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Total Synthesis of Potential Antitumor Agent, (−)-Dictyostatin

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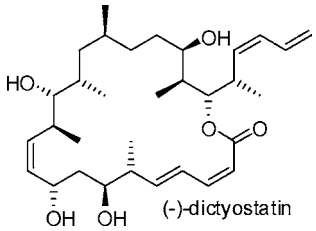
ABSTRACT



The potential antitumor agent (−)-dictyostatin has been synthesized utilizing Brown crotylboration to achieve eight of the eleven chiral centers. The yield for the 26-step longest sequence is ∼4%. The C9−C10 coupling is achieved via a stereoselective vinylzincate addition.

The clinically successful microtubule stabilizing cancer chemotherapeutic agent paclitaxel (Taxol) suffers from limitations, such as low solubility in water, multiple mechanisms of drug resistance, and toxicity.[1] This has led to the search for novel natural and synthetic mitotic spindle poisons. Structurally related dictyostatin[2] and discodermolide,[3] isolated from different species of marine sponges, are examples of such molecules possessing cytotoxicity at low nanomolar levels. Like epothilones,[4] they do not bind to *P*-glycoprotein, a principal mediator of taxane resistance.[5]

(−)-Dictyostatin (**1**) is a 22-membered macrolactone with 11 stereocenters, a *Z*-alkene, and two dienes,[6] whereas (+)-discodermolide is an open-chain carbamate with 13 stereocenters and a δ-lactone moiety. Paterson and Curran simultaneously reported the first two total syntheses of **1**.[7] A third total synthesis, via a titanium-mediated silyloxy enyne cyclization, has been recently published by Phillips.[8] Curran has also reported the synthesis and biological evaluation of several analogues of **1**.[9]

As part of our ongoing projects involving the synthesis of medicinally important natural products via boranes,[10] we were interested in the synthesis of (−)-dictyostatin. Herein, we report a borane-mediated convergent synthesis of **1**. The yield for the 26-step longest sequence, starting from methyl (2*S*)-3-hydroxy-2-methylpropionate (Roche ester), is ∼4%.[11] Figure 1 illustrates the retrosynthetic analysis. Eight of the

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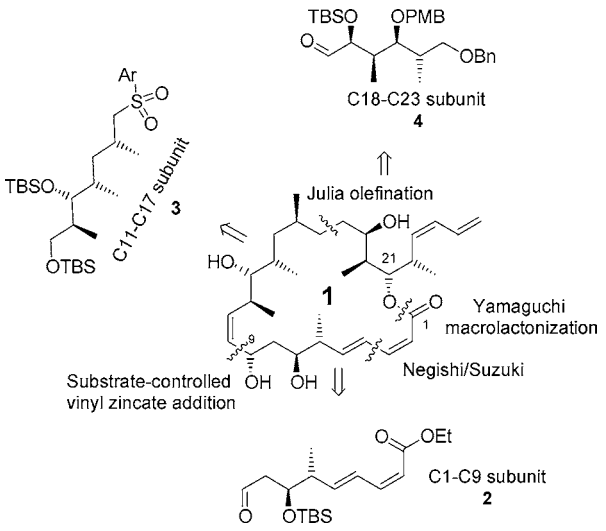
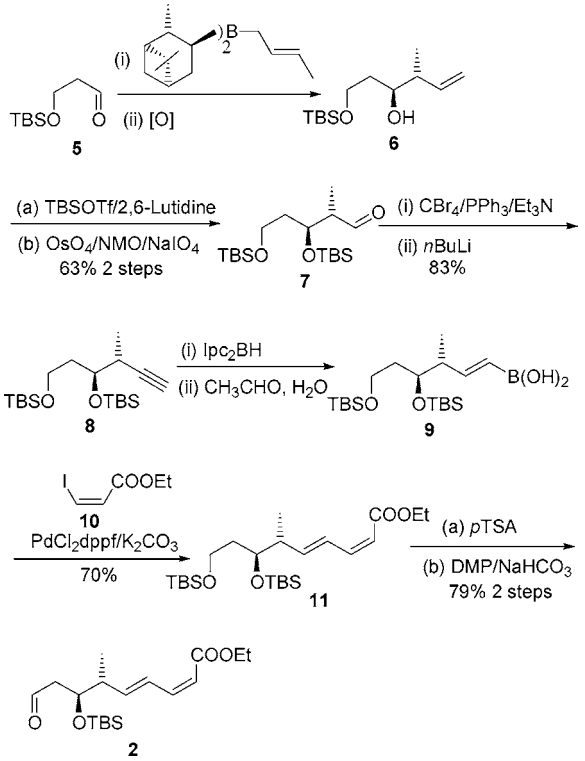


Figure 1. Retrosynthetic analysis for the preparation of **1**.

