Account / Revue

Neopeltolide, a new promising antitumoral agent

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Abstract

Neopeltolide seems to be a new promising antitumoral agent. The isolation, biological activity, as well as the chemical syntheses of neopeltolide are reported. **To cite this article: J. Gallon et al., C. R. Chimie 11 (2008).**
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1. Introduction

In 2007, Wright et al. reported the isolation of a new marine natural product, neopeltolide, from a deep-water specimen of a sponge of the family Neopeltidae which was collected off the northwest coast of Jamaica [1]. The sponge was not identified, but it most closely matches the taxonomic description for the genus *Daedalopelta* [2], and described as a close relative member of *Callipelta* which is a rich source of biologically active marine compounds [3].

2. Biological activity

Biological assays of neopeltolide revealed potent *in vitro* cytotoxicity toward various cancer cell lines such as A-549 human lung adenocarcinoma ($IC_{50} = 1.2$ nM), NCI-ADR-RES human ovarian sarcoma ($IC_{50} = 5.1$ nM), and P 388 murine leukemia ($IC_{50} = 0.56$ nM).

Neopeltolide is also a strong inhibitor of PANC-1 pancreatic and colorectal cell lines, both of which have p53 mutations. It is worthy of note that only 50% cell death was observed over an extended dose range, suggesting a cytostatic rather than a cytotoxic effect [1]. Preliminary investigations into the mechanism of action of neopeltolide suggest that it does not act *via* interaction with tubulin or actin. In addition, neopeltolide is a potent inhibitor of the growth of the fungal pathogen *Candida albicans* with a MIC value of $0.62~\mu g~mL^{-1}$ in liquid cultures [1b].

In a recent report, Kozmin et al. [4] reported that neopeltolide may inhibit mitochondrial ATP synthesis. They have evaluated the activity of the four mitochondrial electron transfer chain complexes in yeast and mammalian cells and found cytochrome bc_1 complex as the principal cellular target. These results provide the molecular basis for the potent antiproliferative activity of this compound.

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3. Structural determination

The structure of neopeltolide was established on the basis of NMR, HRMS [1], and by total synthesis. By NMR and HRMS studies, neopeltolide was identified as a 14-membered macrolactone possessing an *anti*-1,3-oxygenated moiety, a trisubstituted tetrahydropyran, and an oxazole-bearing side chain identical to the side chain of leucascandrolide A [5,6], a compound with a related structure and similar bioactivity to neopeltolide. By using NOESY, and a series of double-pulsed field gradient spin echo (DPFGSE) NOE experiments, and by carefully analyzing the coupling constants by NMR, the relative stereochemistry between the different substituents was determined and the absolute configuration was established, at first, to be (11*R*,13*R*). However, a reassignment of the absolute configuration at C11 and C13 was achieved by total synthesis which has established that the C11 and C13 stereocenters actually possessed the (*S*) configuration (Scheme 1) [7].

4. Synthesis

To date, six syntheses have been published. The first total synthesis of (+)-neopeltolide was achieved by Panek et al. in 2007 [7]. Their initial efforts focused on the synthesis of the proposed neopeltolide structure, and they obtained a compound that showed several ¹H and ¹³C NMR spectroscopic discrepancies with the

data from natural neopeltolide. In order to identify the correct stereochemical configuration of neopeltolide, Panek et al. undertook the synthesis of a set of diastereomers. The spectroscopic comparison of the prepared diastereoisomers allowed them to attribute the (*S*) configuration to the stereogenic centers at C11 and C13 instead of the (*R*) configuration initially proposed by spectroscopic analyses [1].

4.1. Panek et al. total synthesis [7]

Panek et al. synthesized (+)-neopeltolide by coupling the macrocyclic lactone **A** and the oxazole side chain **B** using a Still–Gennari olefination. The key steps involved the construction of the macrocyclic lactone by using a Yamaguchi esterification, a [4 + 2]-annulation strategy with an allylsilane to install the *cis*-disubstituted tetrahydropyran, a ring opening of an enantio-enriched epoxide to control the stereogenic center at C13, and a modified Evans–Tishchenko reduction to control the C11 sterogenic center (Scheme 2).

The synthesis of (+)-neopeltolide started with the preparation of the C7–C11 fragment from the commercially available methyl (*R*)-(+)-3-methyl glutarate **2** (Scheme 3). The chemoselective reduction of the carboxylic acid functionality in **2** (BH₃·Me₂S, THF) [8] to the corresponding primary alcohol, followed by TBDPS protection (TBDPSCl, imidazole) provided silyl ether **3**, which was then transformed to

Initial structure
proposed by Wright *et al.* **1a**

(+)-Neopeltolide [11*S*,13*S*] **1b**

Leucascandrolide A

Scheme 1.

Scheme 2.

dithiane **4** in two steps (reduction of the ester into an aldehyde and thioacetalization). Coupling of dithiane **4** with epoxide **5** [9] led to the C7−C16 fragment of (+)-neopeltolide, *e.g.* compound **6**. Removal of the dithioketal (CaCO₃/MeI) and stereodirected reduction of the resulting β-hydroxy ketone with a modified Evans−Tishchenko reduction [10] resulted in the *anti*-relationship between the ester group at C13 and the hydroxy group at C11 (dr = 14/1). The etherification of the hydroxy group at C11 (Me₃O·BF₄, proton sponge,

molecular sieves 4 Å) [11] afforded **7**. After a deprotection/oxidation sequence (HF, H₂O then Swern oxidation) aldehyde **8** was produced and then involved in a [4 + 2]-annulation with allylsilane **9** [6h] (TfOH, CH₂Cl₂, PhH) thus leading to *cis*-dihydropyran **10** in good yield (75%) and with good diastereoselectivity (dr = 10/1) [6h]. The transformation of **10** to the macrocyclic lactone **11** was achieved in five steps and required the transformation of the mesylate group into a carboxylic acid. Mesylate **10** was treated with NaCN

Scheme 3.

