Natural Product Synthesis

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# A Highly Step-Economical Synthesis of Dictyostatin**

*Stephen Ho, Cyril Bucher, and James L. Leighton**

In 1994 Pettit reported the isolation and anti-cancer activity of the marine sponge-derived macrolide dictyostatin.[1] Wright subsequently isolated a sample that allowed initial biological characterization of dictyostatin as a potent inducer of tubulin polymerization,[2] and that was used by Wright and Paterson to make a full structural assignment in 2004.[3] This assignment was confirmed soon thereafter by total syntheses by Paterson[4] and Curran,[5] and the material thus obtained facilitated more detailed characterization of dictyostatin's mechanism of action.[6,7] Total syntheses by Phillips[8] and Ramachandran,[9] formal syntheses by Micalizio[10] and Cossy,[11] a synthesis of C(9)-epi-dictyostatin by Gennari,[12] second-generation syntheses by Paterson[13] and Curran,[14] and several fragment syntheses[15] followed these initial reports. In addition, the Paterson/Wright[16] and Curran/Day[17] teams have reported extensive structure–activity relationship (SAR) studies, while the Paterson/Díaz/Jiménez-Barbero[18] and Curran/Snyder[19] teams have advanced models for the interaction of dictyostatin with the taxane binding site on β-tubulin. Because dictyostatin and some of the prepared analogs are among the most potent microtubule-stabilizing agents characterized to date, there has been and continues to be intense interest in the possibility of advancing dictyostatin or an analog thereof into the clinic, a goal which might be facilitated by the development of a significantly more efficient and step-economical synthesis. As part of a larger program devoted to the development of new strategies and methods for the synthesis of complex and precious marine macrolides with high levels of step-economy, efficiency, and scalability,[20] we have developed and report herein a synthesis of dictyostatin that comprises just 14 steps in the longest linear sequence.

Similarly to the previous syntheses of dictyostatin, our retrosynthesis disconnected the target into three roughly equally complex fragments, **1**, **2**, and **3** (Figure 1 A). It was in the synthesis of the fragments, and especially the C(12)–C(14) and C(20)–C(22) stereotriad-containing fragments **1** and **2** that we saw an opportunity for a streamlining of the synthesis. Ever since its introduction by Roush more than 20 years ago, what might be called the "Roche ester strategy" has reigned supreme for the synthesis of such stereotriads,[21] and indeed was employed in the Paterson, Curran, and Ramachandran syntheses, in most of the approaches reported by others, and

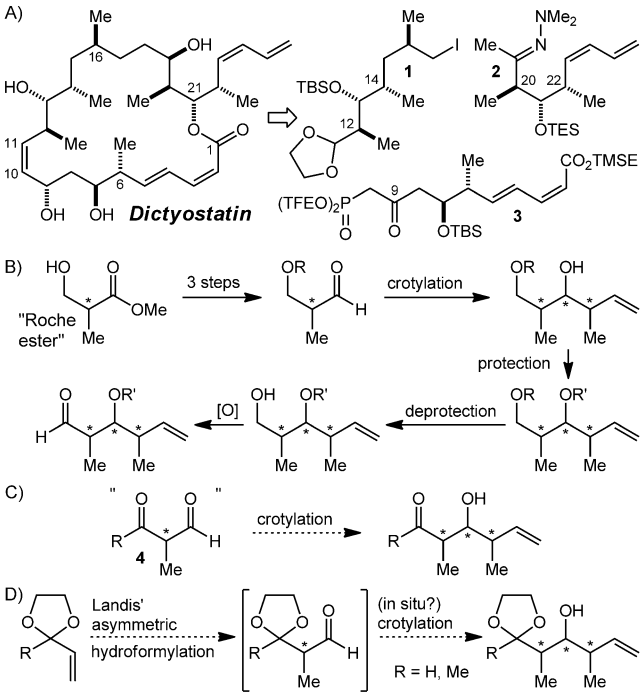


***Figure 1.*** A) Disconnection of dictyostatin into 3 fragments of similar complexity. B) The "Roche ester strategy" for the synthesis of functionalized stereotriads. C) A hypothetical one-step stereotriad synthesis from aldehyde **4**. D) A proposal for the one-pot synthesis of the C(12)–C(14) and C(20)–C(22) stereotriads of dictyostatin.

