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Formal Total Synthesis of Neopeltolide

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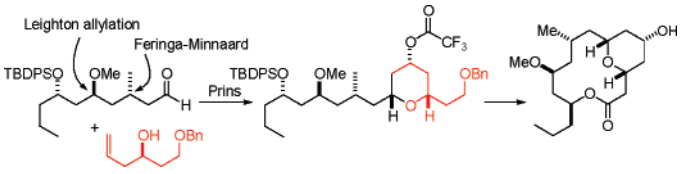
ABSTRACT



A concise synthesis of the core structure of the macrolide neopeltolide was developed featuring a Prins cyclization to fashion the pyran ring. Key steps in the synthesis of aldehyde 16 were a Leighton allylation and a Feringa–Minnaard asymmetric methyl cuprate addition to an unsaturated thioester. For lactonization, a classical Yamaguchi macrolactonization was used. The longest linear sequence consists of 17 steps providing lactone 26 with an overall yield of 23%.

In 2007 the group of A. E. Wright described a novel macrolide named neopeltolide (**1**) (Figure 1).[1] The producing deep-water sponge of the family Neopeltidae was collected off the north Jamaican coast. Neopeltolide turned out to be a very potent antitumor agent, inhibiting the proliferation of various cell lines in the low nanomolar range. The structural features of neopeltolide include a 14-membered macrolactone ring that contains an ether bridge forming a tetrahydropyran subunit. Moreover, there are six stereogenic centers. The hydroxyl group at C5 is acylated with an oxazol- and a carbamate-containing side chain. This substituent occupies an axial position in the pyran ring. The side chain is identical to the one in the macrolide leucascandrolide (**3**).[2,3] Thus, one can assume the same biological targets for these two compounds. Further related natural products with a macrolactone part similar to neopeltolide include polycavernoside[4,5] and callipeltoside.[6−8]

Two recent total syntheses, one by Panek[9] and the other by Scheidt et al.,[10] showed the original structural assignment to be partially wrong. Thus, the stereocenters at C11 and C13 had to be revised. The various hydroxyl functions in 1,3-distance make it clear that neopeltolide is a polyketide. However, one should note that the C9-methyl group is not sitting at a propionate position but rather at a former keto function. The fascinating structure combined with the potent

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biological activity prompted us to embark on a synthesis of **2**. We conceived a strategy that would be flexible enough to access analogs and derivatives that might help to identify the biological target. Furthermore, analogs that could illuminate key structural features important for the activity were planned. For example, analogs with a repositioned methyl group, a strategy that we term propionate scanning, would be desirable.

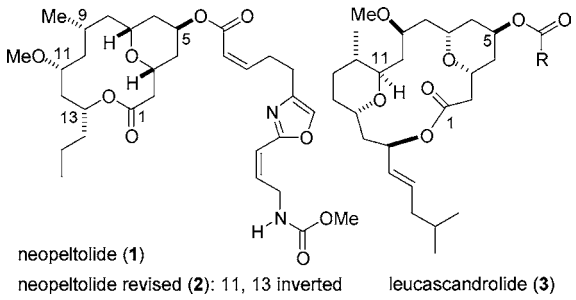
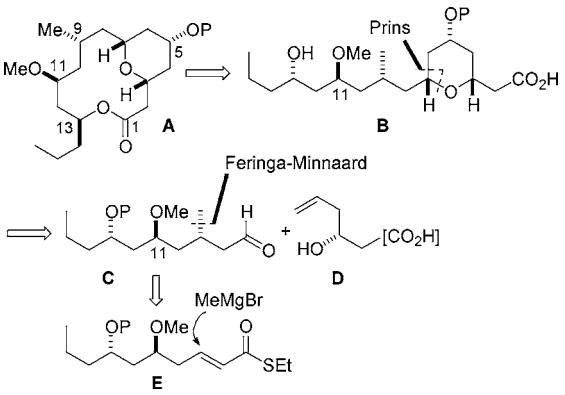


Figure 1. Structures of the related macrolides neopeltolide (**2**) and leucascandrolide (**3**). The acyl side chains at C5 are identical in both compounds.