(DMF), followed by a first treatment with DIBAL-H in Et$_2$O to selectively reduce the ester group at C13, and then by a second treatment with DIBAL-H in CH$_2$Cl$_2$ to reduce the cyano group to the corresponding aldehyde, which was oxidized using a Pinnick oxidation [12] (NaClO$_2$) to the desired carboxylic acid. The obtained seco-acid was then transformed to macrolactone **11** through a Yamaguchi macrocyclization (44% yield). In order to introduce the hydroxyl group at C5, a regioselective oxymercuration [6h] of the intracyclic double bond yielded the axial C5 alcohol **A** as a single isomer.

To complete the synthesis of (+)-neopeltolide, a Still–Gennari olefination [6a] was used to establish the *cis*-enoate of the side chain. At first, acylation of **A** with bis-(2,2,2-trifluoroethyl) phosphonoacetic acid (**12**) [13] gave the corresponding phosphonoacetate, which was then treated with KHMDS (THF, 18-crown-6), and the generated anion was quenched with aldehyde **B** providing a mixture of (+)-neopeltolide **1b** and the corresponding (*E*)-olefin in a 7/1 ratio (62% yield).

The first enantioselective total synthesis required 19 steps for the longest linear sequence. (+)-Neopeltolide was obtained with an overall yield of 1.3%, starting from the commercially available methyl (*R*)-(+)-3-methyl glutarate **2** (Scheme 3).

4.2. Scheidt et al. total synthesis [14]

At the beginning of 2008, the syntheses of **1a** and **1b** were reported by Scheidt et al. [14]. Only the total synthesis of the natural product **1b** will be described

herein as the strategy and the key steps are identical for the two diastereomers.

The synthesis of (+)-neopeltolide was accomplished by involving an intramolecular Lewis acid-catalyzed cyclization [15] between a dioxinone and an *in situ* generated oxocarbenium ion (transition state **A″**) to establish the tetrahydropyran moiety and the macrocyclic ring in a single step. The oxazole side chain was introduced by using a Mitsunobu reaction between carboxylic acid **B′** and the hydroxy group present on the *cis*-substituted tetrahydropyran at the C5 position. The synthesis of **A′** is highly convergent and was achieved from the two compounds **A1** and **A2** (Scheme 4).

The synthesis of (+)-neopeltolide started with the construction of dioxinone **16** which was synthesized from the simple aldehyde **13** and dienoxysilane **14** in four steps. Ti(IV)/(*R*)-BINOL-catalyzed aldol reaction between dienoxysilane **14** [16] and aldehyde **13** afforded secondary alcohol **15** [17] (63% yield, 88% ee). Alcohol **15** was transformed to the corresponding carboxylic dioxinone **16** through a protection/deprotection/oxidation sequence. The synthesis of the second fragment which corresponds to fragment **A1** (compound **21**) began with the two-step conversion of β-hydroxyester **17** to Weinreb amide **18** [18]. Its transformation to the extended ketone **20** was achieved by adding the alkyllithium derived from **19**. The removal of the PMB group in **20** by DDQ was followed by an Evans–Tishchenko reduction, thus creating the requisite *anti*-sterochemistry between the hydroxy groups at C11 and C13. The obtained hydroxyl group was then transformed to a methyl ether (MeOTf,
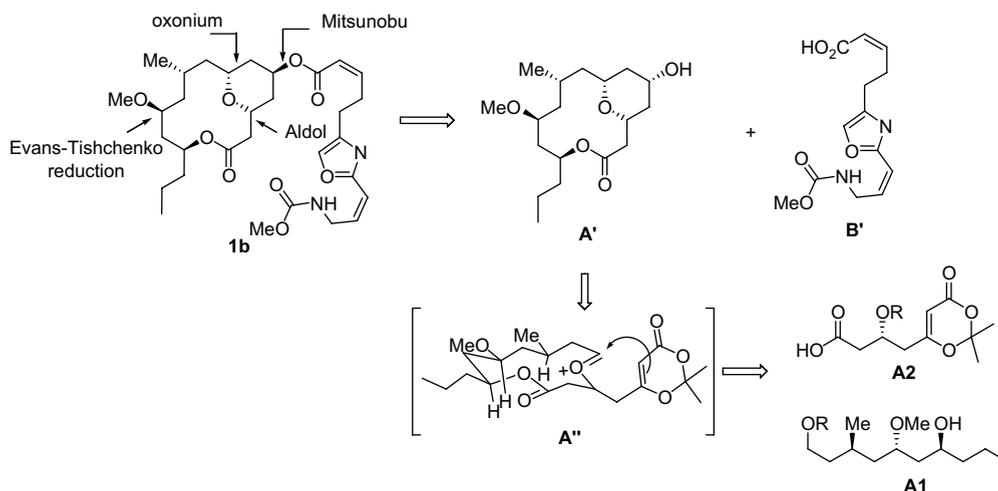
Scheme 4.
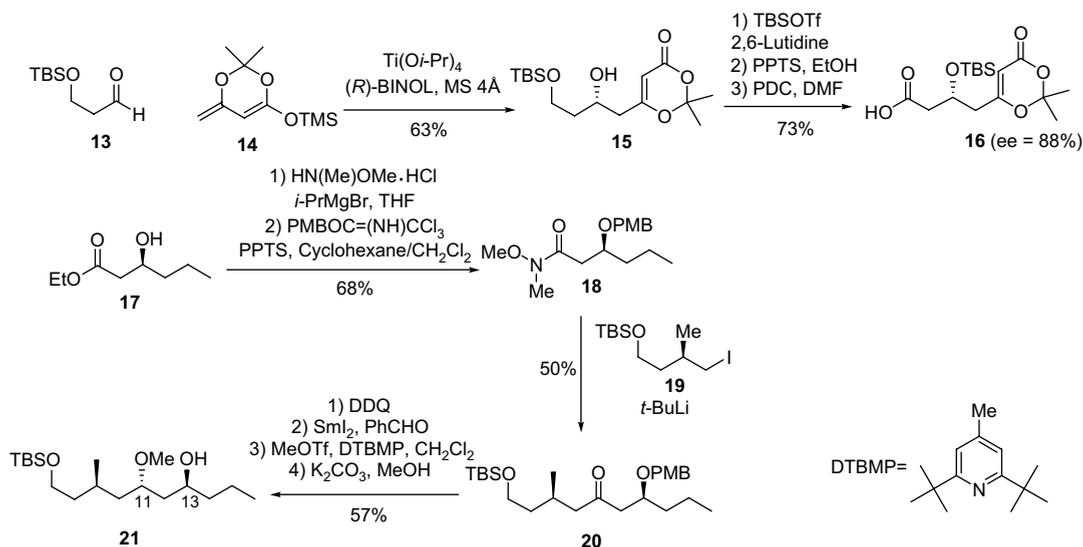
Scheme 5.

