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Studies towards the synthesis of neopeltolide: synthesis of a ring-closing metathesis macrocyclization precursor

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ABSTRACT

An advanced ring-closing metathesis precursor for the synthesis of the marine macrolide neopeltolide is prepared in a stereocontrolled manner by the coupling of the C2–C10 and C11–C16 subunits. The metathesis reaction of **4** with Grubbs' II or Nolan's indenylidene catalyst led to the unexpected formation of cycloheptene **18**.

In 2007, Wright and co-workers reported the isolation of neopeltolide (**1**, Scheme 1) from a deep-water sponge of the family Neopeltidae off the north coast of Jamaica.[1] The structure of the marine natural product contains a 14-membered macrolide and a trisubstituted *cis*-THP ring bearing an unsaturated oxazole-containing side chain at C5. This side chain is identical to that found in the marine macrolide leucascandrolide A, and it has been hypothesized that this appendage is responsible for the biological activity of both natural products.[2] Initial biological testing by Wright and co-workers revealed that neopeltolide displays antifungal activity against the pathogen *Candida albicans* at a concentration of 0.63 μg/mL. Neopeltolide also displays anticancer activity against several cell lines including the P388 murine leukaemia, the A549 human lung adenocarcinoma and the NCI/ADR-RES ovarian sarcoma with IC_{50} values of 0.56, 1.2 and 5.1 nM, respectively. The potent biological activity and challenging structure have attracted the attention of the synthetic community and several total syntheses of the macrolide have been reported.[3] Notably, the first two syntheses of neopeltolide by Panek[3a] and Scheidt[3b] resulted in the reassignment of the C11 and C13 stereocenters. Following these reports, Kozmin and co-workers reported the synthesis of neopeltolide and of a simplified analogue of leucascandrolide A.[2] On the basis of biological testing using those two compounds, Kozmin proposed the cytochrome bc_1 complex as the molecular target of the two macrolides.

As part of our interest in the synthesis of the cyclic ether containing bioactive natural products, we became interested in the synthesis of neopeltolide.[4] Our retrosynthetic strategy is outlined in Scheme 1. The oxazole-containing side chain would be appended directly on aglycon **2** via Mitsunobu esterification, a tactic adopted in many of the previous syntheses of both leucascandrolide A[5] and neopeltolide.[3]

In contrast to the majority of previous syntheses of the neopeltolide aglycon that established all the stereocenters prior to formation of the macrolactone, we envisaged the ambitious use of macrocyclic conformations of suitable precursors to control the introduction of the C3, C9 and C11 stereocenters (Scheme 1). A similar tactic was employed by Floreancig[3g] and Sasaki,[3k] to introduce the C9 stereocenter by hydrogenation of a macrocyclic alkene. This would require the preparation of the key macrolide intermediate **3** via ring-closing metathesis (RCM) of precursor **4**, which in turn could be derived from the coupling of C2–C10 alkyne **5** and C11–C16 aldehyde **6**. Herein, we detail an efficient and stereocontrolled synthesis of **4** and studies of the subsequent RCM macrocyclization reaction.

The synthesis of the C2–C10 alkyne **5** started from D-malic acid (**7**), which was transformed into the known aldehyde **8** in five steps (Scheme 2).[6] Brown allylation[7] using (+)-Ipc_2BOMe and allylmagnesium bromide, followed by protection using TIPSOTf and 2,6-lutidine provided silyl ether **9** in excellent yield and dr.[8] Treatment of silyl ether **9** with a 50% aqueous solution of trifluoroacetic acid effectively cleaved the acetonide group and, reaction of the intermediate diol with sodium hydride and trisyl imidazole afforded epoxide **10** in 98% yield.[9] Epoxide **10** was then opened with the lithium anion of TMS–acetylene in the presence of $BF_3{\cdot}Et_2O$ to provide alkyne **11**. Deprotection of the TMS group using potassium carbonate followed by protection of the C7 hydroxy group using TBSOTf and 2,6-lutidine provided the C2–C10 fragment **5**.

As outlined in Scheme 3, the synthesis of the C11–C16 aldehyde **6** started with vinyl Grignard addition to enantiopure (*S*)-1,2-epoxypentane (**12**, prepared by Jacobsen hydrolytic kinetic resolution of racemic 1,2-epoxypentane).[10,11] Subsequent protection of the intermediate alcohol (TESOTf, 2,6-lutidine) and ozonolysis with PPh_3 work-up provided the C11–C16 aldehyde **6** in excellent yield over three steps.

