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A Highly Stereoselective Total Synthesis of (+)-9-*epi*-Dictyostatin

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Dedicated to Prof. José Barluenga on the occasion of his 70th birthday

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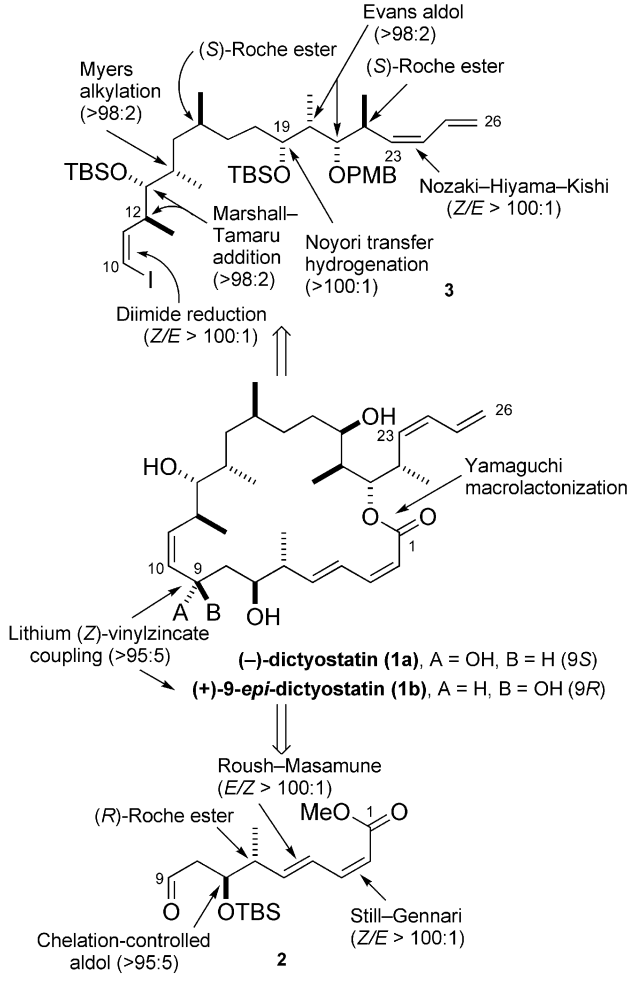
The total synthesis of (+)-9-*epi*-dictyostatin (**1b**), a diastereomer of the antimitotic marine-sponge-derived macrolide (–)-dictyostatin (**1a**), was achieved by creating 11 stereogenic centers and 4 stereogenic double bonds with a high level of stereocontrol. The yield for the 29-step longest linear sequence from Roche ester was 1.53 %. The final key steps to this unnatural product were the vinylzincate C10–C26 addition to aldehyde C1–C9 (leading surprisingly to a complete stereoselectivity for the 9*R*-epimer), followed by Yamaguchi macrolactonization and global deprotection.

Introduction

The sponge-derived macrolide (–)-dictyostatin (**1a**, Scheme 1) has been reported to be a potent, paclitaxel-like inducer of tubulin polymerization and to inhibit human cancer cell proliferation at low nanomolar concentrations, with activity somewhat superior to the already very active discodermolide.[1] With the recent withdrawal of discodermolide from clinical development[2] the importance of dictyostatin further increases. Moreover, (–)-dictyostatin is also extremely potent against paclitaxel-resistant human cancer cell lines overexpressing the P-glycoprotein efflux pump.[1] The structure of (–)-dictyostatin (**1a**) with full stereochemical assignments was established by Paterson and co-workers a few years ago (2004),[3] and four total syntheses were completed in the period 2004–2007.[4] A growing number of research groups have recently been involved in targeting this interesting natural product, and the syntheses of several analogs (e.g., desmethyldictyostatins, *epi*-dictyostatins, bis-*epi*-dictyostatins, hydrodictyostatins, methoxydictyostatins),[5] discodermolide/dictyostatin hybrids,[6] and various fragments and synthetic intermediates[7] have been described. The development of dictyostatin analogs is an appealing goal from a pharmaceutical perspective, which provides interesting opportunities for structural simplification whilst maintaining biological potency, and for better understanding the structure–activity relationships of this class of antitumor agents. In this communica-



Scheme 1. Retrosynthetic approach to (+)-9-*epi*-dictyostatin (**1b**), with key reactions involved and associated diastereomeric ratios.

