Total synthesis of the marine macrolide (+)-neopeltolide†

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A concise total synthesis of the antiproliferative macrolide (+)-neopeltolide has been completed, utilising a Jacobsen hetero Diels–Alder reaction to install the trisubstituted tetrahydropyran ring.

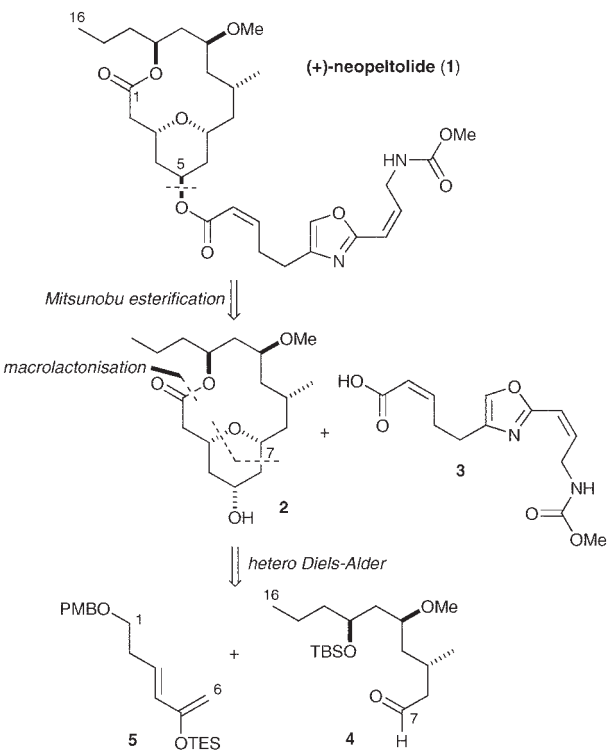
Marine macrolides having potent cytotoxic properties represent promising anticancer agents, provided the supply issue can be resolved.[1] Neopeltolide (**1**, Scheme 1) is a bioactive macrolide isolated from a deep-water Caribbean sponge of the family Neopeltidae by Wright *et al.* in 2007.[2] Initial testing revealed potent antiproliferative activity against several cancer cell lines (*e.g.* IC_{50} = 1.2 and 5.1 nM against A549 lung and NCI/ADR-RES ovarian carcinoma, respectively), as well as inhibition of the growth of the fungal pathogen *Candida albicans*. The key structural features of neopeltolide include a 14-membered macrolactone ring, containing a trisubstituted tetrahydropyran ring, and an oxazole-bearing unsaturated side chain appended at C5 through an ester linkage. This side chain is identical to that found in the 18-membered macrolide leucascandrolide A, which displays a similar biological profile.[1a,3]

The complex macrolide structure and potent biological activity of neopeltolide have stimulated a flurry of synthetic interest, with five total syntheses[4–8] and one formal synthesis[9] reported. Notably, the initially completed total syntheses of (+)-neopeltolide, as reported by the Panek[4] and Scheidt[5] groups, resulted in the stereochemical reassignment of the originally proposed structure. Recently, the Kozmin group[8] achieved a total synthesis of neopeltolide, as well as preparing a simplified analogue of leucascandrolide, enabling more extensive biological analysis and leading to the identification of the cytochrome bc_1 complex as the cellular target for both these antiproliferative macrolides. Importantly, neopeltolide compares favourably to the most potent cytochrome bc_1 complex inhibitors, suggesting that it could be a useful tool for the investigation of eukaryotic energy metabolism.

Herein, we report a new, efficient total synthesis of (+)-neopeltolide (**1**) following a strategy involving the use of only achiral starting materials, with four of the six stereocentres being introduced using asymmetric catalysis. As outlined in Scheme 1, a Mitsunobu esterification reaction of macrocycle **2** with the unsaturated heterocyclic side chain **3**[10] was anticipated to provide neopeltolide directly. Furthermore, we envisaged that the macrolide core in **2** could be constructed using a Jacobsen hetero Diels–Alder reaction[11] between the C7–C16 aldehyde **4** and the C1–C6 siloxydiene **5** to install the tetrahydropyran ring, followed by a suitable macrolactonisation.