A synthesis has to address the formation of the pyran ring and the creation of the region carrying the methyl group. Our retrosynthesis is shown in Scheme 1. Thus, after opening

Scheme 1. Key Retrosynthetic Cuts for the Neopeltolide Core Structure **A**, P = Protecting Group



of the lactone **A**, the seco acid **B** or a derivative thereof could be further disconnected by considering a Prins reaction on the pyran. The TFA-promoted Prins reaction would lead to an equatorial 5-OH group.[11−15] Accordingly, a Mitsunobu reaction would have to be used for the attachment of the side chain. The Prins strategy leads to an aldehyde **C** and a homoallylic alcohol **D**. The alcohol functions in the aldehyde **C** should pose no big problems.[16] A key question relates to the introduction of the subunit with the methyl group. In this regards, we chose a facial selective Michael addition using the Feringa−Minnaard reaction.[17,18] While this makes the route somehow linear, we demonstrate in the following that the conceived synthesis nevertheless is very concise.

The synthesis began with the 3-ketoester **4**, which was subjected to an enantioselelctive Noyori hydrogenation[19,20] using (*S*)-BINAP-Ru(II) as chiral catalyst (Scheme 2).

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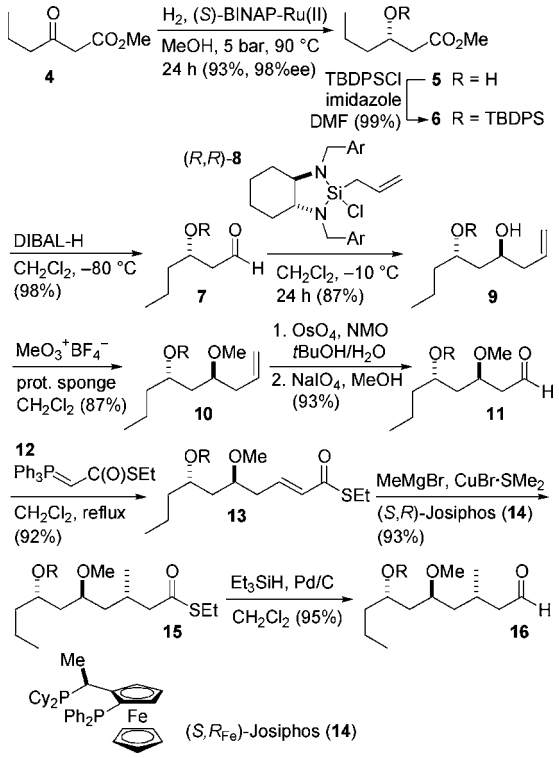
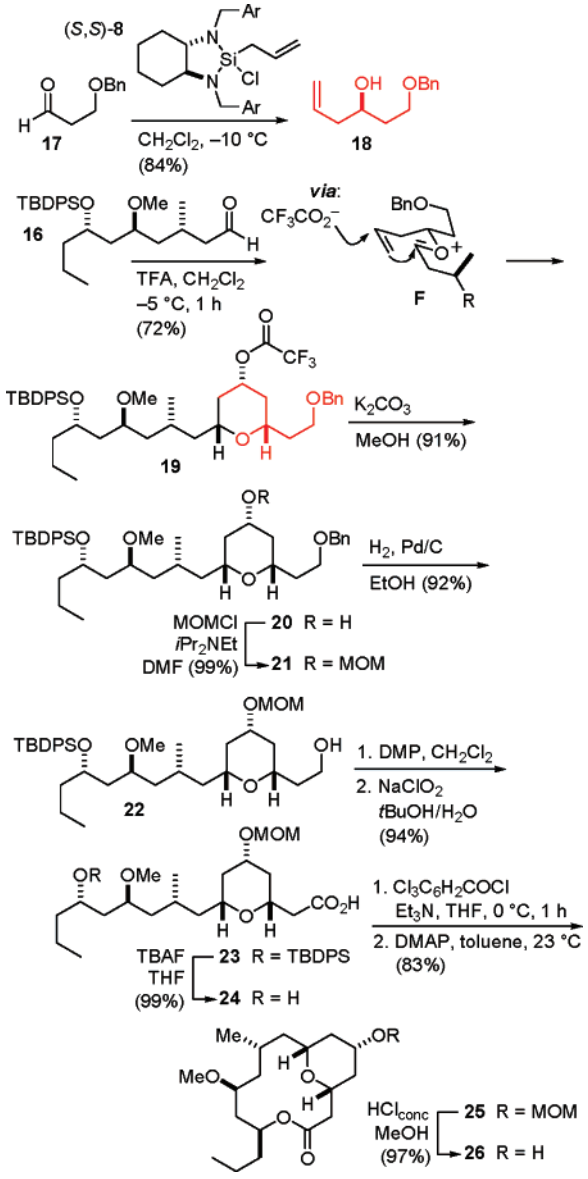
Scheme 2. Synthesis of Aldehyde **16** via Leighton Allylation of Aldehyde **7** and Asymmetric Methyl Cuprate Addition to Enthioate **13**; R = TBDPS, Ar = *p*BrC$_6$H$_4$