in most of the syntheses of the related natural product discodermolide.[22] In this approach, the requisite enantiomer of the Roche ester is protected, reduced, and oxidized to the corresponding aldehyde, which is then subjected to diastereoselective crotylation, followed by several additional functional group manipulations (Figure 1 B). Thus, these stereotriad syntheses typically comprise at least 6–7 steps of which all but one are protecting group or redox reactions. The crotylation of a configurationally stable aldehyde such as **4** would represent an ideal alternative, but of course, no such aldehyde exists (Figure 1 C). Protected versions of **4** do exist, however, and can be prepared using Landis' ligand for asymmetric hydroformylation reactions.[23] Given that hydroformylation reactions tend to be clean, we were optimistic that the crotylation reactions could be carried out in operationally simple one-pot procedures (Figure 1 D). After we began our investigations, Burke reported a similar sequence employing an orthoester-protected acrylate, in which the product aldehyde was reacted in situ with *trans*-crotylpinacolboronate.[24] This elegant demonstration of the power of the concept notwithstanding, significant work remained to establish whether externally controlled crotylations would

[*] S. Ho, C. Bucher, Prof. J. L. Leighton
Department of Chemistry, Columbia University
3000 Broadway, New York, NY 10027 (USA)
E-mail: leighton@chem.columbia.edu

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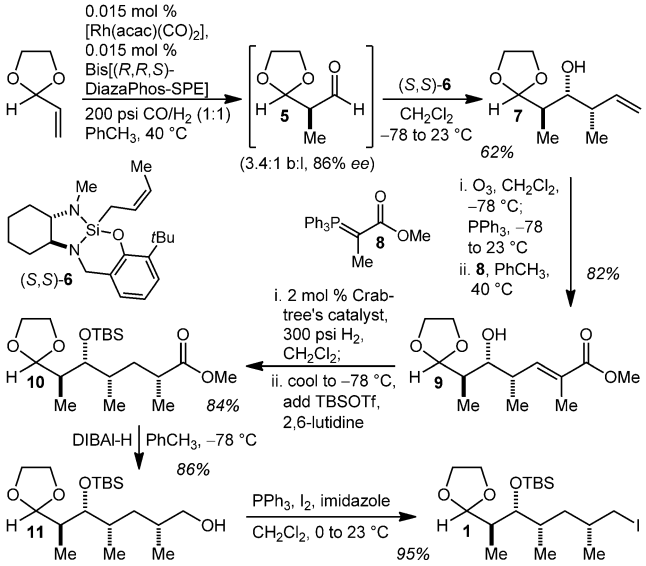
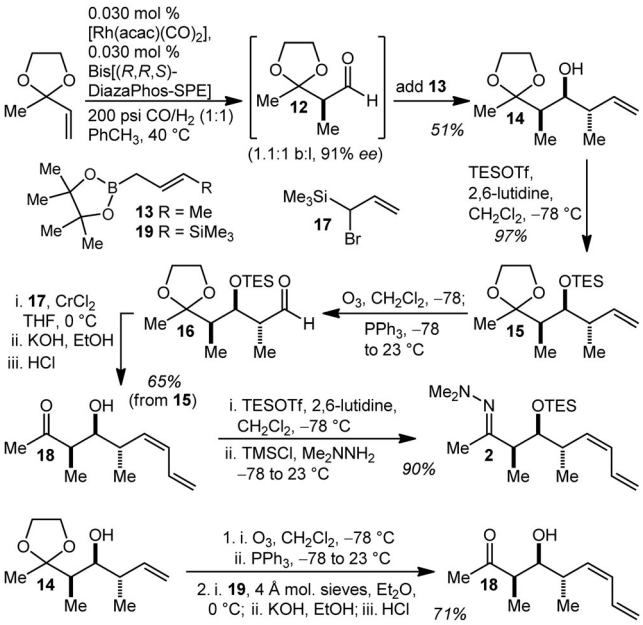
work well with the products of the hydroformylation reactions and, more importantly, to establish whether and how these reactions could be easily and inexpensively scaled.