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tion, we describe a highly stereoselective total synthesis of (+)-9-*epi*-dictyostatin (**1b**), building on our prior work in this field.[7j,7k] Our retrosynthetic approach, shown in Scheme 1, disconnects the macrolide ring into two key intermediates: C1–C9 aldehyde **2**, prepared from the corresponding alcohol,[7k] and C10–C26 vinyl iodide **3**, prepared by taking advantage of a synthetic route similar to that reported for fragment C10–C23.[7j]

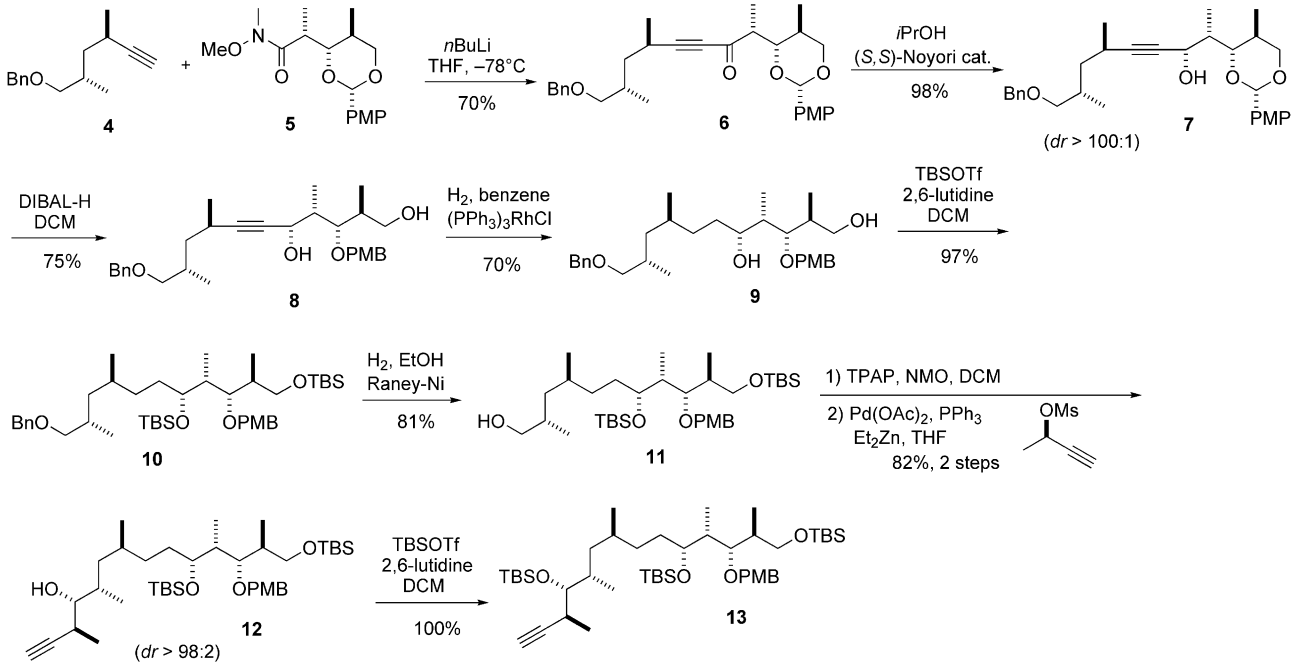
Results and Discussion

The synthesis of C10–C26 fragment **3** started with the preparation of propargylic alcohol **7** (Scheme 2), for which we had previously reported[7j] the direct addition of terminal alkyne **4** to the aldehyde obtained by reduction of Weinreb amide **5** using the Carreira asymmetric alkynylation protocol.[8] However, this procedure proved capricious and poorly reproducible during scale-up. We thus opted for the coupling reaction between alkyne **4**[7j] and Weinreb amide **5** (prepared according to Smith III and coworkers)[9] to form ynone **6** (70%), which was then subjected to Noyori asymmetric transfer hydrogenation[10] to give the desired alcohol **7** in excellent yield (98%) and with a >100:1 diastereomeric ratio (*dr*).