Scheme 3. Prins Cyclization for Formation of Pyran **19** and Yamaguchi Macrolactonization of Hydroxy Acid **24** Leading to the Core Structure **26** of Neopeltolide (**2**)



Silylation of the alcohol **5** produced ether **6** in almost quantitative yield. This was followed by ester reduction using DIBAL-H[21] at −80 °C in dichloromethane leading to aldehyde **7**. Chain extension was performed with the Leighton reagent **8**,[22] containing (*R*,*R*)-1,2-diaminocyclohexane. The alcohol function in the 1,3-*anti*-diol **9** was protected using Meerwein's salt in the presence of a proton sponge.[23] With other conditions partial migration of the silyl group was observed. In the ^{13}C NMR spectrum of **10** there was no other diastereomer visible, indicating the excellent selectivity in the allylation reaction. Oxidative degradation of the double bond of **10** led to aldehyde **11** that was extended to the unsaturated thioester[24] **13** using the stabilized Wittig reagent **12**. A conjugate addition reaction of methylmagnesium bromide (1.2 equiv) to **13** in the presence of CuBr·SMe$_2$ (3.4 mol %) and the chiral diphosphine (*S*,*R*)-Josiphos[25,26] **14** (4 mol %) produced the decanoate **15** in high yield.[18] Only one set of signals was observed for **15** in the ^{13}C NMR spectrum. Reduction of the thioester with Et$_3$SiH in the presence of Pd/C gave an almost quantitative yield of aldehyde **16**.

The homoallylic alcohol **18** required for the Prins reaction was available by allylation of the aldehyde[27] **17** with the Leighton reagent (*S*,*S*)-**8** (Scheme 3). For the crucial Prins reaction the homoallylic alcohol **18** and aldehyde **16** were

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reacted in dichloromethane in the presence of trifluoroacetic acid (10 equiv). This led to the pyran in 72% yield. Besides the major product **20**, the formation of a small amount of another isomer (major/minor = 8:1) was observed. The formation of the desired tetrahydropyran can be envisioned to proceed via oxonium ion **F** with an all equatorial orientation of the substituents in the chairlike transition state. A few simple functional group manipulations, i.e., basic cleavage of the trifluoroacetate, MOM protection of the resulting alcohol **20**, and debenzylation, led to primary alcohol **22**. Oxidation of **22** using a well-established sequence consisting of Dess−Martin and sodium chlorite oxidation[28] furnished acid **23**. Fluoride-induced cleavage of the silylether led to seco-acid **24**. Employing classical Yamaguchi conditions,[29,30] the acid cyclized in high yield to macrolactone **25**. At this stage the minor isomer resulting from the Prins reaction could be separated. A final cleavage of the MOM-protecting group completed the synthesis of the neopeltolide core structure **26** $\{[\alpha]^{20}_{D} = +18.4$ (c 0.1, $CHCl_3$)$\}$. The NMR spectra of **26** perfectly matched the one reported by Scheidt et al.[10]

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In conclusion, an efficient synthesis of the macrolactone part of neopeltolide could be developed. Key steps include two Leighton allylations. One led to the *anti*-diol **9**, and the other one produced the homoallylic alcohol **18**. The fact that the chiral diamine can be recovered makes this method very attractive for large-scale allylations. The methyl-bearing stereocenter (C9) came from an asymmetric methyl cuprate addition to the unsaturated thioester **13** using the Feringa−Minnaard method. Pyran formation could be achieved by classical TFA-mediated Prins reaction between aldehyde **16** and homoallylic alcohol **18**. A Yamaguchi macrolactonization eventually led to the core macrolactone **26** of the novel macrolide neopeltolide (**2**). Since lactone **26** is an advanced intermediate in the total synthesis of neopeltolide by Scheidt et al., our work represents a formal total synthesis of this natural product. Starting from keto ester **4**, the synthesis of lactone **26** required 17 steps in the longest linear sequence and produced lactone **26** in 23% overall yield. In this regard it compares favorably with the other known routes.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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