With alkyne **5** and aldehyde **6** in hand, our attention was focussed on their union and elaboration to the ring-closing metath-

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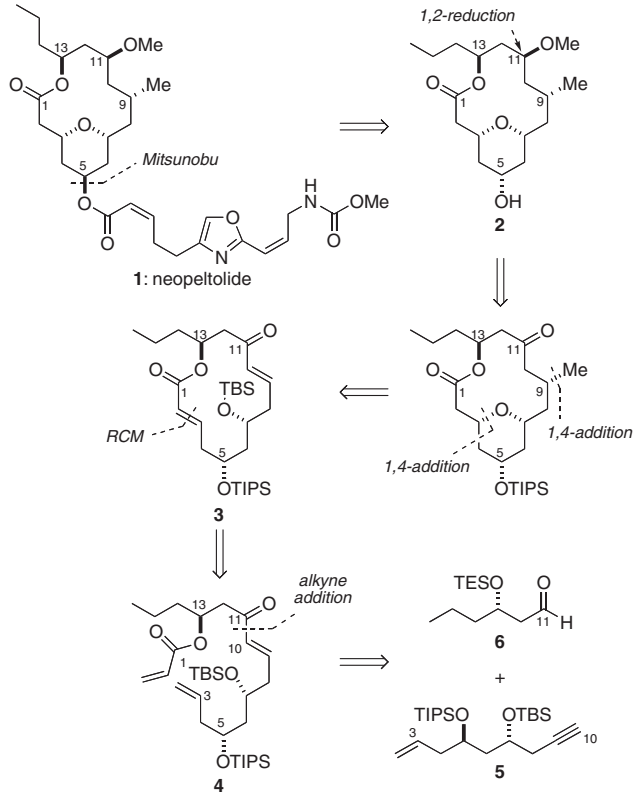
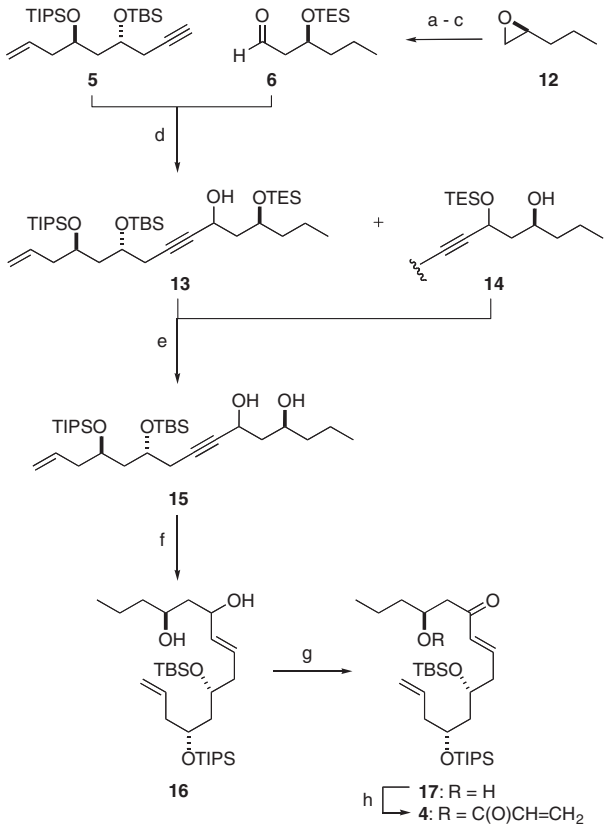
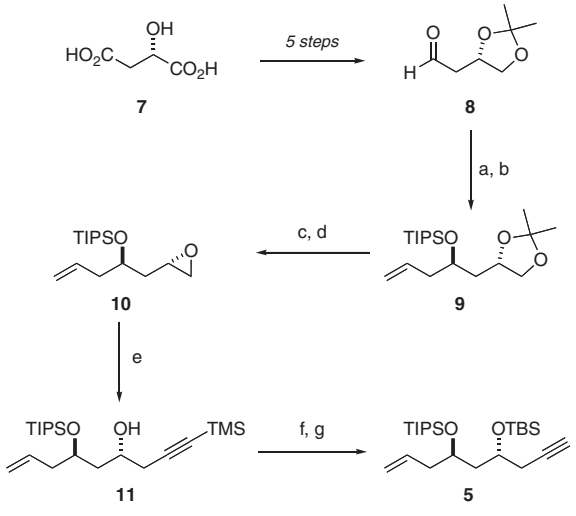


Scheme 1. Retrosynthetic strategy for neopeltolide (1).



