# A highly stereoselective synthesis of the C10–C23 fragment of (−)-dictyostatin†

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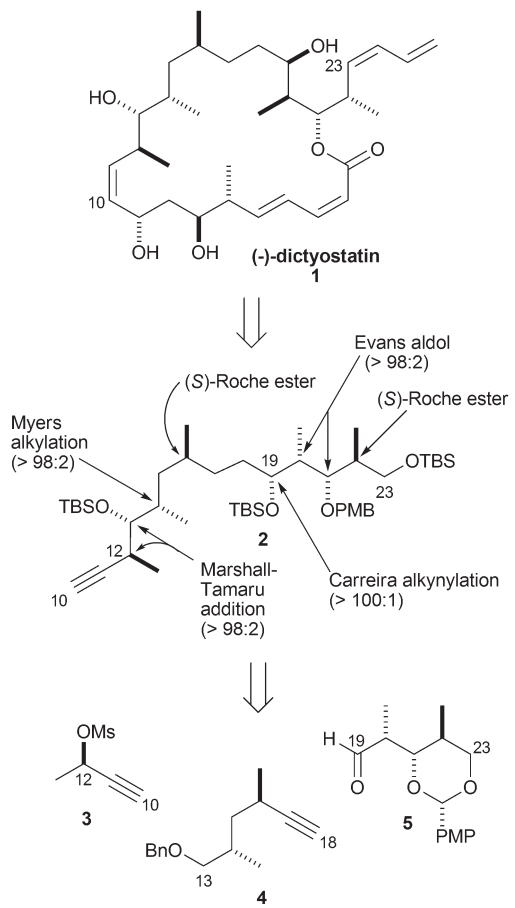
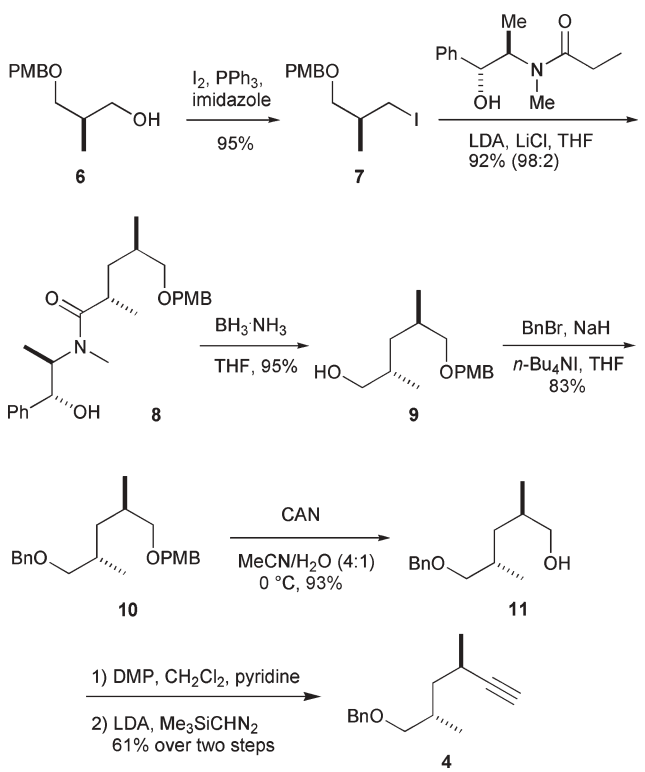
**A highly stereoselective synthesis of the C10–C23 fragment of (−)-dictyostatin has been achieved using a Carreira alkynylation and a Marshall–Tamaru allenylzinc addition as key steps.**

The sponge-derived macrolide (−)-dictyostatin (**1**, Scheme 1) has been reported to exhibit paclitaxel-like effects on cellular microtubules and to inhibit human cancer cell proliferation at low nanomolar concentrations, with activity somewhat superior to the already very active discodermolide ($ED_{50}$ 0.38 nM, P338 leukemia cells).[1] Moreover, (−)-dictyostatin is also extremely active against paclitaxel-resistant cancer cell lines. The structure of (−)-dictyostatin with full stereochemical assignments was established by Paterson and coworkers fairly recently (2004),[2] and four total syntheses were completed in the period 2004–2007.[3] A growing number of research groups have been recently involved in targeting this interesting natural product, and the syntheses of several analogues (*e.g.* normethyldictyostatins, *epi*-dictyostatins, *etc.*),[4] of discodermolide/dictyostatin hybrids[5] and of various fragments and synthetic intermediates[6] have been described. The development of a practical and flexible synthesis of (−)-dictyostatin is still an important goal, particularly as the natural supply is extremely scarce. With the recent withdrawal of discodermolide from clinical development,[7] the importance of dictyostatin increases further.

