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Strategies and Methods for the Synthesis of Anticancer Natural Product Neopeltolide and its Analogs

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Abstract

Neopeltolide, isolated in 2007, with its novel structural features and potent anti cancer cell proliferation activity, has attracted a tremendous amount of synthetic efforts. This review briefly and chronologically summarizes each of the synthesis with the main focus on the strategies and methodologies for the construction of its *cis*-tetrahydropyran-containing macrolactone core.

Keywords

neopeltolide; macrolactone; tetrahydropyran; anticancer; palladium; carbonylation

1. INTRODUCTION

Natural products have always been valuable sources and inspirations for life-saving drug discovery.[1] Macrolide natural products are one of the most important families. Among them, tetrahydropyran (THP) and tetrahydrofuran (THF)-containing macrolides are a diverse subfamily of macrolides with a wide range of biological activities, particularly anticancer activity.[2] Neopeltolide (**1**) is a complex THP-containing macrolide isolated by Wright and co-workers in 2007 from a deep-water sponge of the family of Neopeltidae.[3] Its structure was first proposed as **1a**, which was later revised to **1b** and confirmed by total synthesis work. Structurally, neopeltolide and leucascandrolide A (**2**) [4] share a large portion of substructures, including the acid side chain (cf. **3**) and part of their macrolactone ring systems.

Biologically, neopeltolide was revealed to be an extremely potent anti-proliferation compound against several cancer cell lines including P388 murine leukemia ($IC_{50} = 0.56$ nM), A-549 human lung adenocarcinoma ($IC_{50} = 1.2$ nM), and NCI-ADR-RES human ovarian sarcoma ($IC_{50} = 5.1$ nM). It also showed strong cytostatic inhibitory effects in PANC-1 pancreatic and DLD-1 colorectal cell lines. Additionally, neopeltolide also exhibits potent antifungal activity against pathogenic yeast *Candida albicans*.

The structural complexity and potent anticancer activity of neopeltolide have attracted a great amount of synthetic efforts since its isolation. Many elegant syntheses have been

developed. These syntheses have facilitated the structure-activity relationship study of its in vitro anticancer activity. More importantly, through total synthesis and target identification of the synthetic sample, Kozmin and co-workers have revealed that neopeltolide may inhibit mitochondrial ATP synthesis and identified cytochrome *bc1* complex as the principle cellular target,[5] which provided the molecular basis for the potent antiproliferative activity of neopeltolide and related analogs.

2. SYNTHESIS

This review briefly summarizes the key strategies and methodologies of each synthesis with focus on the THP-containing macrolactone core synthesis. The synthesis of the side chain (cf. **3**) will not be discussed here.[6]

The Panek Total Synthesis

Shortly after the isolation of neopeltolide, Panek and co-workers completed the first total synthesis in 2007 (Scheme 1) and revised the stereochemical assignment of the C₁₁ and C₁₃ stereogenic centers of neopeltolide (**1a** vs **1b**, Figure 1).[7] Their synthesis commenced with compounds **4** and **5**, which contain the C₉ stereocenter and C₁₃ stereocenter of neopeltolide, respectively. After **4** and **5** were converted to **6**, Evans-Tishchenko reduction[8] was used to introduce the C₁₁ carbon center (d.r. 14:1) and the resulting alcohol was further transformed to **7**. Upon treatment of compounds **7** and **8** with triflic acid, a [4+2] annulation took place smoothly to build dihydropyran **9**, which was further advanced to seco-acid **10**. Yamaguchi macrolactonization[9] provided macrolactone **12** in 44% yield. Oxymercuration followed by demercuration converted **12** to **13**. The latter was advanced to neopeltolide (**1b**) with a sequence of esterification and Still-Gennari olefination.[10]

