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Organic Synthesis

A Versatile and Stereocontrolled Total Synthesis of Dihydroxylated Docosatrienes Containing a Conjugated *E,E,Z*-Triene

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Abstract: A versatile strategy featuring a Colvin rearrangement, hydrozirconation, a Sonogashira cross-coupling reaction and a *Z*-selective Wittig olefination, was successfully developed for the construction of a conjugated *E,E,Z*-triene subunit, flanked on both sides by two *Z*-allylic hydroxyl groups. This chemical pattern is found in many endogenous lipid metabolites such as maresin 1 (MaR1), neuroprotectin D1 (NPD1), and its aspirin triggered-isomer AT-NPD1, which not only counter-regulate inflammation but also actively orchestrate (at nanomolar doses) the resolution and termination program of acute inflammation while promoting wound healing, return to homeostasis and neuroprotection. Unlike previous approaches, the advantages of the present strategy are obvious, as it allows us to modify the nonpolar tail, the carboxylated head or both ends of the molecule without repeating the whole synthetic sequence (about 26–34 steps according to the literature). Thus, the first total syntheses of NPD1 methyl ester epimer (which can also be considered as an enantiomer of AT-NPD1) and its n-3 docosapentaenoic acid derived analogue were achieved from a highly functionalized and late advanced pivotal intermediate. This innovative route may be easily adapted to gain access to other dihydroxylated metabolites and analogues of polyunsaturated fatty acids containing a conjugated *E,E,Z*-triene subunit. Different epimers/diastereoisomers may be obtained by purchasing the suitable optically pure (*S*)- and/or (*R*)-1,2,4-butanetriol(s) as a chiral pool for both stereogenic centers.

Introduction

Dihydroxylated (diH) docosatrienes are a class of biologically important polyunsaturated fatty acid (PUFA) metabolites.[1] Among them, the maresin 1 (MaR1),[2,3] neuroprotectin D1 (NPD1),[4] and its aspirin-triggered C17 epimer (AT-NPD1)[5] have emerged as mediators of key events in endogenous anti-inflammation and resolution of inflammation. Interestingly, they are involved in the termination program at nanomolar doses.[6]

These docosatrienes are generated from docosahexaenoic acid (DHA, C22:6 n-3) by the sequential action of lipoxygenases (LOs), followed by an epoxide rearrangement and hydrolysis. However, it is noteworthy that in vitro enzymatic synthesis starting from DHA and lipoxygenases did not yield the expected molecules NPD1 nor MaR1 but instead their corresponding isomers showing a *E,Z,E*-triene unit instead of the desired *E,E,Z*-triene unit.[7,8]

The demand for these compounds for biological investigations coupled with their extremely low availability from natural sources prompted us to investigate possible synthetic strategies for their construction.

Very recently, using metabololipidomics Dalli et al.[9] showed that, in mice and human leucocytes, the endogenous omega-3 docosapentaenoic acid (n-3 DPA, C22:5 n-3) is converted to a dihydroxylated docosatriene with a similar hydroxylation pattern to the one observed in NPD1. Alike NPD1, this newly discovered DPA metabolite showed appealing biological activities, notably protective actions from second organ injury and reduced systemic inflammation in ischemia-reperfusion.[9]

The configuration of the hydroxyl groups has not been established yet. It has, however, been observed that the monohydroxylated lipoxygenase products (17-HDPA and 14-HDPA) are produced with a predominant (*S*)-configuration (*R*/*S* 20:80). The assignment of the stereochemistry of the double bonds has not been stated. No total synthesis has been reported yet.

Thus, the availability of DPA-derived metabolite isomers as chemical standards would make it possible to compare with authentic samples to fully assign both the hydroxyl configurations and the stereochemistry of the double bonds. With synthetic samples in hands, further investigation on their biological properties may also be performed.

Many famous teams have done a great deal of work on the total synthesis of lipoxygenase-mediated PUFA metabolites. For instance, although inverted, a conjugated *E,E,Z*-triene

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system is also encountered in leukotrienes, such as LTB4, and their numerous analogues.