DTBMP), and finally the benzoate group was cleaved to yield alcohol **21** (Scheme 5).

The coupling of **16** with **21** was accomplished using a Yamaguchi esterification [19], which was followed by a deprotection and an oxidation (TEMPO) [20] steps leading to dioxinone aldehyde **22**, which is a precursor of the macrocyclic lactone. The key step in this synthesis is an intramolecular Prins reaction which was achieved *via* an oxonium species of type **A″** generated from **22** using Sc(OTf)$_3$ (CaSO$_4$, MeCN). This single step afforded a tricyclic dioxinone intermediate in a modest yield but with a high degree of complexity. Treatment of the dioxinone with wet DMSO formed the bicyclic ketone **23**. After diastereoselective reduction of ketone **23** to the corresponding equatorial alcohol with NaBH$_4$, a Mitsunobu reaction with acid **B′**[1] produced (+)-neopeltolide (**1b**) (Scheme 6).

This synthesis of (+)-neopeltolide required 15 steps in the longest linear sequence from the chiral hydroxyester **17** and produced (+)-neopeltolide in 2.3% overall yield.

Following these two first syntheses, four other syntheses were reported in the literature in 2008, and for three of them, a Prins cyclization was used as the key step to establish the pyran ring.

4.3. Maier et al. formal synthesis [21]

Similar to the synthesis described by Scheidt et al., the synthesis of (+)-neopeltolide by Maier et al.

utilizes a Mitsunobu reaction to attach the oxazole side chain to the macrocyclic lactone. Their synthesis relied on the obtention of the macrocyclic lactone by using a Yamaguchi macrolactonization. The stereogenic centers were controlled by applying a Leighton ally-lation (C11), a Noyori reduction (C13), a Feringa–Minnaard asymmetric methyl cuprate addition on an unsaturated thioester (C9), and a Prins reaction [22–26] as the key steps. The seco-acid **C** was synthesized from **D** and **E** (Scheme 7).

The synthesis started with β-ketoester **24** which was subjected to an enantioselective Noyori hydrogenation [27,28] using (*S*)-BINAP/Ru(II) to produce hydroxyl-ester **25** (98% ee). After protection (TBDPSCl, imidazole, DMF) and reduction of the ester (DIBAL-H), the obtained aldehyde was treated with Leighton reagent (*R,R*)-**26** [29] to produce an 1,3-*anti*-diol pattern, and the free hydroxyl group at C11 was etherified using Meerwein's salt [30] in the presence of a proton sponge to afford **27**. Oxidative cleavage of the double bond (OsO$_4$, NMO, then NaIO$_4$), followed by an extension of the obtained aldehyde using the Wittig reagent **28** [31] led to the α,β-unsaturated thioester **29**. A conjugated addition of methylmagnesium bromide to **29** in the presence of CuBr·Me$_2$S and the chiral diphosphine (*S,R*)-Josiphos **30** [32] produced compound **31** after Fukuyama reduction [33] of the thioester (Et$_3$SiH, Pd/C) (Scheme 8).

The homoallylic alcohol **33** required for the Prins reaction was available by allylation of aldehyde **32** with the Leighton reagent (*S,S*)-**26** [29]. The crucial Prins reaction was then performed between aldehyde **31** and homoallylic alcohol **33**. By treatment with TFA (10 equiv), the desired trifluoroacetate **34** was isolated in

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[1] Carboxylic acid **B′** was prepared according to refs. [6a,b].

1) Cl₃C₆H₂COCl, DMAP, THF
2) HF·Py, THF
3) TEMPO, PhI(OAc)₂, CH₂Cl₂

76%

1) Sc(OTf)₃, CaSO₄, MeCN
2) DMSO, H₂O, 130 °C

21%

1) NaBH₄, MeOH, 0 °C
2) DIAD, PPh₃, B'

76%
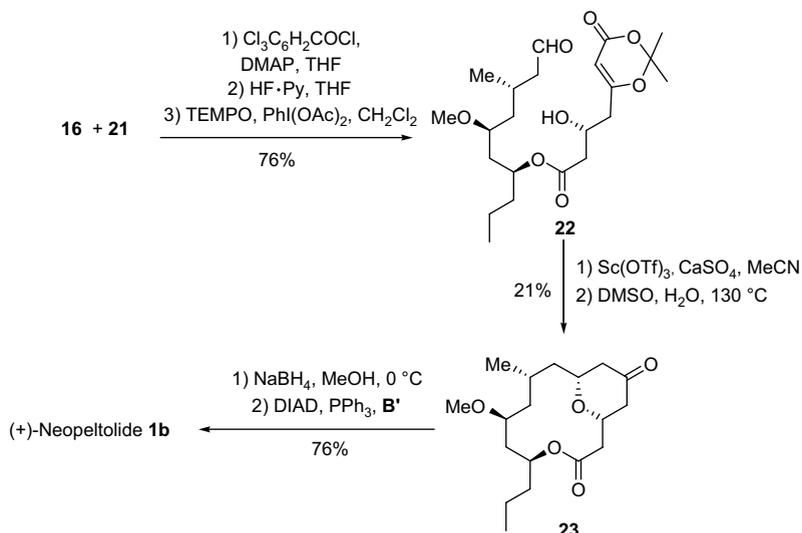
Scheme 6.

72% yield (major/minor 8/1) *via* the formation of an oxonium species of type **F**. After a saponification/protection/deprotection sequence, alcohol **35** was isolated. Its transformation to the seco-acid **36** was achieved in two steps, after an oxidation (Dess−Martin periodinane and sodium chlorite oxidation) [12,34] of the primary alcohol and a cleavage of the silyl ether (TBAF). Seco-acid **36** was obtained and transformed to the macrocyclic lactone **A'** by using a Yamaguchi protocol followed by the final cleavage of the MOM ether.