The synthesis of iodide **1** commenced with the rhodium-catalyzed hydroformylation of 2-vinyl-1,3-dioxolane with Landis' bis[(*R*,*R*,*S*)-DiazaPhos-SPE] ligand[23] to produce aldehyde **5** (Scheme 1). At first, we employed [Rh(acac)(CO)$_2$] and ligand loadings of 0.50 and 0.55 mol%, respectively, according to Landis' original procedure, and these conditions produced **5** with 4.2:1 regioselectivity and in 92% *ee*. Because the ligand is far and away the most expensive component of the reaction, however, and because Sigma–Aldrich discontinued the sale of the ligand during the course of this project, we were highly motivated to investigate how low we could get the catalyst/ligand loadings and eventually settled on 0.015 mol%.[25] This did result in a small drop in both regioselectivity (3.4:1) and *ee* (86%), but in terms of the amount of **5** produced per unit of ligand, this represented a truly significant increase in efficiency. Asymmetric crotylation of **5** using our recently reported and more easily scaled crotylsilane (*S*,*S*)-**6**[26] was effectively carried out in situ, and this one-pot procedure resulted in the isolation of **7** in 62% yield. It is worth emphasizing again that because the starting dioxolane is relatively inexpensive, this yield figure is not particularly meaningful as a measure of the true efficiency of this reaction. It should be noted instead that this optimized procedure allowed the production of more than a gram of **7** using just 2 mg of the Landis ligand. Ozonolysis of **7** and subsequent Wittig reaction with stabilized ylide **8** could be rendered as a simple one-pot procedure and resulted in the isolation of **9** in 83% yield ($\geq$10:1 *E*:*Z*). Alcohol-directed hydrogenation[27] with Crabtree's catalyst[28] proceeded highly diastereoselectively ($\geq$20:1 d.r.) and led, after in situ alcohol silylation with *tert*-butyldimethylsilyl triflate (TBSOTf), to the isolation of **10** in 80% yield. Finally, ester reduction with DIBAl-H gave alcohol **11** (86% yield), which was converted to iodide **1** in 95% yield. This 5-step synthesis of **1** proved readily scalable and was used to prepare multi-gram amounts of both **11** and **1** in just a few weeks.




***Scheme 1.*** An efficient synthesis of iodide **1** in just 5 steps. TBSOTf = *tert*-butyldimethylsilyl triflate, DIBAl-H = diisobutylaluminum hydride.

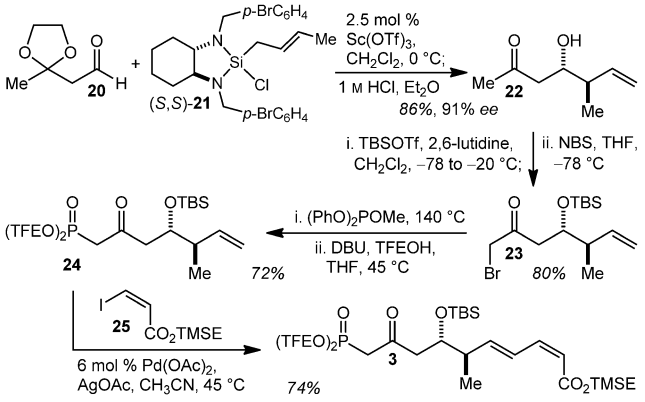
The synthesis of hydrazone **2** began in a similar fashion with the asymmetric hydroformylation of 2-methyl-2-vinyl-1,3-dioxolane (Scheme 2). Because this substrate is more hindered, the catalyst/ligand loading could not be reduced quite as much, but could nevertheless be effectively dropped to 0.030 mol%. These conditions resulted in the production of **12** with 1.1:1 regioselectivity and in 91% *ee*. Felkin-selective crotylation of aldehyde **12** with *trans*-crotylpinacolboronate **13** was highly diastereoselective ($\geq$20:1) and was easily performed in one-pot in analogy to the Burke procedure.[24] Once optimized, this sequence produced **14** in 51% yield (as above, we note that a more meaningful measure of the efficiency of this reaction is the fact that more than a gram of **14** may be produced using only 4 mg of the Landis ligand). On larger scales, however, we found it more convenient to chromatographically separate the aldehyde regioisomers prior to the crotylation reaction, both to avoid wasting large amounts of **13** and to avoid a more tedious separation of the crotylation products. Alcohol silylation with triethylsilyl triflate (TESOTf) proceeded smoothly to give **15** in 97% yield and was followed by ozonolysis to give aldehyde **16**. Without further purification, **16** was subjected to the *cis*-selective diene synthesis using allylsilane **17** that was developed by Paterson as part of a discodermolide synthesis.[29] Following in situ base-promoted Peterson elimination,[30] HCl was added to hydrolyze the ethylene ketal and this resulted in TES ether hydrolysis as well, giving **18** in 65% overall yield




***Scheme 2.*** An efficient synthesis of hydrazone **2** in just 5 steps. TESOTf = triethylsilyl triflate, TMSCl = trimethylsilyl chloride.

from **15**. Resilylation with TESOTf was followed in situ by hydrazone formation to give **2** in 90% yield. This synthesis of **2** requires just 5 or 6 steps (depending on whether or not **12** is isolated) and allowed the preparation of more than 21 g of **2** in a campaign carried out by a single chemist in less than 3 weeks. Because this route required two separate silylations of the same alcohol, we have developed an alternative route: **14** may be directly subjected to ozonolysis, and the resulting aldehyde may be treated with Matteson's reagent (**19**)[31] followed by in situ base-promoted Peterson elimination, to deliver **18** in 71% yield. This modification results in a 4- or 5-step synthesis of **2** and obviates the use of large amounts of $CrCl_2$ during scale-up.