The Scheidt Total Synthesis

In the same year, Scheidt and co-workers completed an elegant total neopeltolide and revised its structure assignment as well (Scheme 2).[11] Their synthesis features a Mitsunobu reaction to install the side chain and a Prins-type macrocyclization to synthesize the THP-containing macrolactone core in one operation. As delineated in Scheme 2, a Ti(IV)-(S)-BINOL-catalyzed asymmetric aldol reaction was employed to introduce the C₃ stereocenter in intermediate **18**. Compound **19** (derived from Noyori asymmetric hydrogenation) and **20** carrying the C₁₃ and C₉ stereocenters of neopeltolide, respectively, were eventually united together to provide compound **21**, which underwent an Evans-Tishchenko reduction followed by methylation and removal of benzoate to produce **22**. Scheidt and co-workers used a Yamaguchi reaction to join **22** and **18**. The resulting ester was then transformed to aldehyde **23**, which upon treatment with Sc(OTf)₃, underwent an efficient Prins-type macrocyclization to build the THP ring and the macrocyclic ring system in one step and provided compound **24** in 40% yield. The latter was then converted to neopeltolide smoothly via a sequence of decarboxylation, reduction and Mitsunobu esterification.

The Maier Total Synthesis

In 2008, Maier and co-workers first reported a formal synthesis of neopeltolide followed by a total synthesis.[12] As summarized in Scheme 3, starting from aldehyde **26**, which was synthesized from Noyori asymmetric hydrogenation followed by DIBAL-H reduction, a Leighton asymmetric allylation[13] was used to synthesize compound **28** with the C₁₁ stereocenter. After **28** was converted to α,β -unsaturated thioester **29**, a Feringa-Minnaard reaction enabled the introduction of the C₉ methyl group in a stereoselective manner.[14] Reduction of thioester **31** afforded aldehyde **32**. The latter underwent a Prins reaction with homoallylic alcohol **33** (again derived from a Leighton asymmetric allylation) to provide tetrahydropyran product **34** in 72% yield (d.r. 8:1). After **34** was converted to seco-acid **35**, Maier and co-workers used a Yamaguchi macrolactonization to synthesize **36**, which was then advanced to neopeltolide via MOM-deprotection and Mitsunobu reaction. Notably, Maier and co-workers have provided insightful SAR information about the acid side chain's effect on neopeltolide's anticancer activity. A slightly more potent analog has been identified.

The Lee Total Synthesis

In the same year, Lee and co-workers reported an elegant total synthesis of neopeltolide featuring a Prins-type macrocyclization as a key step to build the THP-macrolactone in one step (Scheme 4).[15] Their synthesis started with a crotyl transfer reaction from **38** to aldehyde **37**. The resulting homoallylic alcohol was further converted to **39** via benzyl protection and ozonolysis. They then used a titanium (IV)-mediated diastereoselective methallylation followed by esterification with **41** to synthesize **42** which was equipped with a directing group for the next hydroformylation. The substrate-directed hydroformylation of **42** preferentially produced desired aldehyde **43**, which was further converted to dimethyl acetal **44**. Removal of the benzyl-protecting group followed by DCC promoted esterification with acid **45** gave ester **46**. After oxidative removal of the PMB-protecting group, a Prins-type macrocyclization took place smoothly to set up two stereocenters (C₅ and C₇) and the THP-macrolactone core in one step and provided **48** in good yield, which was converted to neopeltolide shortly. Notably, Lee and co-workers also developed an alternative Prins-cyclization to synthesize **48**.