The macrocyclic core of (+)-neopeltolide was obtained in 17 steps from the β-ketoester **24** with an overall yield of 23% (Scheme 9).

4.4. Lee et al. total synthesis [35]

In a similar fashion to Maier et al., Lee et al. used a Mitsunobu reaction in between macrocyclic lactone **A'**

and carboxylic acid **B'** to introduce the oxazole side chain, and an intramolecular Prins reaction was also used to form the functionalized tetrahydropyran moiety. An asymmetric crotyl transfer reaction and a titanium-mediated methallylation were considered to control the stereogenic centers at C11 and C13, and a substrate-directed hydroformylation was applied to control the sterogenic center at C9. A convergent synthesis using a Prins reaction was conceived from **F** which would be obtained after a Yamaguchi esterification between **G** and **H** (Scheme 10).

After a CSA-mediated Loh crotylation [36] of aldehyde **37**, followed by the protection of the hydroxyl group at C13 using BnBr, the ozonolysis of the double bond afforded aldehyde **39** (49%, three steps). A diastereoselective methallylation in the presence of TiCl₄ led to a homoallylic alcohol which was acylated with 2-diphenylphosphinobenzoic acid **40** to produce ester **41**. After the diastereoselective
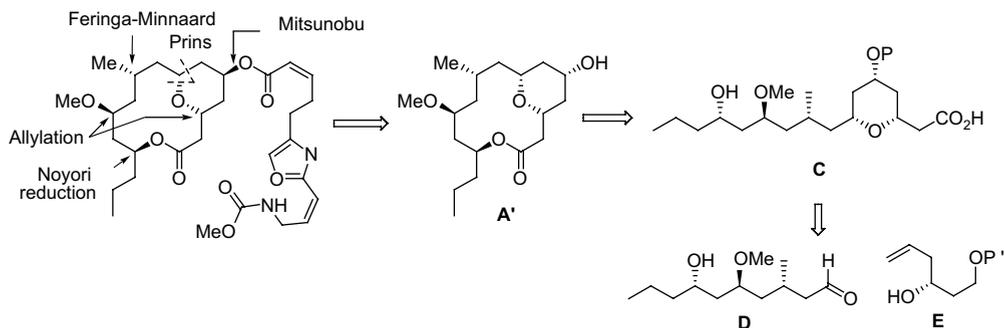
Scheme 7.
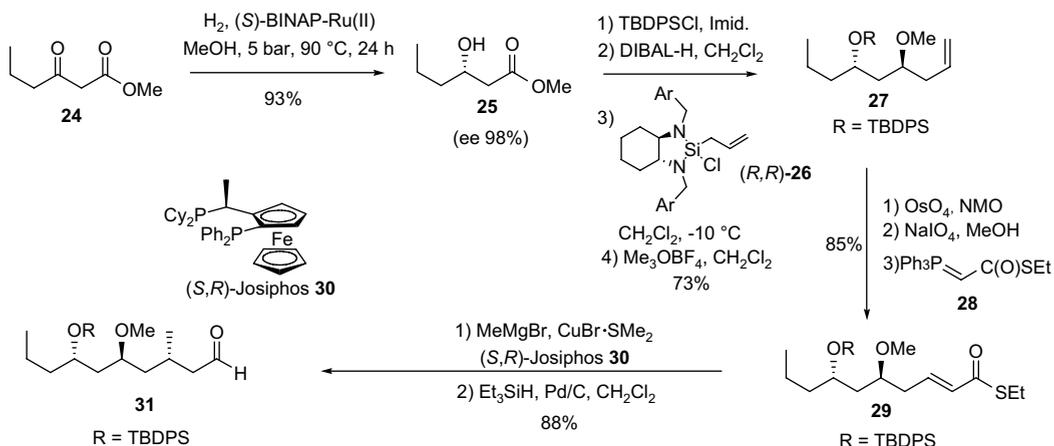
Scheme 8.

substrate-directed hydrofomylation of **41**, aldehyde **42** was formed in a 5/1 ratio and then transformed in three steps (acetalization, saponification, then *O*-methylation) to dimethyl acetal **43**. This compound corresponds to the C7—C16 fragment (compound of type **G**) of (+)-neopeltolide. The second fragment, carboxylic acid **45**, was prepared from the known olefin **44** [37] after removal of the silyl protecting group and oxidation of the resulting primary alcohol (Scheme 11).