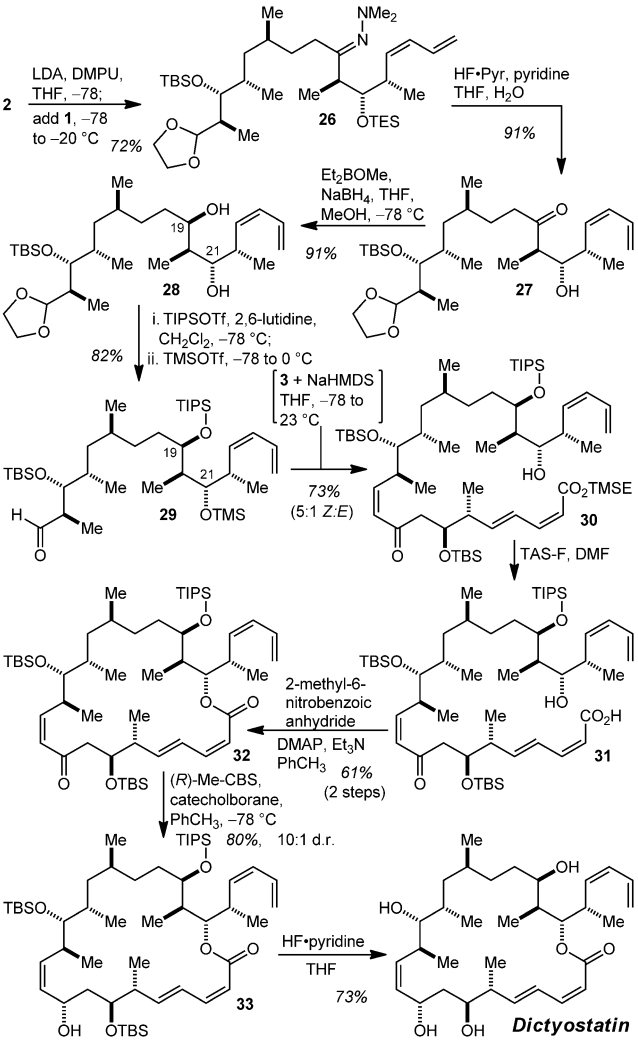
The two most significant challenges in the synthesis of phosphonate **3** are the *cis*-dienoate and the Still–Gennari type phosphonate. The former task has typically required multi-step solutions, while the latter—due to the failure of tris(trifluoroethyl)phosphite to engage productively in Arbuzov reactions—has been accomplished by the (in our hands, technically difficult, capricious, and poorly scalable) addition of the metalated methyl phosphonate to an acid chloride at −100 °C. As described here, we have devised novel single-step solutions for both of these challenges. $Sc(OTf)_3$-catalyzed crotylation[32] of known (and commercially available) aldehyde **20**[33] with (*S*,*S*)-**21**[34] (with an HCl work-up optimized for ketal hydrolysis) gave ketone **22** in 86% yield and 91% *ee* (Scheme 3). Treatment of **22** with 2.1 equiv of TBSOTf both




***Scheme 3.*** An efficient synthesis of phosphonate **3** in just 4 steps. TBSOTf = *tert*-butyldimethylsilyl triflate, NBS = *N*-bromosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFEOH = 2,2,2-trifluoroethanol, TMSE = 2-(trimethylsilyl)ethyl.