The Kozmin Total Synthesis

In 2008, Kozmin and co-workers reported an elegant total synthesis of neopeltolide as well as a simplified analog of leucascandrolide A (Scheme 5).[5] More importantly, they have shown that neopeltolide and leucascandrolide A may inhibit mitochondrial ATP synthesis and identified cytochrome *bc1* complex as the principle cellular target, which provided the molecular basis for the potent antiproliferative activity of neopeltolide and leucascandrolide A. Their synthesis initiated with a Prins desymmetrization of **49** to form the THP-ring. Benzyl protection followed by Wacker oxidation converted the Prins cyclization product to ketone **50**. Boron enolate promoted aldol reaction between **50** and **51** gave **52** in high stereoselectivity at C₁₁ (>98:2). While the stereochemical outcome at C₁₁ is opposite from what is required for the synthesis of neopeltolide, this new stereocenter facilitated the introduction of the C₁₃ stereocenter via a 1,3-syn selective reaction (cf. **53**→**54**) and was

inverted to the desired one via a Mitsunobu reaction at a later stage. Yamaguchi macrolactonization was used to build the 14-membered lactone in preference of a more strained 12-membered lactone. Kozmin and co-workers then developed a diastereoselective hydrogenation to introduce the C₉ stereocenter by taking advantage of macrocyclic stereochemical control and product **56** was obtained in 61% yield (d.r. 3:1), which was advanced to **25** then to neopeltolide smoothly with two Mitsunobu reactions as the key transformations.

The Fuwa and Sasaki Total Synthesis

Fuwa, Sasaki and co-workers reported their first generation total synthesis of neopeltolide in 2008 as well (Scheme 6).[16] Their synthesis features a B-alkyl Suzuki cross coupling to unite compounds **57** and **58** to provide diene **59**, which underwent a ring closing metathesis reaction followed by hydrogenation to provide product **60** with the desired *cis*-THP ring. The latter was further advanced to seco-acid **61**. Again, Yamaguchi reaction was used to prepare the macrolactone ring. The macrocyclization product was transformed to neopeltolide upon removal of BOM-protecting group and Mitsunobu reaction with **3**.

In 2010, Fuwa and Sasaki reported their second-generation synthesis, which features a hydroxyl group directed cross-metathesis over a ring closing metathesis to convert **62** to **64**. [17] After protection group adjustment, DBU-promoted intramolecular oxa-conjugate addition of **65** afforded compound **66** in 73% yield (d.r. >20:1). The latter underwent Yamaguchi esterification with alcohol **68** to give diene **69** in excellent yield. Ring closing metathesis using the Grubbs second-generation catalyst built the macrocyclic ring. The RCM product was converted to **25** with a one-pot hydrogenation to remove both the BOM-protecting group and the double bond. Notably, unlike Kozmin's case of hydrogenation of the exo-methylene group, a single diastereomer was obtained in Fuwa and Sasaki's case with an internal double bond. The two synthetic approaches allowed Fuwa, Sasaki and co-workers to extensively explore the structure-activity relationship of neopeltolide's anticancer activity.[18]

The Paterson Total Synthesis

Paterson and Miller reported their total synthesis of neopeltolide in 2008 (Scheme 7).[19] Unlike the previous syntheses, they used an asymmetric hetero-Diels-Alder reaction to construct the THP-ring. Their synthesis started with aldehyde **70**, which underwent Brown methallylation with **71** followed by methylation to provide **72**. The latter was advanced to aldehyde **73** shortly. Paterson and Miller employed a MacMillan organocatalytic hydride reduction to introduce the C₉ stereocenter while with 76:24 diastereoselectivity. With aldehyde **75** in hand, they used a Jacobsen asymmetric hetero-Diels-Alder reaction between **75** and **76** to provide **78** in 78% yield with Cr(III) catalyst **77**. The latter was advanced to **79**, then to neopeltolide with a Yamaguchi macrolactonization and a Mitsunobu reaction as the key steps.