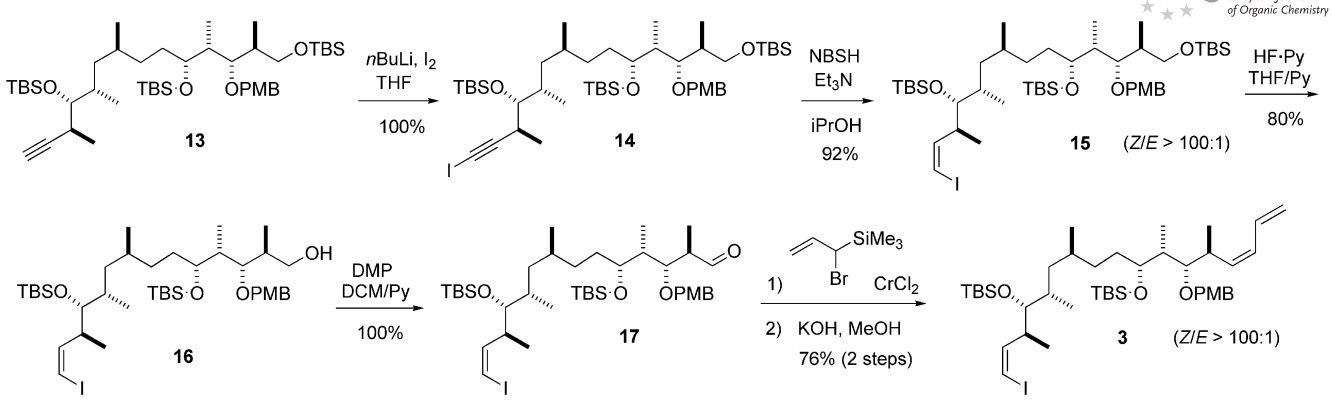
Acetal **7** was cleaved with DIBAL-H to generate diol **8** in 75% yield. Hydrogenation (under 4 bar H_2 pressure) of propargylic alcohol **8**, in the presence of a catalytic amount (10%) of Wilkinson's catalyst, afforded the desired saturated compound **9** (70%), which was then silylated to give the fully protected tetraol **10** in 97% yield. Selective removal of the benzyl group over the PMB group (H_2, Raney-Ni, EtOH)[11] furnished primary alcohol **11** in 81% yield. TPAP/NMO oxidation[12] of alcohol **11** followed by a Marshall–Tamaru palladium-catalyzed allenylzinc addition[13] with the mesylate of (*R*)-3-butyn-2-ol gave alcohol **12** (82% over two steps) with a high level of diastereoselectivity (>98:2) in favor of the desired *anti*,*syn* adduct. TBS protection of alcohol **12** afforded alkyne **13**, which was then lithiated with *n*BuLi and converted into the corresponding alkynyl iodide **14** in quantitative yield (Scheme 3). Reduction of compound **14** with diimide[5d,14] provided (*Z*)-vinyl iodide **15** as a single diastereoisomer (*Z*/*E* > 100:1) in excellent yield (92%). The primary *tert*-butyldimethylsilyl ether of **15** was selectively cleaved (HF-Py, THF/Py, 80%) to give compound **16**, which was converted into aldehyde **17** by oxidation with Dess–Martin periodinane. The latter compound was treated with (1-bromoallyl)trimethylsilane under Nozaki–Hiyama–Kishi coupling conditions ($CrCl_2$),[15] followed by a Peterson elimination (KOH, MeOH) to give C10–C26 fragment **3** in good yield (76%, 2 steps) and excellent diastereoselectivity (*Z*/*E* > 100:1).[16]

Following Ramachandran's lead,[4d] lithiation of (*Z*)-vinyl iodide **3** (*t*BuLi) and subsequent treatment with dimethylzinc provided the corresponding lithium (*Z*)-vinylzincate,[17] which was added to β-silyloxy aldehyde **2** to give the coupling product **18** in moderate yield (40%) and excellent diastereomeric ratio (>95:5; Scheme 4).[18] On the basis of the structural assignment of final product **1b** (vide infra), the stereochemistry of the newly created stereogenic center in compound **18** turned out to be (9*R*). We found this outcome quite surprising, as the addition of the same (*Z*)-vinylzincate to a very similar aldehyde (with the ethyl ester in **2** instead of the methyl ester) was reported to give an excellent ratio in favor of the (9*S*) stereoisomer.[4d]