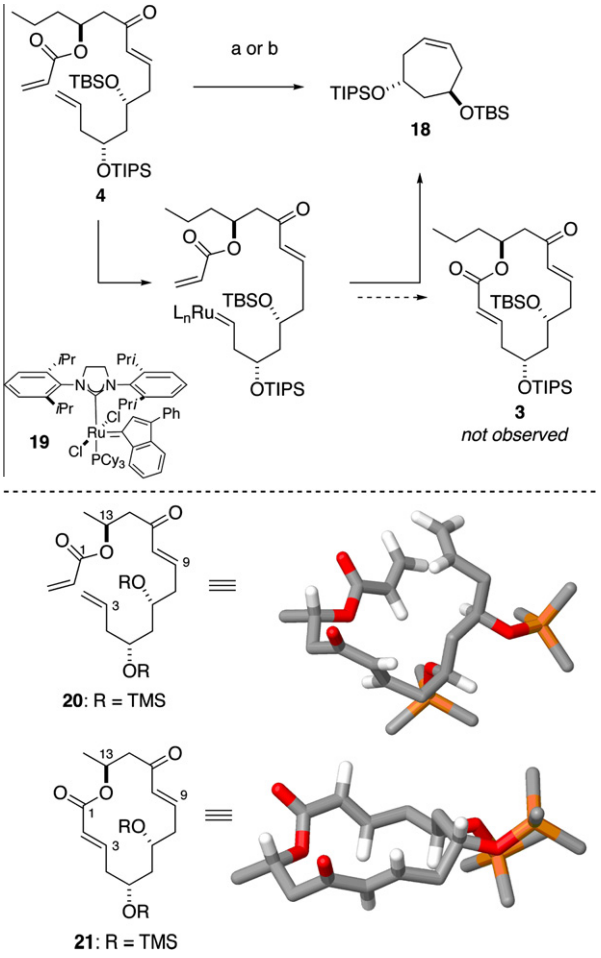
Scheme 3. Synthesis of RCM precursor **4**. Reagents and conditions: (a) vinylMgBr, CuI, THF, −78 °C to rt, 3 h, 85%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 1 h, 97%; (c) O_3 then Ph_3P, CH_2Cl_2, −78 °C to rt, 2 h, 96%; (d) **5**, *n*-BuLi 1.6 M in hexane, TMEDA, THF, −78 °C, 0.5 h; then **6**, −78 °C to −20 °C, 2 h, 81%; (e) CSA, MeOH/CH_2Cl_2 (1:1), 0 °C, 30 min, 77%; (f) Red-Al™, Et_2O, rt, 1.5 h, 94%, *E*:*Z* = 6:1; (g), MnO_2, Et_2O, rt, 5 h, 64%; (h) acrylic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, $PhCH_3$, rt, 1 h, 51%.

esis precursor **4** (Scheme 3). Thus, treatment of alkyne **5** with *n*-butyllithium and TMEDA, followed by addition of aldehyde **6** provided the desired addition product **13** as a 1:1 mixture of diastereomers at C11, co-isolated with the [1,5] Brook rearrangement product **14**, in a combined 81% yield. This mixture of addition products was treated with CSA in MeOH/CH_2Cl_2 to remove cleanly the TES ether to provide diol **15** in 77% yield. Reduction of the C9–C10 alkyne **15** with Red-Al™ provided the corresponding *E*-allylic alcohols **16** (*E*:*Z* = 6:1), which could be selectively oxidized with manganese dioxide to afford hydroxy-enone **17** in 64% yield.[12] Yamaguchi esterification of the C13-hydroxy group with acrylic acid using trichlorobenzoyl chloride, triethylamine and DMAP completed the synthesis of the ring-closing metathesis precursor **4** in 51% yield.[13,14]



Scheme 2. Synthesis of the C2–C10 fragment **5**. Reagents and conditions: (a) allylMgBr, (+)-Ipc2BOMe, $PhCH_3$, −78 °C, 1 h; then 2 M NaOH, H_2O_2, 3 h, 90%, 97:3 dr; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 2 h, 97%; (c) TFA 50% aq, CH_2Cl_2, rt, 30 min, 71%; (d) NaH, TrisIm, THF, 0 °C to rt, 1.5 h, 98%; (e) TMS-C≡C–H, *n*-BuLi 1.6 M solution in hexane, $BF_3{\cdot}Et_2O$, THF, −78 °C to −20 °C, 1.5 h, 95%; (f) K_2CO_3, MeOH, rt, 16 h, 88%; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 1 h, 97%.