Various organometallic cross-coupling reactions (Miyaura–Suzuki,[10–12] Sonogashira[13–16]), stereoselective olefination reactions (Horner–Wadsworth–Emmons[17–20] or Wittig reactions[21–23]), intramolecular[24] or radical[25] rearrangements, addition of *Z*-vinylbromide to aldehyde, and also addition of vinyl lithium reagents to pyrilium tetrafluoroborates[26] have been successfully reported to build the conjugated triene. These interesting papers document the difficulty in the syntheses of PUFA metabolites containing a conjugated triene and thus, some previously retrosynthetic approaches may be borrowed to achieve the synthesis of dihydroxylated docosatrienes. Indeed, two total syntheses of both NPD1[27,28] and MaR1[29,30] have been recently published. Sasaki et al.[29] utilized for the first time a Julia–Kocienski olefination to establish the *E,E,Z*-triene unit.

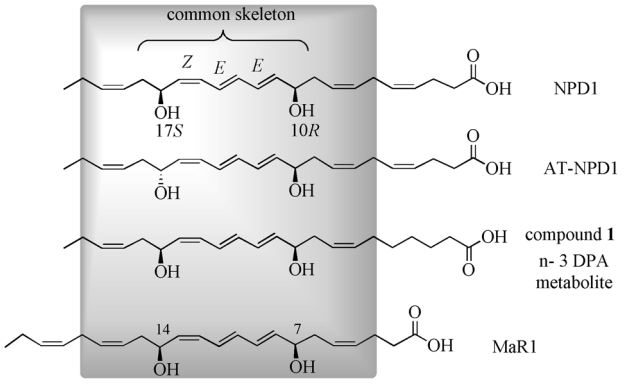
However, till now, probably due to the poor stability of such a functionalized and conjugated olefinic moiety, most of the approaches preferred to build the triene system or its corresponding *E,E*-ynediene at the very end of the synthesis. The carboxyl and omega chains were always introduced at the very beginning of the precursor syntheses, thus targeting only one molecule at a time. And yet, the total synthesis of these linear polyunsaturated metabolites is expected to be sensitive, rather long (at least twenty-six steps), and time-consuming.

Only one approach suggested introducing the lateral chains of LTB4 late in the synthesis. However, the authors struggled with sequential condensations of aldehydes on (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene or (1*E*,3*E*,5*Z*)-1-bromo-7,7-diethoxyhepta-1,3,5-triene, obtaining a modest yield of a racemic mixture only along with many side products.[31]

We tackled the challenging task of developing a versatile strategy that can provide access to NPD1, maresins, and analogue structures from a same late advanced key intermediate.

Comparison of structures

The dihydroxylated PUFA metabolites depicted in Scheme 1 exhibit a high degree of structural similarity. On closer examination of their structures, one observes that their skeletons



Scheme 1. Comparison of noncyclic endogenous dihydroxylated docosatriene structures.

embody a common central fragment, that is, a conjugated *E,E,Z*-triene flanked, on both sides, by two hydroxyl groups, which are both allylic and homoallylic alcohols. NPD1 and AT-NPD1 are epimers at C17. NPD1 and MaR1 are positional isomers. They both possess a bis-allylic moiety but not on the same side of the common central fragment. NPD1 and its n-3 DPA-derived analogue (compound **1**) share the C22 chain length and dihydroxylation pattern at C10 and C17. Based on the biogenic synthesis, the more likely configurations are expected to be the same as the ones observed in NPD1, that is, as depicted in compound **1** (Scheme 1). They simply differ by the degree of unsaturation found in their fatty acid chains. The supplementary C4–C5 olefin encountered in DHA but not in n-3 DPA is not involved in enzymatic reaction leading to NPD1.