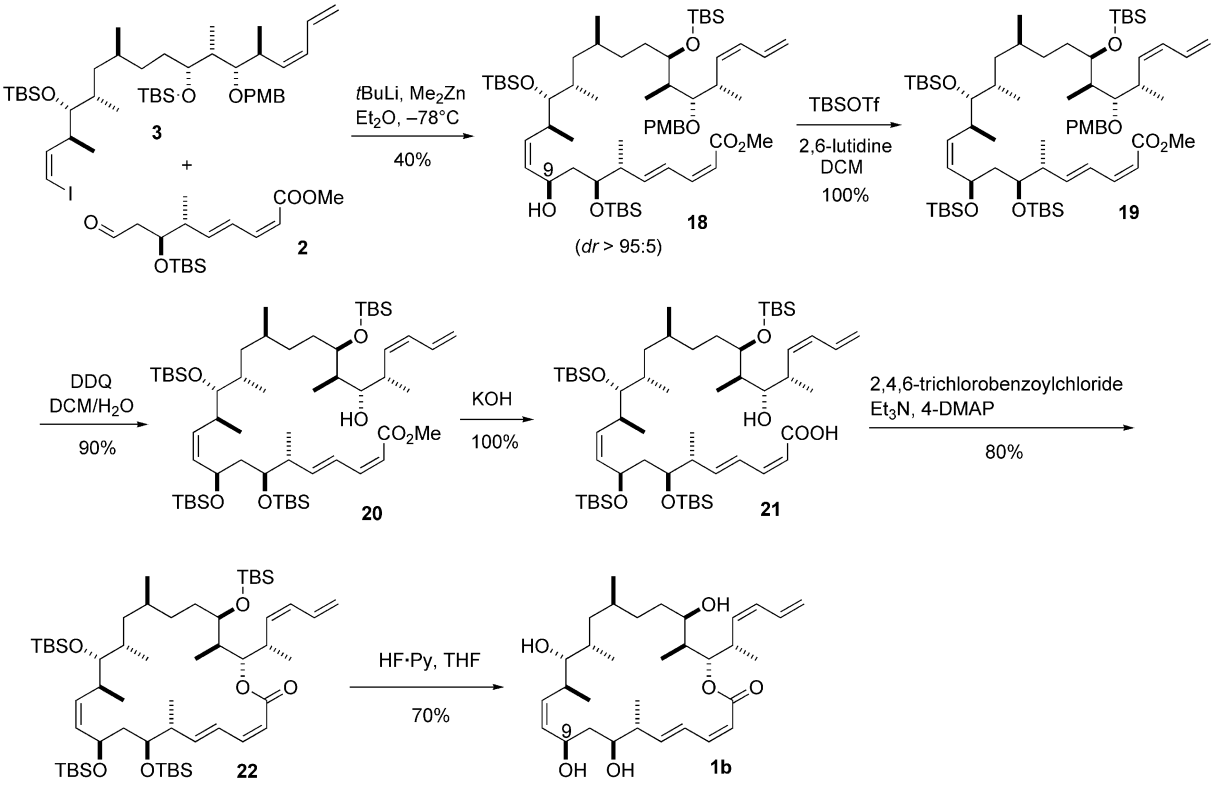
In principle, compound **18** should be easily conveyed into the total synthesis of (–)-dictyostatin (**1a**) by oxidation of the (9*R*)-allylic alcohol to the corresponding 9-ketone, com-



Scheme 2. Synthesis of C10–C23 fragment **13**.



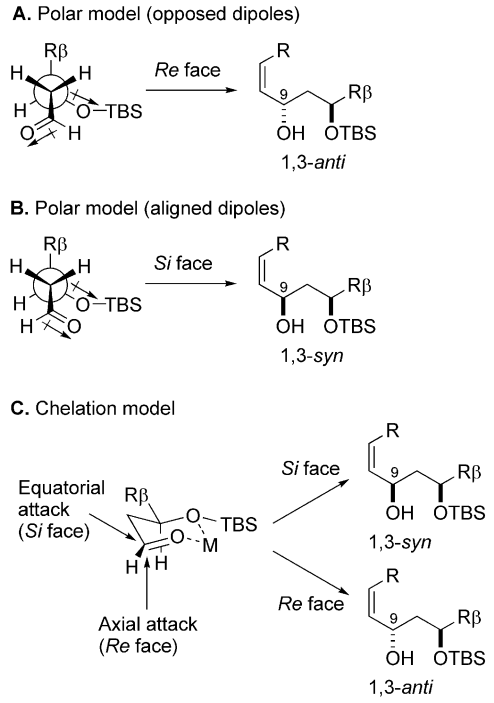
Scheme 3. Synthesis of C10–C26 fragment **3**.