In this communication, we report on a highly stereoselective synthesis of the C10–C23 fragment of (−)-dictyostatin (**2**, Scheme 1), containing eight of its eleven stereocentres.




**Scheme 1** Retrosynthetic approach to fragment C10–C23 of dictyostatin, with key reactions involved and associated diastereomeric ratios.




**Scheme 2** Synthesis of alkyne **4**.

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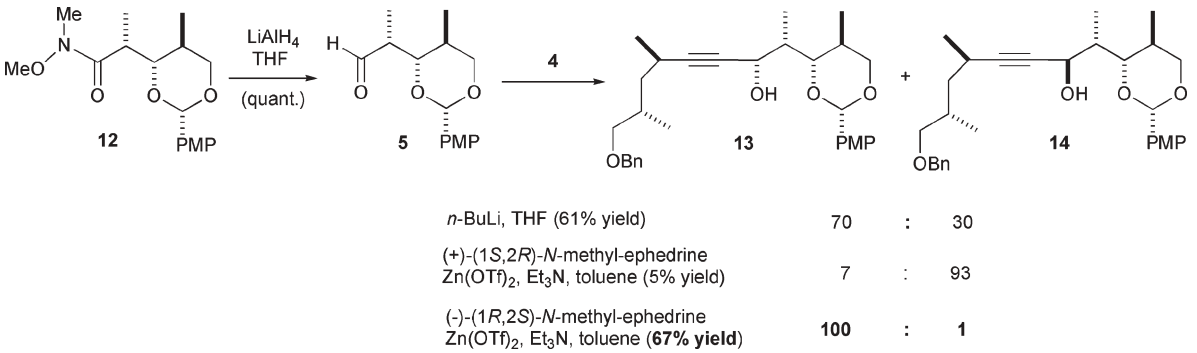
† Electronic supplementary information (ESI) available: experimental procedures and characterization data for new compounds along with copies of NMR spectra ($^1H$, $^{13}C$). See DOI: 10.1039/b708820e