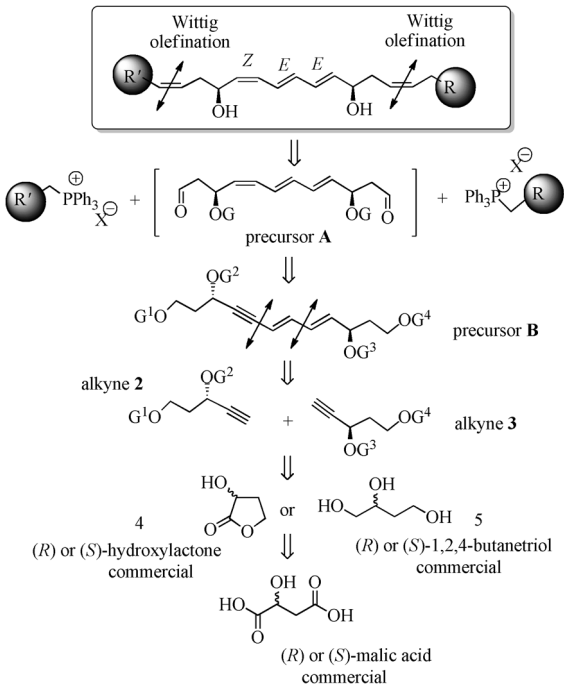
Retrosynthetic analysis

Many retrosynthetic analyses are conceivable. We envisioned a versatile strategy featuring a stereoselective Wittig olefination to append both the carboxyl-head and the omega-tail chain in the late stage of the synthesis, a stereocontrolled elaboration of the triene unit through cross-coupling reactions. Due to the expected poor chemical stability of the conjugated *E,E,Z*-triene unit, we have chosen to postpone the introduction of the *Z* double bond to the end of the synthesis, by using a chemoselective and stereoselective semireduction of a *E,E*-ynediene moiety. The triple bond may also be useful when it becomes necessary to prepare radioactive precursors for quantification and metabolism studies. Control of the configurations at stereogenic centers will be preferentially obtained by using enantiopure starting material from a chiral pool.

In addition, throughout the synthesis, the sensitivity of the conjugated *E,E,Z*-triene and bis-allylic system limits reagent selection and dictates attentive handing during isolation, purification, and storage.

The overall retrosynthetic plan with the main disconnections and building blocks is shown in Scheme 2. Disconnection of both homoallylic *Z* double bonds leads to a virtual dialdehyde (precursor **A**) which in turn may be produced from its suitably protected tetraols (precursor **B**). Subsequently, focusing on the *E*-enyne system and disconnection of its central bond leads to a terminal alkyne **2** and a vinyl halide as potential precursors, whereas a further disconnection of the conjugated *E,E*-diene system also reveals terminal alkyne **3** as a precursor for an *E*-hydrometalation reaction. Usefully, regardless of the protecting groups, alkynes **2** and **3** are indeed epimers. They both may be derived from the suitable enantiomer of the hydroxyl-lactone **4** or 1,2,4-butanetriol **5** by a Bestmann–Ohira homologation.

A salient problem was the choice of the protecting groups for the hydroxyl functions. The G^1 and G^4 groups will have to be orthogonal to the G^2 and G^3 groups. The later will have to be resilient enough to survive the twenty or so steps. On the other hand, the final sensitive dihydroxylated-triene will have to withstand the deprotection conditions. Therefore, we have decided to use the range of silylated derivatives only.



Scheme 2. Retrosynthetic analysis.

Although the (*R*)-1,2,4-butanetriol is commercially available, it is prohibitively expensive considering our operating budget. Thus, we decided to first investigate the feasibility of our strategy only using its much cheaper (*S*)-enantiomer. In that case, the suggested strategy will furnish the NPD1 epimer at C10, which is actually the enantiomer of the endogenous AT-NPD1. Like AT-NPD1, this targeted isomer may be used as an interesting standard in LCMS analyses of enflamed biological fluids.

