Conclusions

We have described an efficient asymmetric synthesis of the C1-C9 fragment of dictyostatin. Notable features of this approach include asymmetric Sharpless epoxidation, Myashita methodology for regioselective nucleophilic substitution on a γ,δ -epoxy acrylate, and a Horner-Wadsworth-Emmons reaction using Ando's protocol to construct the 1,3-diene moiety. The synthesis required 12 steps from homoallylic alcohol **8** in 4.0% overall yield. Extension of this work toward completion of the synthesis of dictyostatin is underway, and the results will be described in due course.

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Supplementary Information

Product characterization as well as copies of NMR spectra for the prepared compounds are available free of charge at <http://jbcs.sbq.org.br> as a PDF file.

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