silylated the alcohol and converted the ketone into the corresponding TBS enol ether, and was followed by in situ silyl enol ether bromination with *N*-bromosuccinimide (NBS) to give bromoketone **23** in 80% yield. To get around the failure of tris(trifluoroethyl)phosphite to engage productively in Arbuzov reactions, we wondered whether it might be possible to first perform an Arbuzov reaction with a different phosphite, and then simply transesterify the product with trifluoroethanol. Indeed, we have reduced this idea to practice: **23** was subjected to an Arbuzov reaction with $(PhO)_2POMe$, and the resulting diphenylphosphonate was treated in situ with trifluoroethanol and DBU to give the desired Still–Gennari-type phosphonate **24** in 72% yield. Finally, a $Pd(OAc)_2$-catalyzed Heck reaction with *cis*-iodoacrylate **25** gave *cis*-dienoate **3** in 74% yield.[35] This last reaction results in a significant improvement in step-economy and overall efficiency relative to, for example, the corresponding cross-coupling approach to the dienoate synthesis that requires pre-activation of the alkene coupling partner. Principally due to the development of the one-pot Arbuzov/transesterification reaction and the Heck approach to the *cis*-dienoate, this synthesis of **3** requires just 4 steps, and made possible the preparation of multi-gram quantities of **24** (we did not want to store large amounts of *cis*-dienoate **3** and made only what was necessary for the completion of the synthesis) in less than 2 weeks.

Fragment coupling and completion of the synthesis proceeded as described in Scheme 4. Deprotonation of




***Scheme 4.*** Fragment coupling and completion of the synthesis in 9 steps from **1** and **2**, and in 5 steps from **3**. LDA = lithium diisopropylamide, DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TIPSOTf = triisopropylsilyl triflate, TMSOTf = trimethylsilyl triflate, NaHMDS = sodium hexamethyldisilazide, TAS-F = tris(dimethylamino)-sulfonium difluorotrimethylsilicate, DMAP = 4-dimethylamino pyridine.

hydrazone **2** with LDA under Evans' carefully designed hexane-free conditions[36] and alkylation of the resultant metalloenhydrazide with iodide **1** gave **26** in 72% yield. Treatment of **26** with HF·pyridine in wet THF led to hydrolysis of the TES ether and the hydrazone to give **27** in 91% yield. Narasaka's *syn*-selective β-hydroxyketone reduction[37] using Prasad's protocol[38] proceeded highly diastereoselectively (≥ 20:1 d.r.) to give diol **28** in 91% yield. Selective silylation of the C(19) hydroxy group with triisopropylsilyl triflate (TIPSOTf) was followed in situ by silylation of the C(21) hydroxy group with trimethylsilyl triflate (TMSOTf), which also resulted in acetal hydrolysis[39] to produce aldehyde **29** in 82% yield. Still–Gennari olefination[40] of **29** with phosphonate **3** proceeded with ca. 5:1 *Z*:*E* selectivity, and the desired *Z*-enone **30** (the C(21) TMS ether was hydrolyzed in the work-up) was isolated in 73% yield. Deprotection of the 2-(trimethylsilyl)ethyl (TMSE) ester was accomplished with tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TAS-F)[41] to deliver hydroxy acid **31**, which was directly subjected to the macrolactonization reaction without purification. Following Curran's demonstration of its superiority in this context,[42] the macrolactonization was carried out using Shiina's protocol with 2-methyl-6-nitrobenzoic anhydride,[43] and led to the isolation of macrolactone **32** in 61% yield over two steps from **30** and without significant isomerization of the C(2)–C(3) *Z*-alkene. Diastereoselective reduction of the C(9) ketone was accomplished using the CBS protocol with catecholborane[44] and gave **33** in 80% yield. Finally, global silyl ether deprotection with unbuffered HF·pyridine delivered dictyostatin in 73% yield.

Our synthesis of dictyostatin proceeds with a longest linear sequence of 14 steps. Each of the 3 fragments (**1**–**3**) was prepared in just 4 or 5 steps, and this unrivalled step-economy was achieved through a combination of methodological and strategic innovation and the successful telescoping of steps into technically simple and effective one-pot procedures at several points in the route. The important innovations realized in the course of this project include the one-pot syntheses of stereotriads **7** and **14**, the one-pot Arbuzov/transesterification route to Still–Gennari-type β-ketophosphonate **24**, and the Heck approach to the synthesis of the C(1)–C(5) *cis*-dienoate. The ready scalability of the 3 fragment syntheses that accrued from this step-economy was amply demonstrated by the preparation of multi-gram quantities of each of them in just a few weeks or less. Should a dictyostatin analog emerge that merits clinical evaluation, we believe our synthesis could serve as the starting point for the development of a process that could deliver large amounts of each of the fragments with significantly reduced costs in terms of time, effort, and money. The step-economy of our synthesis, and more specifically the multi-gram quantities of the 3 fragments that we have been able to stockpile as a direct result, may also have the far more immediate and tangible benefit of greatly facilitating our own efforts to design and then rapidly synthesize analogs in pursuit of a clinical candidate.

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