The cleavage of the benzyl ether in **43** led to a secondary alcohol at C13 which was acylated with acid **45** to furnish, after prolonged exposure to DDQ, the aldehydic homoallylic alcohol **46** (81%), which is the substrate of the Prins intramolecular cyclization. Compound **46** was treated under the Prins conditions [(TESOTf (20 equiv), TMSOAc (30 equiv), AcOH)] and then subjected to a methanolysis (K_2CO_3, MeOH) to give bicyclic macrolide **A′** in good yield (68%); this bicyclic system was constructed efficiently with complete stereocontrol of the two newly created stereocenters. Finally, a Mitsunobu reaction of **47** with carboxylic acid **B′** produced (+)-neopeltolide.
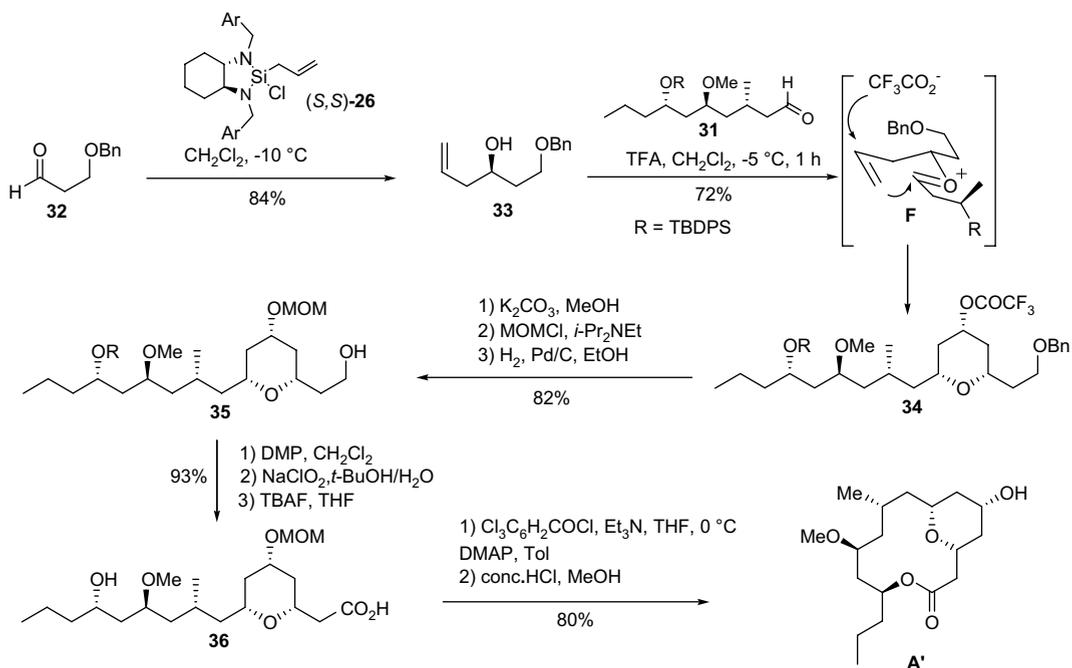
Scheme 9.
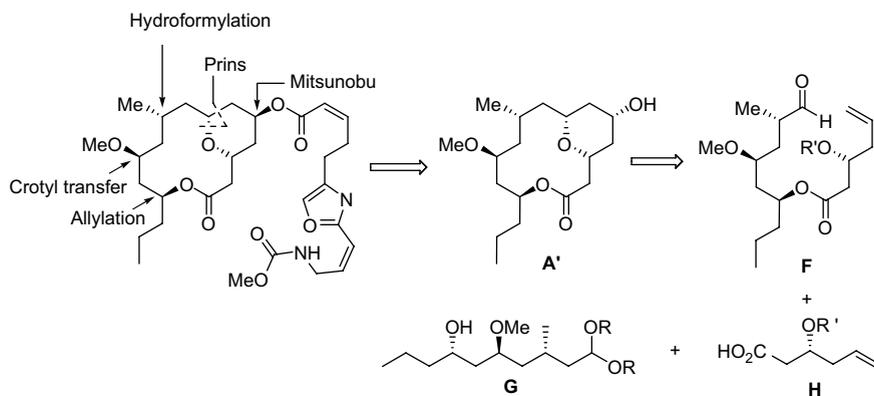
Scheme 10.

In this approach, (+)-neopeltolide was synthesized in 15 steps for the longest linear sequence from butyraldehyde **37** with an overall yield of 6.7% (Scheme 12).

4.5. Kozmin et al. racemic total synthesis [4a]

Recently, Kozmin et al. reported the synthesis of racemic neopeltolide. In their approach, they applied a Prins desymmetrization in order to establish the highly functionalized THP moiety [38]. They previously applied the same strategy to the racemic synthesis of leucascandrolide.

The racemic synthesis of neopeltolide started with the Prins desymmetrization [38] of diene **47** (CF$_3$COOH, NH$_4$OH) followed by the protection of the generated hydroxyl group at C5 (BnOC(=NH)CCl$_3$, TfOH) and a Wacker alkene oxidation to produce ketone **48**. An aldol condensation [39] between a boron-enolate generated from ketone **48** and aldehyde **49**, gave the expected aldol product (dr > 98/2) which was then transformed to **50** by using a Wittig methylenation (Ph$_3$PMeBr, KHMDS) followed by acidic treatment in order to remove the dioxolane (HCl) (75% yield, 2 steps). After a diastereoselective
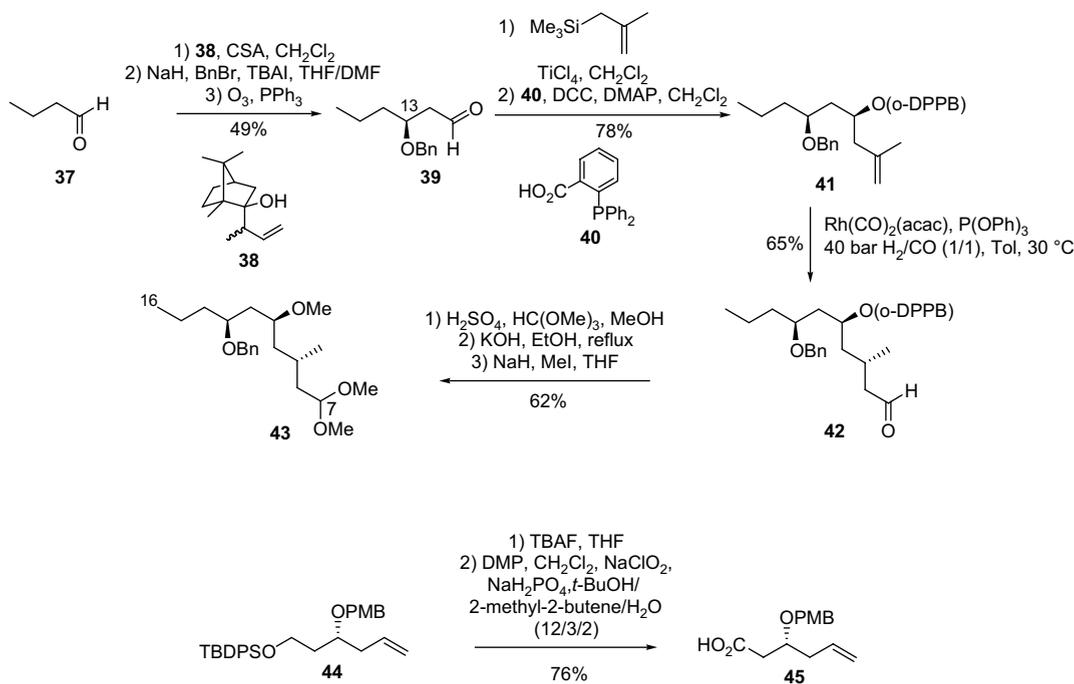
Scheme 11.
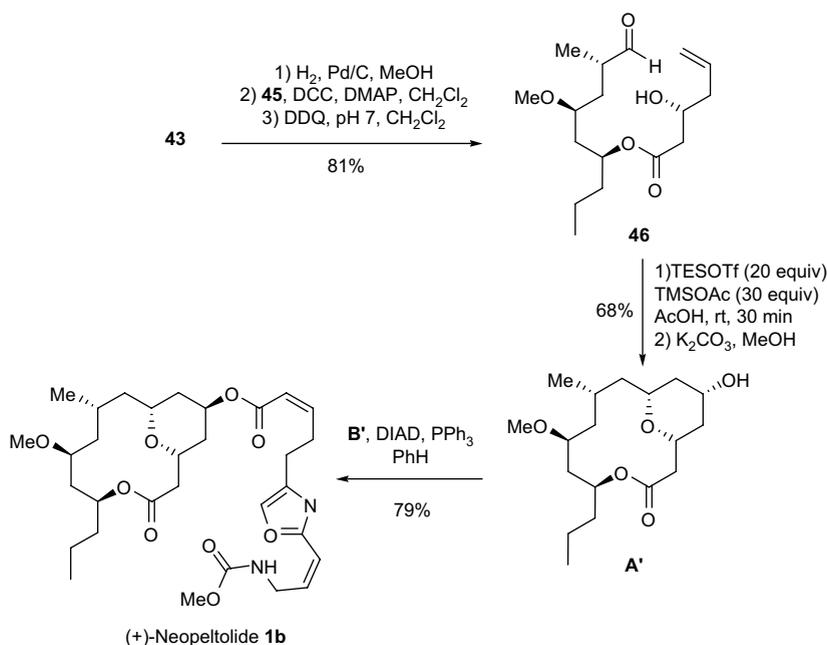
Scheme 12.