The synthesis of the required aldehyde **4** commenced with a Noyori asymmetric hydrogenation[12] of the β-keto ester **6** using the (*S*)-BINAP–Ru(II) catalyst to give the desired (13*S*)-alcohol[5,9] (Scheme 2). Subsequent TBS ether formation and DIBALH reduction of the ester gave the enantiopure aldehyde **7** in 76% overall yield.[13] Next, a Brown methallylation[14] of **7** with the reagent derived from 2-methylpropene (*n*BuLi, TMEDA, Et_2O) and (−)-Ipc_2BOMe installed the required C11 alcohol with high diastereoselectivity (81%, 94 : 6 dr), which was transformed (NaH, MeI) into the methyl ether **8**. Ozonolysis of **8** gave the methyl ketone, which was used in a HWE reaction with trimethyl phosphonoacetate (NaH, THF) to give ester **9** as an inconsequential mixture of *E*/*Z* isomers (75 : 25).[15] Reduction of ester **9** to the corresponding alcohol with DIBALH followed by Dess–Martin oxidation then provided aldehyde **10**.

We planned to perform a diastereoselective organocatalytic hydride reduction of enal **10**, using chemistry developed by MacMillan.[16] Thus, exposure of the mixture of *E*/*Z* isomers of **10** to the imidazolidinone catalyst **11**·TFA (20 mol%) and



Scheme 1 Retrosynthesis of (+)-neopeltolide (**1**).

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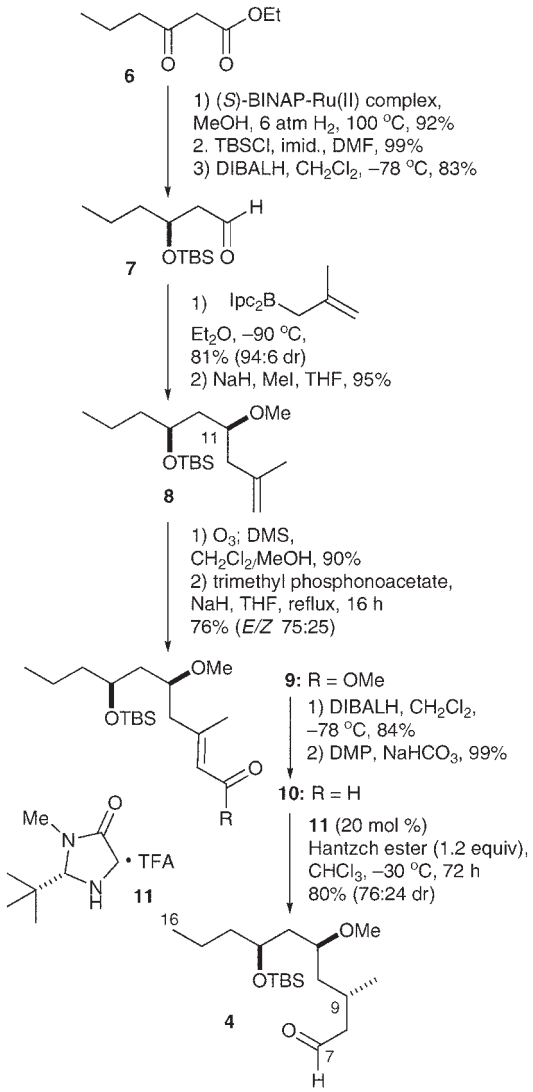
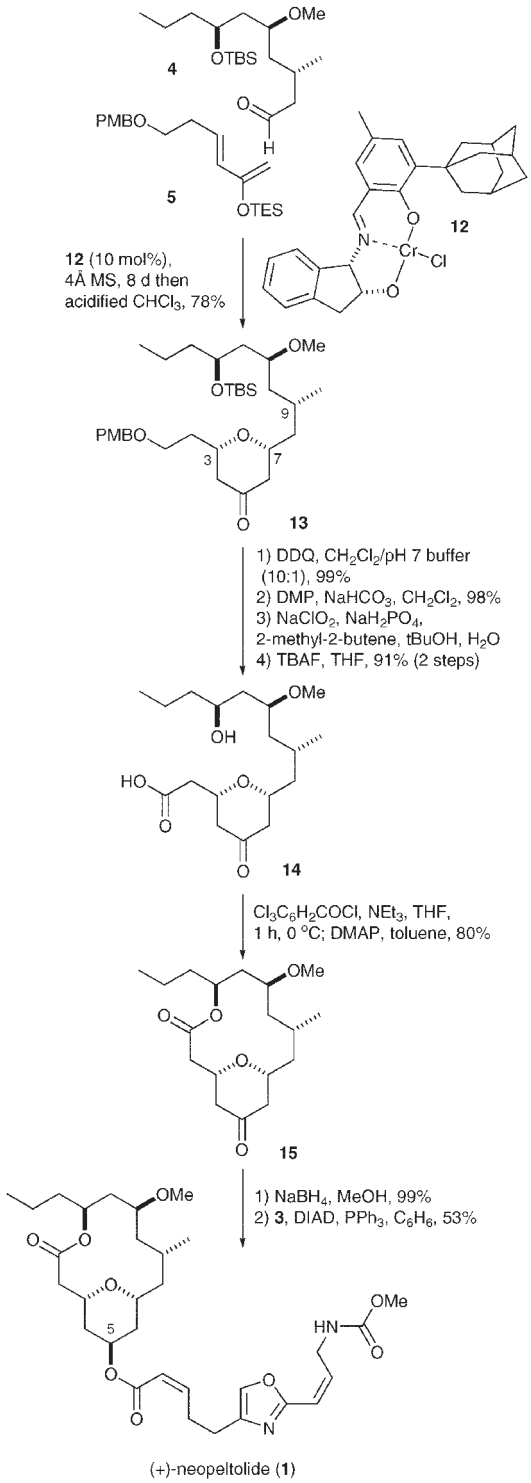