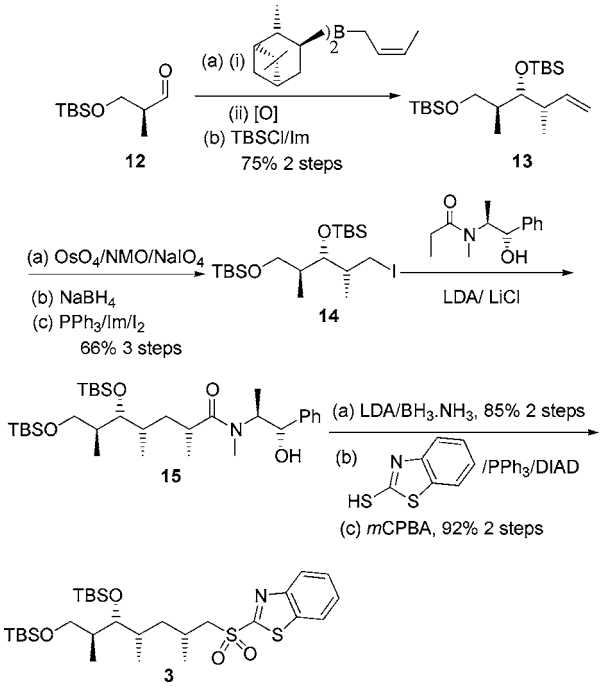
11 stereocenters were created via four pinane-mediated crotylborations,[12] and the Roche ester and Myers' alkylation[13] provided two more stereocenters. The three subunits were assembled via Julia olefination[14] and a substrate-controlled vinylzincate addition, which provided the remaining stereocenter.

The synthesis of **2** (Scheme 1) began with a pinane-based *E*-crotylboration of **5** to provide the homoallylic alcohol **6** as a single diastereomer,[15] which was protected as a TBS

Scheme 1. Synthesis of C1−C9 Subunit **2**



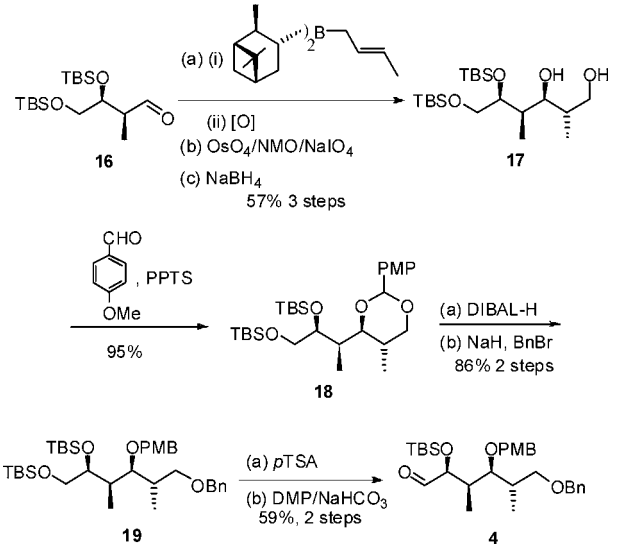
Scheme 2. Synthesis of C11−C17 Subunit **3**



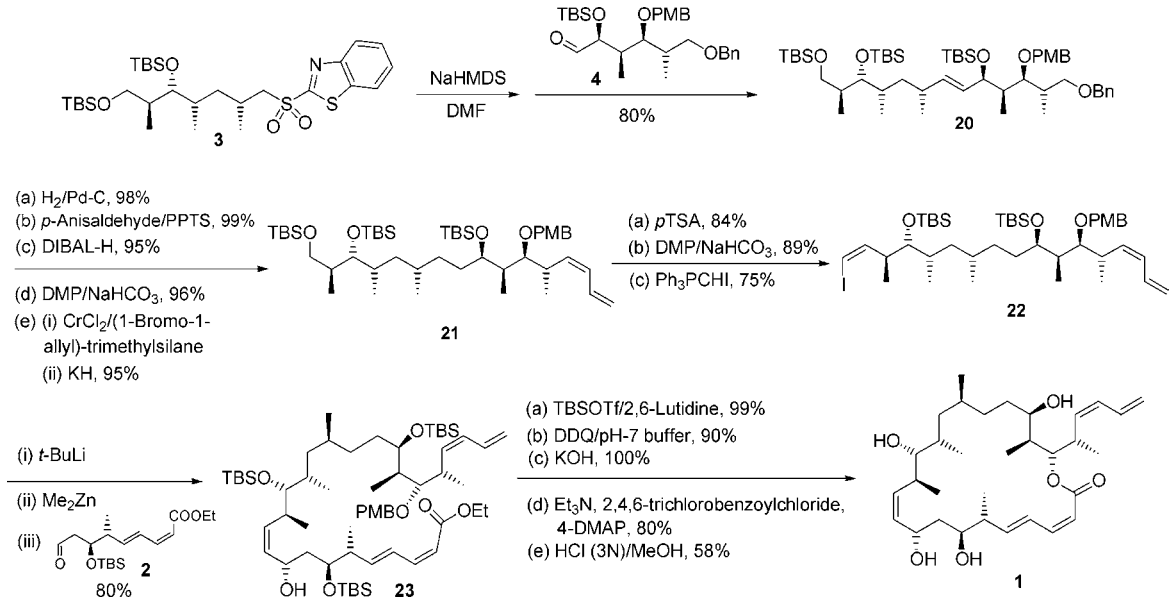
ether and converted to the aldehyde **7**. This was then converted to the alkyne **8** by a Corey−Fuchs reaction[16] and to the boronic acid **9** via hydroboration with diisopinocampheylborane, followed by elimination of α-pinene.[17] Suzuki coupling[18] with the *Z*-vinyl iodide **10**[19] resulted in the diene ester **11**.[20] Selective deprotection of the TBS ether of the 1°-ol and Des−Martin periodinane (DMP) oxidation provided **2**.