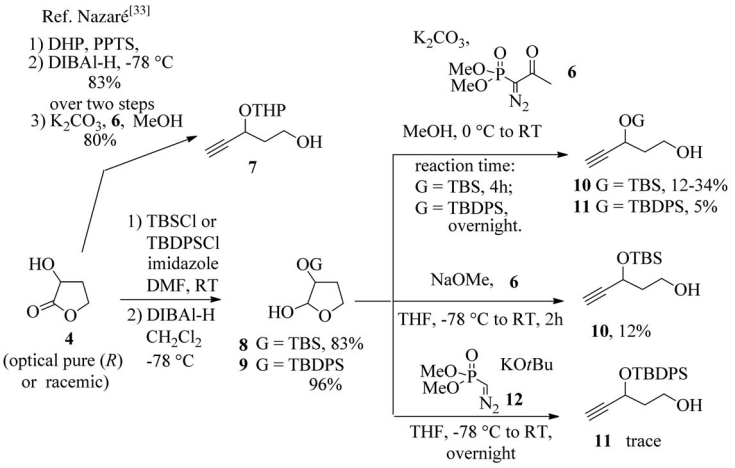
Results and Discussion

In the following discussion, the successful implementation of our synthetic plan will be detailed.

Synthesis of the terminal alkynes

The terminal alkyne **2** has been used quite often in the literature. Its synthesis is always rather long for such a small sized molecule (by reduction of an alkyne ketone, epoxidation of an alkene, or asymmetric addition of an alkyne anion onto an aldehyde). Nazaré reported a strategy[32,33] featuring the ring opening of *O*-tetrahydropyranyl (THP)-protected α-hydroxybutyrolactone from a Bestmann–Ohira alkynylation reaction. This strategy seemed appealing since the α-hydroxybutyrolactone **4** is now commercially available in both optically active pure forms. Thus, we applied this strategy with replacement of the THP-group by a silylated protection. Unfortunately, our first attempts using both ring-opening Bestmann–Ohira[34,35] or Seyferth–Gilbert[36–38] reactions failed with *O*-silylated γ-butyrolactols **8** and **9** (Scheme 3), probably due to a silyl migration from the α-hydroxy position to the anomeric alcohol as observed with a δ-functionalized α-hydroxybutyrolactone by Boger et al.[39] While full consumption of the starting material was observed on TLC, the desired alkyne **10** or **11** was isolated as the only product but only in poor yield (12–34%). Surprisingly, the cleavage of the TBDPS group was detected on TLC as soon as the reaction started although many examples in the literature[40–43] showed that TBDPS ether groups withstand Bestmann–Ohira or Seyferth–Gilbert conditions.

To confirm our assumption about silyl migration, we have treated the assumed mixture **8** with triethylamine (Scheme 4). Indeed, we have observed a clear change in the ^{1}H NMR spectrum (Scheme 4a and b): the ratio between the doublet of doublets ($\delta = 5.22$ ppm) and the singlet ($\delta = 5.18$ ppm) changed from 0.70:0.30 to 0.28:0.72. Using this sample pretreated with triethylamine, the following Bestmann–Ohira reaction markedly improved to 55% yield. However, these results were poorly reproducible, probably due to fast reconversion. Effectively, we noticed that, the ratio between the same doublet of doublets ($\delta = 5.22$ ppm) and the singlet ($\delta = 5.18$ ppm) equilibrated back to a 0.65:0.35 ratio (Scheme 4c) when the same NMR sample ($CDCl_3$) was kept at RT. Hence, this lactone