With access to alkene **4** established, the stage was set to attempt the ring-closing metathesis reaction to form the 14-membered macrolide (Scheme 4). This proved to be an insurmountable obstacle and unfortunately, refluxing alkene **4** under high dilution conditions with 5 mol % of Grubbs' second generation catalyst[15] was not successful and only led to the unexpected, but efficient, formation of cylcoheptene **18** in 70% yield.[16] Likewise a similar result was obtained by reacting **4** with 20 mol % of Nolan's indenylidene complex **19** to provide **18** in a comparable 65% yield at room temperature.[17] In the light of this unexpected outcome, inspection of the low energy conformations of the simplified model **20**,[18] suggest that upon loading of the ruthenium complex on the terminal C3-olefin, the intermediate carbene can undergo addition to either of the Type II olefins, with the acrylate at C13 appearing more readily accessible than the C9–C11-enone in **20**. However, the exclusive formation of the cycloheptene suggests that either conformational flexibility of **20** and the intermediate carbene complex leads to preferential of C3–C7 metathesis directly, or that the transient formation of a 14-membered macrolide **21** is followed by a transannular metathesis reaction due to the conformational restraint imposed by the macrocycle.[15] Further experimental and computational studies are currently looking to establish the precise metathesis pathway using simplified model diene and triene systems.



Scheme 4. Ring-closing metathesis of precursor **4**. Reagents and conditions: (a) Grubbs II (5 mol %), CH_2Cl_2, reflux, 16 h, 70%; (b) **19** (20 mol %), CH_2Cl_2, rt, 4 h, 65%.

In summary, we have prepared an advanced RCM macrocyclization precursor for the synthesis of neopeltolide in an expedient and stereocontrolled manner from C2–C10 (**5**) and C11–C16 (**6**) subunits. However, the RCM of **4** led to the unexpected formation of cycloheptene **18** under a range of conditions. Alternative strategies for the synthesis of the key macrolide **3** for the synthesis of neopeltolide aglycon are currently underway and will be reported in due course.

Acknowledgements

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14. Spectroscopic data for RCM precursor **4**: $[\alpha]_D^{20}$ −17.7 (*c* 1.7, $CHCl_3$); IR (KBr, neat) 2946, 2865, 1727, 1674, 1463, 1406, 1258, 1192, 1085 cm−1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, dt, *J* = 15.9, 7.2 Hz), 6.39 (1H, dd, *J* = 17.4, 1.8 Hz), 6.16–6.05 (2H, m), 5.91–5.79 (2H, m), 5.38 (1H, quin, *J* = 6.3 Hz), 5.11–5.05 (2H, m), 3.96–3.91 (2H, m), 2.94 (1H, dd, *J* = 15.9, 6.6 Hz), 2.73 (1H, dd, *J* = 15.9, 6.3 Hz), 2.44–2.26 (4H, m), 1.79–1.38 (6H, m), 1.07 (21H, m), 0.94 (3H, t, *J* = 7.2 Hz), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 165.5, 144.6, 134.4, 132.5, 130.5, 128.6, 117.3, 70.6, 69.6, 69.1, 44.8, 44.1, 41.9, 40.7, 36.2, 25.8, 18.5, 18.2, 18.0, 13.8, 12.7, −4.2, −4.3; LRMS (ES^+) *m/z* 617 (100, $[M+Na]^+$); HRMS (ES^+) calcd for $C_{33}H_{62}O_5NaSi_2$ $[M+Na]^+$ 617.4034; found 617.4015.
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16. Spectroscopic data for cycloheptane **18**: $[\alpha]_D^{20}$ −119.2 (*c* 1.8, $CHCl_3$); IR (KBr, neat) 2957, 2927, 2856, 1462, 1377, 1256, 1199 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69–5.67 (2H, m), 4.16–4.03 (2H, m), 2.41–2.26 (4H, m), 2.03 (2H, t, *J* = 5.6 Hz), 1.07 (21H, s), 0.89 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.0, 127.9, 66.9, 66.8, 37.2, 37.1, 25.8, 18.15, 18.12, 12.3, −4.8, −4.9; LRMS (ES^+) *m/z* 397 (65, $[M-H]^+$); HRMS (ES^+) calcd for $C_{22}H_{45}O_2Si_2$ $[M-H]^+$ 397.2953; found 397.2946.
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