The Taylor Formal Synthesis

The Taylor group at the University of Notre Dame developed a radical cyclization strategy to build the *cis*-THP-ring and completed a formal synthesis of neopeltolide.[20] As shown in

Scheme 8, their synthesis started with commercially available compound **80** containing the C₉ stereocenter, which was furnished to **81**. They employed the Soderquist asymmetric allylation[21] to install the C₇ alcohol, which was further protected as BOM-ether **83**. Compound **83** was then linked with β -hydroxysulfide **84** using the Rychnovsky method to produce β -hydroxy ketone **85** in 92% yield.[22] Evans-Tishchenko reduction of **85** introduced the C₁₁ alcohol with excellent stereoselectivity. The newly generated alcohol was converted to the desired methyl ether **86**. The highlight of the Taylor synthesis is an iodo-ether transfer reaction to convert **86** to **87** with the desired C₅ stereocenter in 71% yield (d.r. >20:1). The ether transfer reaction also released the C₇ alcohol for the next oxa-conjugate addition to **88** to provide compound **89**, which underwent a radical reaction to form compound **90** with the desired *cis*-THP-ring in excellent yield and selectivity. Compound **90** was then quickly advanced to Panek's intermediate **13**. Again, Yamaguchi macrolactonization was used to build the neopeltolide macrolactone.

The Roulland Total Synthesis

The saga of neopeltolide synthesis continues in the year of 2009. Roulland and Guinchard developed an elegant total synthesis featuring a tandem ene-yne coupling followed by oxa-Michael addition to construct the *cis*-THP-ring of neopeltolide.[23] As shown in Scheme 9, 1,2-addition of Grignard reagent **92** to Weinreb amide **91** (prepared using asymmetric hydrogenation as key step) followed by Evans-Tishchenko reduction provided compound **93** in excellent yield. Esterification of the latter followed by ring-closing metathesis gave α,β -unsaturated lactone **94**, which was converted to aldehyde **95** with a substrate-controlled hydrogenation to introduce the C₉ stereocenter as a key step. In^{III}-catalyzed asymmetric propargylation reaction with **96** converted **95** to homopropargylic alcohol **97**. [24] This reaction occurred with a full stereoselective transfer of the trimethylsilylpropynyl group from chiral alcohol **96** to **95**. Roulland and Guinchard then developed an efficient Rucatalyzed tandem alkyne-enal coupling/stereoselective oxa-Michael addition sequence to convert **97** to **99**. The latter, upon a sequence of oxidative cleavage of the C-C double bond, oxidation of the aldehyde to carboxylic acid, Yamaguchi macrolactonization, stereoselective ketone reduction and Mitsunobu reaction, was advanced to neopeltolide.

The Hong Formal Synthesis

Hong and co-workers developed a tandem allylic oxidation/oxa-Michael addition to synthesize 2,6-*cis*-tetrahydropyrans and applied it nicely to a formal synthesis of neopeltolide (Scheme 10).[25] Their synthesis started with sequential coupling of dithiane **100** with iodide **101** and (*R*)-epichlorohydrin followed by epoxide opening to provide **102**. After removal of the thioketal, Evans-Tishchenko reduction provided the desired *anti*-1,3-diol, which was methylated to give product **103**. They then used Sharpless dihydroxylation to introduce the C₇ stereocenter. The resulting diol was further converted epoxide **105**. Again, dithiane coupling was used to connect **105** and **106** to provide key intermediate **107**. Upon treatment of MnO₂, the allylic alcohol of **107** was oxidized to an α,β -unsaturated aldehyde to trigger an oxa-Michael addition to form the 2,6-*cis*-THP ring. Further oxidation with the condition of MnO₂, DBU, and **108** in methanol converted the resulting aldehyde to ester **109**. This allylic oxidation/oxa-Michael reaction/oxidation sequence was

chemoselective and stereoselective. After hydrolysis of **109**, Shiina macrolactonization was used to synthesize the neopeltolide macrolactone, which was further converted to known alcohol **25** upon thio-ketal removal and reduction of the resulting ketone.