Scheme 2 Synthesis of C7–C16 aldehyde **4**.

1.2 equiv. of ethyl Hantzch ester ($CHCl_3$, −30 °C) resulted in complete conversion to the 1,4-reduction product **4** (80%), obtained as a mixture (76 : 24) of epimers at the newly formed C9 stereocentre. Attempts to improve the diastereoselectivity by carrying out the reaction on the pure *E* isomer of **10**, lowering the temperature and changing the solvent proved unrewarding, with the same ratio of C9 epimers being obtained. These findings suggest that the *E*/*Z* isomers converge to the same product, as expected from the results obtained for the 1,4-reduction of achiral enals,[16] and that the lower level of selectivity obtained with enal **10** may be due to the influence of the existing stereocentres.

With the aldehyde **4** in hand, we turned our attention to the formation of the tetrahydropyran ring of neopeltolide (Scheme 3). Thus, a Jacobsen asymmetric hetero Diels–Alder reaction between **4** and the readily available 2-siloxydiene **5**,[10] promoted by the chiral tridentate chromium(III) catalyst **12**[11] (10 mol%), was carried out. This key reaction led to the corresponding [4 + 2] cycloadducts, which, upon workup with mild acid, gave the expected *cis*-tetrahydropyranones with complete control over the introduction of the C3 and C7



Scheme 3 Completion of the total synthesis of (+)-neopeltolide.

stereocentres. At this stage, the major isomer **13** (60%) could be separated from its C9 epimer.

With the correctly configured tetrahydropyran installed, our attention was directed towards the formation of the macrocyclic ring. Thus, oxidative removal of the PMB group of **13** with DDQ provided the primary alcohol. Dess–Martin oxidation then gave the corresponding aldehyde, which was oxidised to the acid, followed by cleavage of the TBS ether to give the

seco-acid **14**. Cyclisation of **14** under Yamaguchi conditions[17] provided the 14-membered macrolactone **15** cleanly (80%). At this stage, we had completed a formal synthesis of neopeltolide, with all spectroscopic data for lactone **15** being in good agreement with that reported by Scheidt and co-workers (see the ESI†).[5] All that remained for the endgame was reduction of the ketone **15** to the equatorial alcohol **2** ($NaBH_4$, MeOH), followed by a Mitsunobu esterification reaction with the side chain acid **3**,[10] as employed by other groups,[5–8] providing (+)-neopeltolide (**1**) in 52% yield. The spectroscopic data and specific rotation, $[\alpha]_D^{20}$ +22.1 (c 0.06, MeOH), obtained for synthetic **1** were in full accord with those reported for the natural product (see the ESI†).[2]

In summary, a concise and efficient total synthesis of the potent antiproliferative macrolide (+)-neopeltolide (**1**) has been achieved in 18 steps (longest linear sequence) and 5.8% overall yield, involving a Jacobsen hetero Diels–Alder reaction as the key step. Notably, our strategy involves the use of only achiral starting materials, with four of the six stereocentres (C3, C7, C9 and C13) being introduced using asymmetric catalysis, a tactic which should be readily adaptable to the synthesis of a variety of structural analogues.

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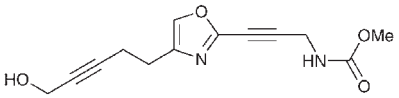

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