The Roche ester was converted to aldehyde **12** in three steps and 75% yield to initiate the preparation of sulfone **3** (Scheme 2). Crotylboration with (+)-*B*-(*Z*)-crotyldiisopinocampheylborane,[12] followed by protection of the 2°-ol as the

Scheme 3. Synthesis of C18−C23 Subunit **4**



Scheme 4. Assembly of Subunits of **1**



TBS ether, gave **13**. The olefin was converted to the aldehyde using a periodate cleavage and then converted to the iodide **14** via the alcohol. This was then transformed to the chiral amide **15** using Myers' protocol[13] to stereoselectively introduce the methyl group at the C-16 position of dictyostatin. A similar sequence was utilized by Paterson and Curran also in their total syntheses of **1**.[7] The amide was reduced to the 1°-ol using a lithium aminoborohydride reagent,[13,21] and finally, the subunit **3** was realized via a Mitsunobu reaction[22]−oxidation sequence.

Aldehyde **16** was prepared from commercially available ethyl glyoxylate via a pinane-based *Z*-crotylboration,[12] reduction, TBS protection, and periodate cleavage sequences in 62% yield. A second crotylboration with (−)-*B*-(*E*)-crotyldiisopinocampheylborane,[12] periodate cleavage, and reduction sequences gave the 1,3-diol **17**, which was converted to the PMP acetal **18**. Regioselective deprotection of the acetal and reprotection of the 1°-ol as the benzyl ether provided **19**. Selective deprotection of the TBS ether of the 1°-ol at the other end, followed by DMP oxidation, gave the aldehyde **4** (Scheme 3).

With the three required subunits in hand, we focused on their assembly (Scheme 4). Julia coupling[14] of the sulfone **3** and aldehyde **4** provided the alkene **20**. The hydrogenation of the alkene and the benzyl ether was achieved at high pressure (500 psi) at the expense of the PMB ether, which was reintroduced using the same protocol as that for the conversion from **17** to **19**, and the resulting 1°-ol was oxidized to the aldehyde. The terminal diene of **21** was introduced via a standard protocol utilized in the synthesis of discodermolide[23] and the prior syntheses of **1**.[7] The TBS ether of the 1°-ol was selectively removed, oxidized, and treated with the Wittig salt to obtain the *Z*-vinyl iodide **22**.

A lithium−halide exchange, followed by transmetalation with dimethylzinc, provided the *Z*-vinylzincate,[24] which was added to **2** to provide, fortuitously, only the desired epimer of **23**. This was established by analyzing the ^{13}C NMR spectrum, as described by Rychnovsky.[25] For this purpose, **23** was converted to the 1,3-diol and the acetonide using TBAF and 2,2-dimethoxypropane/*p*TSA, respectively. The tertiary carbon of the acetonide was observed at δ 100.51 ppm, and the methyl carbons were observed at δ 24.45 ppm in the ^{13}C spectrum. Selective deprotection of the TBS ether

(11) In comparison, Paterson's synthesis of **1** involved 27 steps for the longest linear sequence in 3.8% yield (ref 7a). Curran's 34 steps afforded 1% yield (ref 7b), and the 26-step longest sequence by Phillips yielded ~1% (ref 8).

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at C7 was possible because it has a neighboring carbon with an *anti*-methyl group, whereas the TBS ethers at C13 and C19 have *syn*-methyl groups on adjacent carbons. We are examining this reaction in detail to understand the stereoselectivity.

Conversion of **23** to **1** was achieved via the following sequence of reactions: TBS protection, PMB deprotection, hydrolysis, Yamaguchi macrolactonization,[26] and global deprotection of the TBS ethers.[7b,27]

In summary, we have achieved a convergent synthesis of naturally occurring (−)-dictyostatin. This protocol is amenable to scale-up. The availability of both antipodes of α-pinene makes the synthesis of diastereomers of **1** relatively simple. We are currently preparing analogues of **1** via modified crotylborane reagents.[28] We are also collaboratively examining the folate-mediated delivery of **1**.[29]

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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