The Floreancig Total Synthesis

Floreancig and co-workers have developed an oxidative C-C bond formation for the synthesis of *cis*-THP ring in the presence of macrocycles. They further applied this strategy to the total synthesis of neopeltolide and its analogs (Scheme 11).[26] Their synthesis commenced with a convergent approach to unite three building blocks **112**, **113**, and **114** together via an etherification and Sonogashira cross coupling to provide compound **115**. They then used a Pt(DVDS)-mediated intramolecular hydrosilylation followed by Tamao oxidation to convert one of the alkyne groups to a ketone (cf. **115**→**116**) in a regioselective fashion. Again, Evans-Tishchenko reduction was used to install the C₁₁ stereocenter. Compound **116** was then advanced to seco-acid **117**, which underwent a Yamaguchi macrolactonization to provide 12-membered lactone **118** in 72% yield. The synthesis of the oxidative cyclization precursor **119** was accomplished by a ruthenium-mediated addition of HOAc across the alkyne in 82% with 5:1 regioselectivity. DDQ oxidation of **119** promoted the oxidative carbocation cyclization to form the desired *cis*-THP ring. The resulting product was then converted to **79** via macrocycle-controlled hydrogenation, which was further converted to neopeltolide via NaBH₄ reduction and Mitsunobu reaction.

The Yadav Formal Synthesis

Yadav and co-workers started with chiral pool (*S*)-citronellol (**120**), which contains the C₉ stereocenter of neopeltolide (Scheme 12).[27] After (*S*)-citronellol was advanced to aldehyde **121** via oxidative degradation, a Prins cyclization of **121** and (*S*)-pent-4-ene-1,2-diol (**122**) was utilized to set up the C₁₁ and C₁₃ stereocenter in one operation. The unwanted stereocenter from **122**, after serving as a chiral auxiliary in the Prins cyclization step was removed with a reductive elimination of iodide **124**. The open chain product **125** was further converted to **126**, a key intermediate for Lee's synthesis. Following Lee's Prins macrocyclic protocol, Yadav and co-workers completed a formal synthesis of neopeltolide in 2009.

The Jennings Formal Synthesis (–)-Neopeltolide

The Jennings' synthesis was reported in 2010 (Scheme 13).[28] Jennings and co-worker developed two synthetic approaches to synthesize **127**. One involves a Reformatsky reaction; the other one involves a ring closing metathesis to form the 6-membered lactone. Substrate-controlled hydrogenation converted **127** to **128** and introduced the C₉ stereocenter. After advancing **128** to **129**, they used a Brown asymmetric allylation followed by cross metathesis catalyzed by the second-generation Grubbs catalyst to produce **131**. Following the Evans protocol for the diastereoselective synthesis of 1,3-syn-diols,[29] ester **131** was converted to **132** with the treatment of benzaldehyde and catalytic amount of KO^tBu. After converting **132** to **133**, Jennings and co-worker used a stereoselective reduction with the combination of TFA/Et₃SiH to synthesize **134** with the desired *cis*-THP ring in 70% yield

with excellent diastereoselective (d.r. >20:1). Compound **134** was successfully converted to the neopeltolide macrolactone ent-**13** with Yamaguchi reaction as a key transformation.

The She Formal Synthesis

She and co-workers from Lanzhou University report an elegant synthesis of the neopeltolide macrolactone in 2011 (Scheme 14).[30] Their synthesis commenced with an efficient iridium-catalyzed double asymmetric carbonyl allylation developed by the Krische group to convert 1,3-propanediol **136** to the C_2 -symmetric diol **138** in 72% yield.[31] The latter was then subjected to the Semmelhack's palladium-catalyzed alkoxycarbonylation reaction[32] to provide tetrahydropyran **139** in excellent yield and stereoselectivity (d.r. > 20:1). After **139** was furnished to **140**, Shiina's protocol was used to connect **140** and **68** together and provide diene **141**. Ring closing metathesis catalyzed by Hoveyda-Grubbs second-generation catalyst converted **141** to macrocyclic compound **142**, which was further advanced to known intermediate **25** upon removal of the benzyl-protecting group and the unsaturated double bond in one pot.