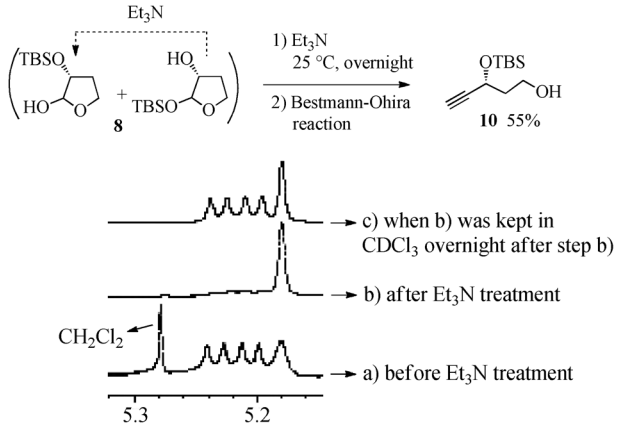


Scheme 3. Alkynylation by ring opening of α-hydroxybutyrolactone **4**. DIBAL-H = diisobutylaluminium hydride; PPTS = pyridinium *p*-toluenesulfonate; TBDPS = *tert*-butyldiphenylsilyl.

route was abandoned in favor of a strategy involving a selective 1,3-di-*tert*-butylsilylene ether protection of the commercially available 1,2,4-(*S*)-butanetriol **5** (Scheme 5).

As reported by Panek et al.[44] and Yu et al.[45] upon selective 1,3-*O*-silylation of 1,2,4-(*S*)-butanetriol **5** with di-*tert*-butylsilyl ditriflate,[46] Swern oxidation of the resulting free primary hydroxyl group **13** furnished aldehyde **15** in excellent yield. The latter was subsequently converted to the terminal alkyne **16** by using Bestmann–Ohira reaction conditions.

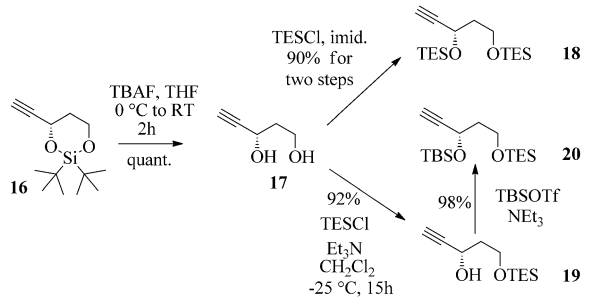
In our experiments, whatever the base employed for the silylation step (2,6-lutidine, or pyridine), the formation of about 5–10% of the seven-membered silylene ring byproduct (compound **14**, from 1,4-diol protection) could not be prevented