reduction of the hydroxyketone **50** (Et$_2$BOMe, NaBH$_4$) followed by a saponification (TMSOK, Et$_2$O) and a Yamaguchi macrolactonization, macrolide **51** was obtained (55% yield).

Five steps were then necessary to transform macrolactone **51** to **A′**. After a diastereoselective hydrogenation of the olefin at C9 (Pd/C, H$_2$), an inversion of the alcohol at C11 using a Mitsunobu reaction, followed by the methanolysis of the formed *p*-nitrophenylbenzoate, a subsequent methylation of the generated alcohol and, after hydrogenolysis of the benzyl ether, lactone **A′** was obtained in 40% yield from **51**. The final coupling step between macrolactone **A′** and carboxylic acid **B′** under standard Mitsunobu conditions provided (±)-neopeltolide.

(±)-Neopeltolide was efficiently synthesized in 14 steps for the longest linear sequence from diene **47** with an overall yield of 8.7% (Scheme 13).

4.6. Fuwa–Sasaki et al. total synthesis [40]

As in most syntheses of (+)-neopeltolide, the introduction of the oxazole-containing side chain was achieved by using a Mitsunobu reaction between macrolactone **A′** and carboxylic acid **B′**. The macrocyclic lactone **A′** was prepared from tetrahydropyran **I**. To construct this latter, contrary to the previous syntheses employing a Prins reaction, a Suzuki–Miyaura coupling of the enol phosphate **J** and

alkylborane **K** was used, followed by a RCM of the obtained diene to build **I** (Scheme 14).

The synthesis of enol phosphate of type **J**, compound **56**, started with the asymmetric allylation [41] of aldehyde **52**, furnishing alcohol **53** [(+)-Ipc$_2$BOMe, allylMgBr, then NaOH, H$_2$O$_2$, 98% yield]. After protection of the hydroxyl group (MPMOC(=NH)CCl$_3$, La(OTf)$_3$, toluene, rt) followed by a cross-metathesis with methyl acrylate (Grubbs II = G-II) and reduction of the obtained α,β-unsaturated ester (DIBAL-H, CH$_2$Cl$_2$), homoallylic alcohol **54** was isolated. A Sharpless epoxidation [(−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOH, CH$_2$Cl$_2$, 97%] was followed with a reductive iodination (I$_2$, PPh$_3$, imidazole; Zn, AcOH, EtOH, 72.5%) to open the epoxide, allowing the isolation of the vinylic alcohol **55**. This latter compound was then converted to the enol phosphate **56** in four steps. At first, alcohol **55** was protected (BOMCl, *i*-Pr$_2$NEt), and then the MPM ether was cleaved (DDQ, CH$_2$Cl$_2$, buffer pH = 7). A subsequent acetylation (Ac$_2$O, Et$_3$N, DMAP, 99%) led to the corresponding acetate which, after enolization with KHMDS in the presence of (PhO)$_2$P(O)Cl, furnished enol phosphate **56** (Scheme 15).

The synthesis of the precursor of borate of type **K**, iodide **60**, commenced with nitrile **57** [42]. After reduction with DIBAL-H, followed by asymmetric allylation [41] of the obtained aldehyde [(+)-Ipc$_2$-BOMe, allylMgBr then NaOH, H$_2$O$_2$, 87%], allylic alcohol **58** was isolated. The methylation of alcohol **58** (MeOTf, 2,6-di-*t*-butylpyridine, CH$_2$Cl$_2$) followed by
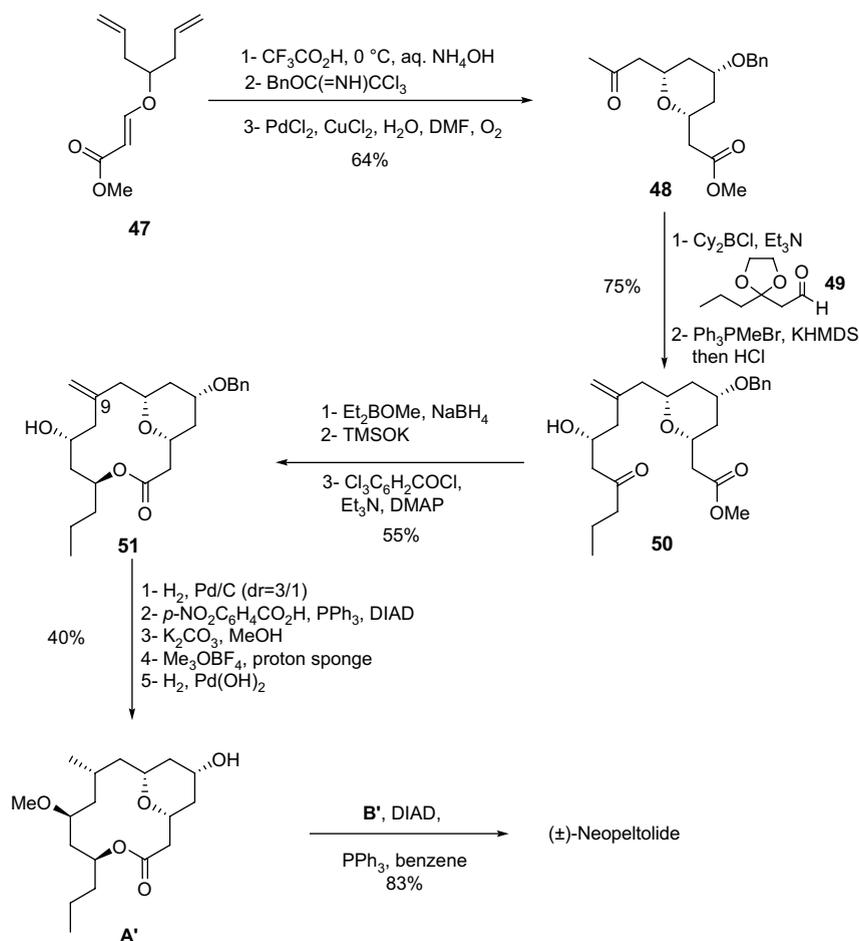
Scheme 13.