The Sharma Formal Synthesis

Sharma and co-workers synthesized both **143** and **144** from chiral pool L-malic acid (Scheme 15).[33] After DDC coupling of them, a ring closing metathesis was used to form the 14-membered macrocyclic ring with a different disconnection from the She and Fuwa/Sasaki syntheses. After oxidative removal of the PMB-protecting group, they developed an elegant transannular oxy-mercuration of **146** to build the *cis*-THP ring and provide **147** in 84% yield and excellent selectivity. Notably, poor diastereoselectivity was obtained when a related transannular iodo-etherification was employed. Radical removal of mercury followed by hydrolysis of MOM-ether converted **147** to the Panek intermediate **13**.

The Raghavan Formal Synthesis

Raghavan and co-worker used the MacMillan's organocatalytic hydride reduction catalyzed by **74** to reduce enal **148** to introduce the C_9 stereocenter and produce aldehyde **149** (Scheme 16).[34] Hetero-Diels-Alder reaction catalyzed by (*S,S*)-Cr(III)-salen between **149** and the Danishefsky diene **150** proceeded smoothly to produce **151** in 75% yield with high stereoselectivity at C_7 . The C_7 stereocenter controls the reduction of the carbonyl group of **151** by the Luche protocol to introduce the C_5 stereocenter, which was transferred to C_3 via a Claisen rearrangement (cf. **152**→**153**). The Claisen product was further advanced to **154**. Treatment of **154** with LDBB and aldehyde **70** gave an epimeric mixture of alcohols, which were oxidized by IBX to yield ketone **155**. After several functional group manipulations, **155** was converted to the Panek seco-acid **10**, then to macrolactone **12** uneventfully.

The S. Ghosh Formal Synthesis

The S. Ghosh's synthesis started with known alcohol **156**, which was converted to **157** with two Jacobsen hydrolytic kinetic resolutions as key steps to introduce the C_{11} and C_{13} stereocenters (Scheme 17).[35] Compound **157** was then condensed with ketophosphonate **158** by a Horner-Wadsworth-Emmons reaction to provide enone **159** in 77% yield. The authors then developed a palladium(II)-catalyzed oxa-Michael reaction to build the *cis*-THP

ring and product **160** was produced in 48% yield accompanied by 12% of the undesired stereoisomer. Uneventfully, compound **160** was advanced to the known enone **79** with a Yamaguachi macrolactonization as the key step to form the macrolactone ring.

The A. Ghosh Total Synthesis

The A. Ghosh group at Purdue University completed an elegant total synthesis of neopeltolide in 2013 (Scheme 18).[36] Their synthesis commenced with an enzymatic desymmetrization of 3-methylglutaric anhydride **161** using PS-30 “Amano” lipase to introduce the C₉ stereocenter. The reduced product **162** was then converted to **163** with two Brown asymmetric allylations as key steps to install the C₁₁ and C₁₃ stereocenters. Compound **163** was further converted to **164** equipped with a diene functional group for the next hetero-Diels-Alder reaction to build the *cis*-THP ring. The Jacobsen Cr(III)-catalyst **166** served well to catalyze the hetero-Diels-Alder reaction between **164** and **165** to provide **167** in 83% yield. Notably, this hetero-Diels-Alder reaction is very sensitive to the length of the aldehyde side chain. After **167** was advanced to seco-acid **168**, Yamaguchi macrolactonization was used to synthesize macrolactone **79**, which was then converted to neopeltolide shortly.