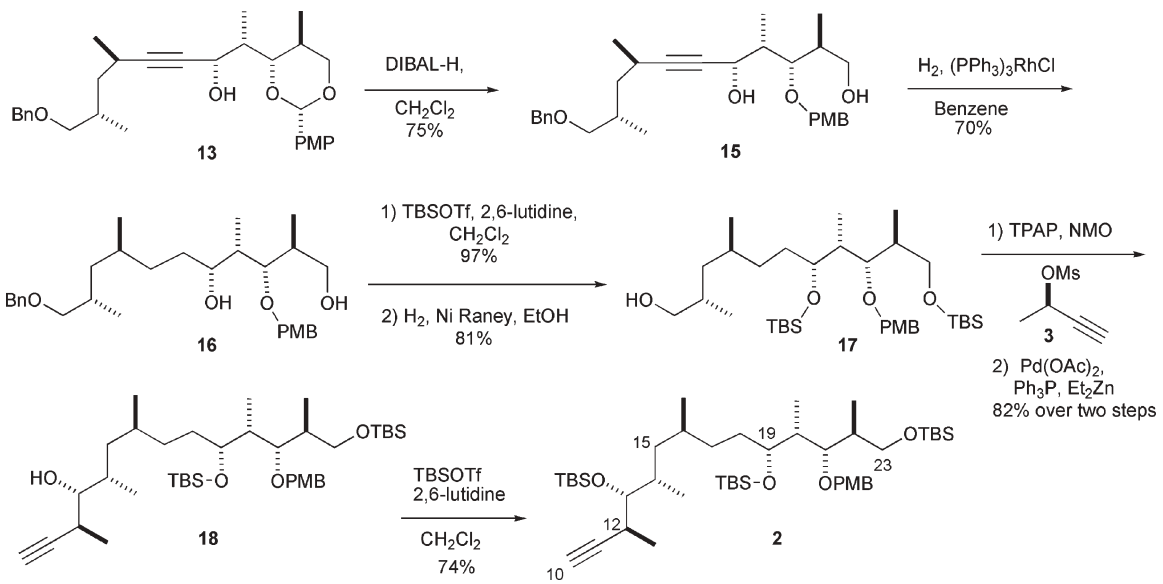



**Scheme 3** Stereoselective Carreira alkynylation.

We initially focused our synthetic efforts on the C13–C18 fragment (alkyne **4**, Scheme 1, 2). Alcohol **6**[8] was used as starting material and converted ($I_2$, $PPh_3$, imidazole) into iodide **7** in high yield (95%). Myers' alkylation[9] gave amide **8** in 92% yield and with a >98 : 2 diastereomeric ratio, in favour of the desired diastereomer. Reduction with the borane–ammonia complex afforded alcohol **9** in 95% yield. Benzyl protection (NaH, BnBr, *n*-$Bu_4NI$, 83%), followed by selective removal of the PMB group over the benzyl group [ceric ammonium nitrate, MeCN/Water (4 : 1)], delivered alcohol **11** in 93% yield. Dess Martin oxidation furnished an aldehyde, which was not isolated but directly homologated to alkyne **4**. The Ohira–Bestmann protocol [$CH_3COC(N_2)PO(OMe)_2$, $K_2CO_3$, MeOH, rt][10] gave a good conversion (88%), but caused extensive epimerization of the α-stereocentre (diastereomeric ratio = 75 : 25). Alternatively, the Seiferth–Gilbert procedure [$HC(N_2)PO(OMe)_2$, *t*BuOK, THF][11] gave a lower yield (59%) with less epimerization (diastereomeric ratio = 90 : 10). Finally, the Shioiri's lithiodiazomethane protocol[12] (Colvin rearrangement) led to alkyne **4** in a reasonable yield (61%) as a single diastereomer.

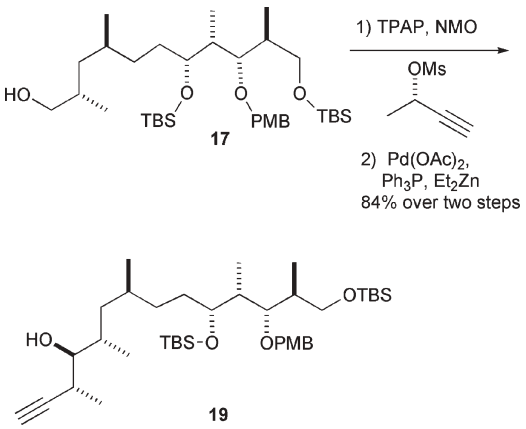
Alkyne **4** was treated with *n*-BuLi in THF at −78 °C and then with aldehyde **5** (prepared according to Smith III and co-workers, Scheme 3)[8] to study the intrinsic preference of the two chiral coupling partners: a mixture of the two diastereomeric propargylic alcohols **13** and **14** in a 7 : 3 ratio (61% yield, Scheme 3) was obtained. Alternatively, a Carreira asymmetric alkynylation [$Zn(OTf)_2$, $Et_3N$, toluene, rt][13] was carried out with either of the two enantiomers of *N*-methyl-ephedrine; the reaction with (−)-(1*R*,2*S*)-*N*-methyl-ephedrine (matched pair) gave the desired *S*-alcohol **13** in 67% yield as a single diastereomer (Scheme 3). In this reaction, slow addition of the aldehyde to the reaction mixture proved to be crucial to increase the yield, reducing the self-condensation of the aldehyde.[14] On the contrary, the Carriera coupling with (+)-(1*S*,2*R*)-*N*-methyl-ephedrine (mismatched pair) afforded the addition product in 5% yield, with a 93 : 7 diastereomeric ratio in favour of the undesired *R*-alcohol **14**.

Acetal **13** was then cleaved with DIBAL-H to generate diol **15** in 75% yield (Scheme 4). Hydrogenation (under 4 bar $H_2$ pressure) of the propargylic alcohol **15**, in the presence of a catalytic amount (10%) of Wilkinson's catalyst, gave the desired saturated compound **16** (70%), which was then silylated (TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 97%). Selective removal of the benzyl group over the PMB group ($H_2$, Raney-Ni, EtOH),[15] furnished alcohol **17** in 81% yield. TPAP/NMO oxidation[16] of alcohol **17**, followed by a Marshall–Tamaru palladium-catalysed allenylzinc addition[17] of (*R*)-mesyl-butynol **3**, gave alcohol **18** (82% over two steps) with




**Scheme 4** Synthesis of the C10–C23 fragment of (−)-dictyostatin.




**Scheme 5** Synthesis of the C10–C23 fragment of 12,13-*epi*-dictyostatin.

very high diastereoselectivity (>98 : 2) in favour of the desired *anti*, *syn* adduct. Using the enantiomeric (*S*)-mesyl-butynol, the diastereomeric adduct (**19**, Scheme 5) was prepared (84% yield) with a 95 : 5 *anti*, *anti* : *anti*, *syn* ratio, which could be used to access 12,13-*epi*-dictyostatin,‡ a compound for which structure–activity relationships are still completely lacking.[4d] Finally, TBS protection of alcohol **18** afforded the desired fragment **2** (Scheme 4) ready for further elongation of the carbon chain.

In conclusion, we have synthesised the C10–C23 fragment of (−)-dictyostatin using a highly convergent and stereocontrolled route. Besides targeting the natural product, this route can be used to access a number of analogues (*e.g.* 12,13-*epi*-dictyostatin) and gain a better understanding of the structure–activity relationships of this class of molecules.

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## Notes and references

‡ For more details on the addition of either (*R*)-mesyl-butynol or (*S*)-mesyl-butynol, see the ESI†.

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