Scheme 4. Completion of the synthesis of (+)-9-*epi*-dictyostatin (**1b**).

pletion of the synthetic sequence (as outlined in Scheme 4) and reduction of the enone to the (9*S*)-allylic alcohol ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, –30 °C)[4a] immediately before final deprotection.

The preference for the 1,3-*syn* diastereomer observed in compound **18** can be rationalized on the basis of 1,3-asymmetric induction models thoroughly investigated by Evans.[19] Steric interactions in the aldehyde conformations are minimized when the β-alkyl substituent (Rβ) is oriented *anti* to the Cα–C=O bond as in structures **A** and **B** shown in Scheme 5. Usually, β-OTBS substituted aldehydes afford preferentially the 1,3-*anti* diastereomer via polar model **A**, where dipoles are opposed.[19] When aluminum Lewis acids (Me_2AlCl or $MeAlCl_2$) are used, exceptional chelation control reinforces the 1,3-*anti* stereochemical outcome (model **C**, axial attack).[20] Recently, Curran and co-workers studied the addition of a (*Z*)-vinyllithium compound to aldehyde **2** and reported a ca. 2:1 1,3-*anti*/1,3-*syn* diastereomeric ratio.[5i] Addition of other (*Z*)-vinyllithium compounds to similar aldehydes gave 1,3-*anti*/1,3-*syn* ratios ranging from 1.5:1 to 1:1.6.[5d,5i] Apparently, models **B** and/or **C** (equatorial attack), leading to the 1,3-*syn* diastereomer, start making a substantial impact in these addition reactions. Surprisingly, when a lithium dimethylalkenylzincate[17,21] is used, the stereochemical outcome is determined only by models **B** and/or **C** (equatorial attack), leading to complete selectivity in favor of the 1,3-*syn* diastereomer.



Scheme 5. 1,3-Asymmetric induction models.

The secondary alcohol of compound **18** was subsequently silylated with TBSOTf to give the fully protected intermediate **19** (100%). Selective PMB removal with DDQ provided compound **20** (90%), which was then saponified under basic conditions (KOH) to provide *seco*-acid **21** (100%). Yamaguchi macrolactonization[22] of *seco*-acid **21** gave macrolide **22** in good yield (80%), together with a small amount (5–10%) of the (2*E*,4*E*)-dienoate ($J_{H2,H3}$ = 15.2 Hz), probably formed through a reversible Michael addition of DMAP to the (2*Z*,4*E*)-dienoate,[4e] and which could be separated by flash chromatography. Global deprotection of the TBS groups with 3 N HCl/MeOH in THF (2.2:1 volume ratio)[4d] caused an extensive degradation of the product, whereas the use of HF·Py in THF[4c,4e] converted **22** cleanly into (+)-9-*epi*-dictyostatin (**1b**) in 70% yield. Our synthetic compound **1b** produced analytical data (^{1}H NMR in CD_3OD, $[\alpha]_D$) in disagreement with those recorded from an authentic sample of (–)-dictyostatin (**1a**) kindly provided by Prof. Ian Paterson (University of Cambridge, UK). Our synthetic compound **1b** was identical (^{1}H NMR and ^{13}C NMR in [D_6]benzene, $[\alpha]_D$, HRMS, IR, R_f) to those described by Paterson[5c] and Curran[5i] for (+)-9-*epi*-dictyostatin (see the Supporting Information for full analytical details).

Conclusions

A highly stereoselective synthesis of (+)-9-*epi*-dictyostatin (**1b**) has been carried out in 1.53% overall yield over 29 steps (longest linear sequence from the Roche ester). Unfortunately, unnatural configuration at C9 is known to cause a substantial drop in cytotoxicity relative to dictyostatin (**1a**).[5c,5i] The new synthetic route is flexible enough to allow (i) inversion at C9 by oxidation–reduction[4a,4e] and (ii) the preparation of other non-natural analogs of dictyostatin [e.g., 12,13-bis-*epi*-dictyostatin by using the mesylate of (*S*)-3-butyn-2-ol in the Marshall–Tamaru palladium-catalyzed allenylzinc addition]. Future work will be focused on the synthesis of such analogs, which can be insightful for better understanding the structure–activity relationships of this class of antitumor agents.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for new compounds along with copies of the NMR spectra (^{1}H, ^{13}C).

Acknowledgments

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