The Dai Synthesis of 9-Demethylneopeltolide[37]

We recently developed a palladium-catalyzed alkoxycarbonylative macrolactonization method to synthesize various THP-containing macrolactones with different ring sizes and functional groups (Scheme 19, **169**→**170**). This reaction also worked smoothly for the macrolactonization of tertiary alcohols. To demonstrate its application in synthesizing complex natural products and their analogs, we used it to synthesize 9-demethylneopeltolide, a simplified analog of neopeltolide but with similar anti-cancer activity as neopeltolide. When substrate **171** was subjected to the palladium-catalyzed alkoxycarbonylative macrolactonization conditions, desired product **172** was produced in 58% yield with excellent *cis*-selectivity. Compound **172** was then converted to 9-demethylneopeltolide **174** via a sequence of ketal removal, NaBH₄ reduction and Mitsunobu reaction. The palladium-catalyzed alkoxycarbonylative macrolactonization enabled the installation of the *cis*-THP-ring and the macrolactone ring in one operation. Carbon monoxide was used as the carbonyl sources. No pre-carboxylate synthesis is required.

The Hoveyda Total Synthesis of Neopeltolide

Very recently, Hoveyda and co-workers have reported an elegant total synthesis of neopeltolide.[38] Their synthesis started with an enantioselective boron conjugate addition catalyzed by chiral *N*-heterocyclic carbene **176** to convert **175** to **177** with the desired C₁₃ stereocenter. The latter was then advanced to known intermediate **68** quickly with a sequence of 1,2-addition, Evans-Tishchenko reduction, methylation and hydrolysis. They synthesized tetrahydropyran **181** with a powerful enantioselective ring-opening cross-metathesis involving oxabicyclic alkene **178** and vinyl ether **179** in the presence of Mo MAP complex **180**. Upon hydrolysis and oxidation, **181** was converted to acid **182**, which was then coupled with alcohol **68** to provide diene **183**. The latter underwent ring-closing metathesis smoothly with Mo bis(aryloxide) **184** as catalyst and product **142** was produced

in 89% yield in gram-scale, which was further advance to neopeltolide with a sequence of hydrogenation and Mitsunobu reaction. Notably, Hoveyda and co-workers also developed a short and stereoselective route to synthesize linear acid **3** featuring two highly Z-selective cross-metathesis steps to construct the two *cis*-double bonds of acid **3**.

3. CONCLUSION

Since its isolation in 2007, neopeltolide has aroused many interests in the fields of organic synthesis, chemical biology, and anticancer drug discovery, due to its intriguing structure and potent anticancer activity. Many elegant syntheses have been developed. These syntheses have enabled (i) the elucidation of its correct structure, (ii) preparation of sufficient material for biological evaluations, (iii) identification of its potential cellular targets, (iv) establishment of structure-activity relationship, (v) identification of simplified analogues with similar biological activity, and (vi) development of different strategies and novel synthetic methodologies. These practices demonstrated the importance of total synthesis. They also paved the way for future anticancer drug discovery based on neopeltolide and related natural products.

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Figure 1.
Structures of neopeltolide and leucascandrolide A

Scheme 1.
The Panek synthesis (2007)

Scheme 2.
The Scheidt synthesis (2007)

Scheme 3.
The Maier synthesis (2008)

Scheme 4.
The Lee synthesis (2008)

Scheme 5.
The Kozmin synthesis (2008)

Scheme 6.
The Fuwa and Sasaki synthesis (2008 and 2010)

Scheme 7.
The Paterson synthesis (2008)

Scheme 8.
The Taylor synthesis (2008)

Scheme 9.
Roulland synthesis (2009)

Scheme 10.
The Hong synthesis (2009)

Scheme 11.
The Floreancig synthesis (2009)

Scheme 12.
The Yadav synthesis (2009)

Scheme 13.
Jennings synthesis (2010)

Scheme 14.
The She synthesis (2011)

Scheme 15.
The Sharma synthesis (2012)

Scheme 16.
The Raghavan synthesis (2012)

Scheme 17.
The S. Ghosh synthesis (2012)

Scheme 18.
The A. Ghosh synthesis (2013)

Scheme 19.

The Dai synthesis of 9-demethylneopeltolide (2014)

Scheme 20.
The Hoveyda synthesis (2014)