oxidative cleavage of the double bond (O_3 then PPh_3, 85%), afforded aldehyde **59**. A second asymmetric allylation [41] [(−)-IpcBOMe, allylMgBr then NaOH, H_2O_2, 96%] and a hydrogenation of the obtained homoallylic alcohol (H_2, Pd/C, EtOAc, 100%) allowed the introduction of the terminal alkyl chain. Finally, protection of the remaining hydroxyl group (MPMOC(=NH)CCl$_3$, La(OTf)$_3$, 75%) followed by desilylation (TBAF, 87%), afforded the corresponding alcohol which was transformed to iodide **60** (47% yield) under standard conditions (Scheme 16).

Assembly of enol phosphate **56** and iodide **60** was realized *via* the formation of an alkylborate intermediate generated *in situ*. For this coupling, lithiation of iodide **60** with *t*-BuLi in the presence of *B*-OMe-9-BBN was achieved and furnished alkylborate intermediate **61**, which was treated *in situ* with enol phosphate **56** (Cs$_2$CO$_3$, Pd(PPh$_3$)$_4$, DMF) to give the acyclic enol ether **62**. Subsequent RCM of **62** (Grubbs II, toluene) led to the cyclic enol ether **63** (78% yield).

The stereoselective hydrogenation of the double bond (H_2, Pd/C, EtOAc/MeOH) formed the *cis*-tetrahydropyran as a single diastereomer. The TIPS protecting group was then removed (TBAF, THF, 99%), and an oxidation/esterification sequence (Py·SO$_3$, Et$_3$N, DMSO/CH$_2$Cl$_2$ then NaClO$_2$, NaH$_2$PO$_4$ and then TMSCHN$_2$, 89%) furnished ester **64**. The completion of the synthesis of macrolactone **A'** was achieved in four steps. At first the cleavage of the MPM ether (DDQ, 100%) followed by saponification of the methyl ester (TMSOK, 100%) led to a seco-acid, which was treated under the Yamaguchi conditions to form the macrolactone core. A final hydrogenolysis of the BOM protecting group (H_2, Pd(OH)$_2$/C, 100%) gave intermediate **A'**. The Mitsunobu reaction with carboxylic acid **B'** provided (+)-neopeltolide (61%).

Even if, compared to the other syntheses, this latter one is longer (25 steps for the longest linear sequence), the excellent overall yield of 8.3% shows the efficiency of the employed reactions (Scheme 17).
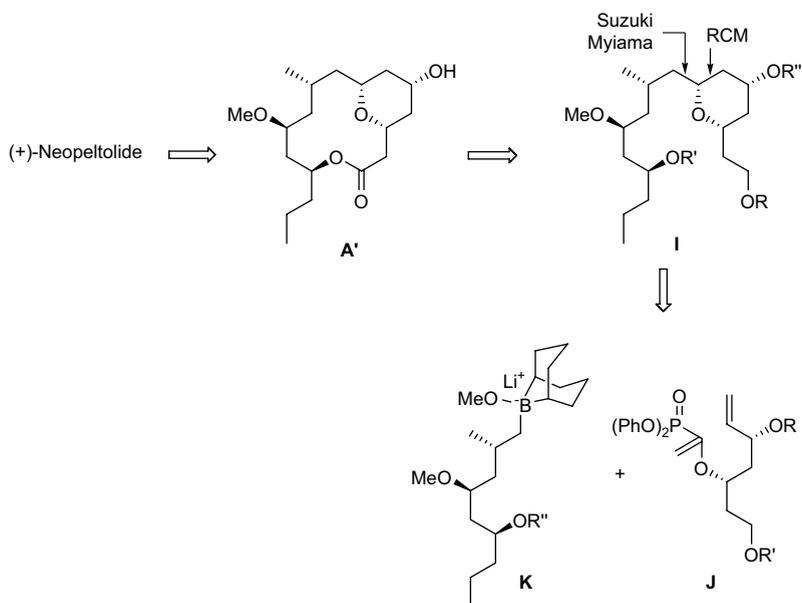
Scheme 14.

5. Conclusion

Since the discovery of (+)-neopeltolide by Wright et al. in 2007, six syntheses (one formal synthesis, five total syntheses) have been reported. The most efficient syntheses of (+)-neopeltolide were achieved by using intra- or intermolecular Prins reactions as these reactions allow the formation of the *cis*-trisubstituted tetrahydropyrans with the control of two new stereogenic centers. The recent investigations on the mechanism of
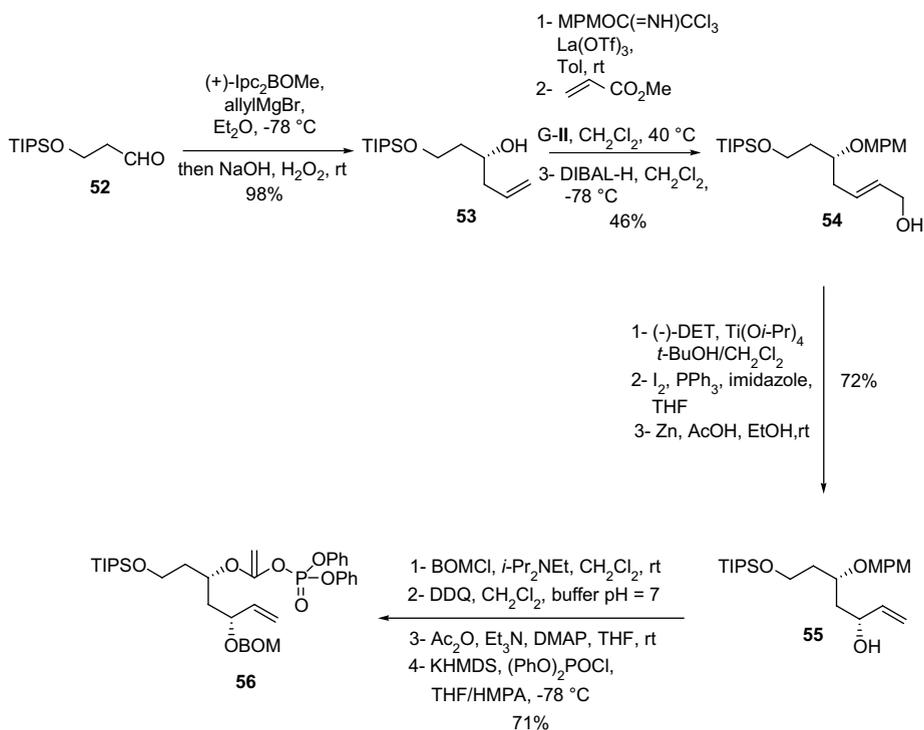
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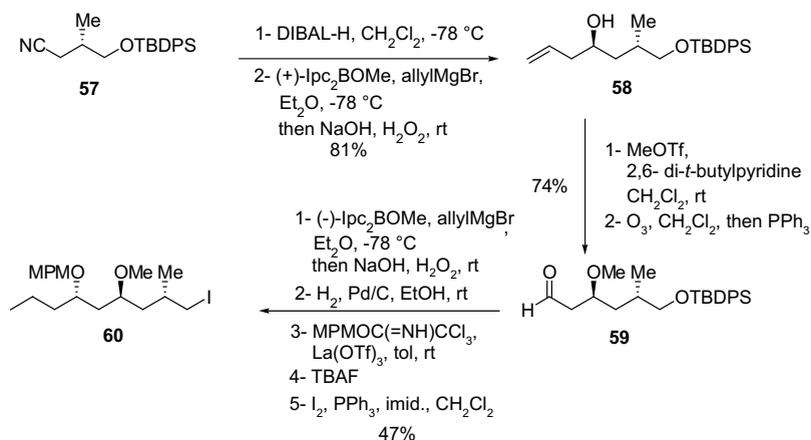
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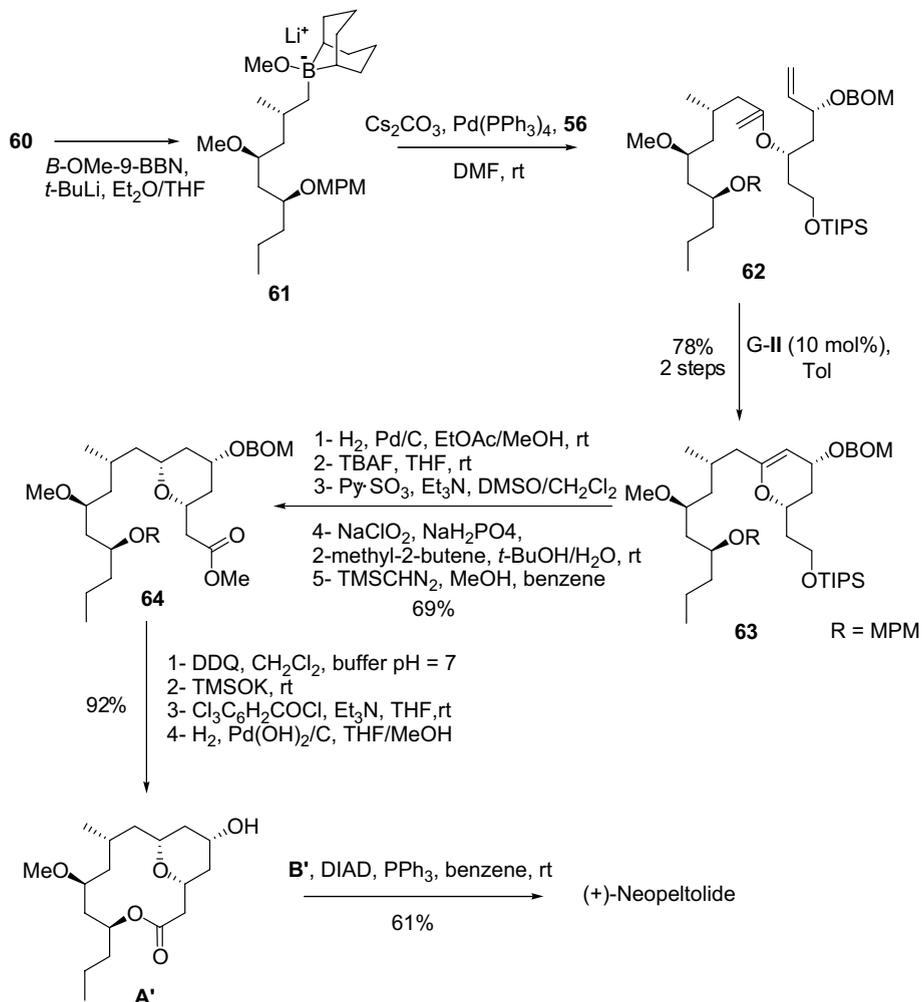
Scheme 17.

action of neopeltolide [4] will probably stimulate the synthesis of neopeltolide analogues for SAR studies.

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