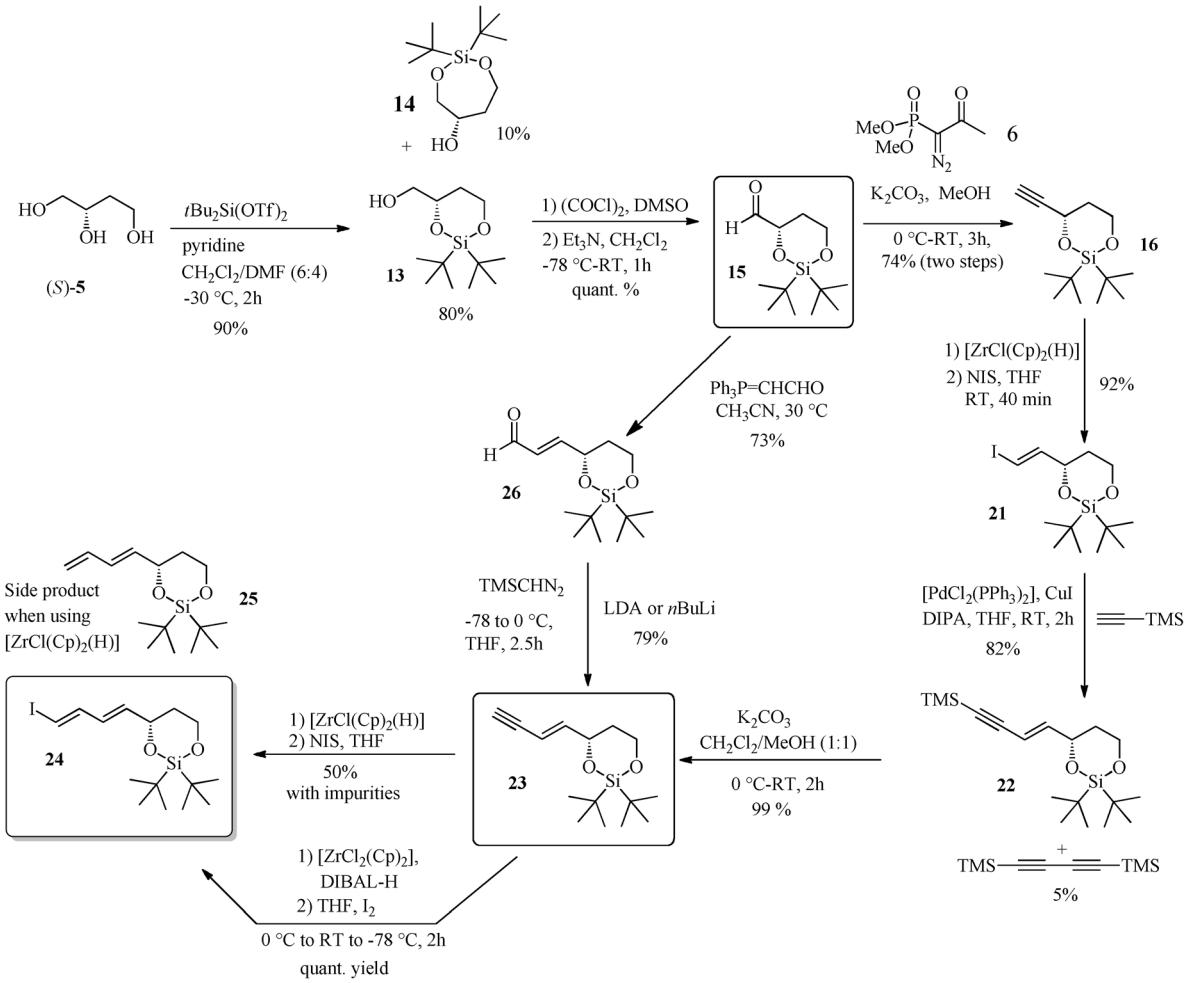
Scheme 4. Evolution of the ^{1}H NMR spectra (around 5.2 ppm), with or without NEt_3 treatment.

entirely. In addition, the corresponding 1,4-di-*tert*-butylsilylene ether-ketone was detected after oxidation, but was readily removed at the alkyne stage.

Interestingly, the resulting terminal alkyne **16** serves as a pivotal intermediate in the current strategy. On one hand, the di-*tert*-butylsilylene ring plays the role of both G^3 and G^4 protecting groups (Scheme 2, alkyne **3**). On the other hand, its deprotection and subsequent selective TES then TBS protection (as outlined in Scheme 6, alkynes **18**–**20**) provides access in excellent yields to the second terminal alkyne shown in the retrosynthesis (Scheme 2; alkyne **2**, G^1 and G^2 groups, respectively), required for the construction of the ynediene precursor.



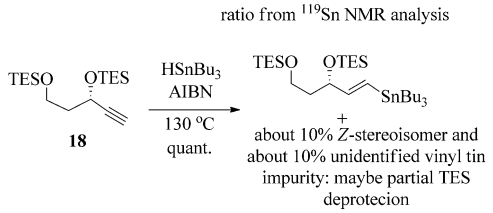
Scheme 6. Synthesis of terminal alkynes **18**, **19**, and **20**. TESCl = triethylchlorosilane.



Scheme 5. Synthesis of iododiene **24** by 1,3-diol selective silylene protection of 1,2,4-(*S*)-butanetriol **5**. LDA = lithium diisopropylamide; NIS = *N*-iodosuccinimide.

Synthesis of the sensitive *E,E*-iododiene 24

At first, we planned to build the *E,E*-diene unit through Stille coupling reactions. Based on the literature precedent[47–49] on protected α-hydroxyalkynes, several radical hydrostannylation reactions have been carried out to obtain *E*-vinylstannanes or *E*-vinylhalides. However, in our test, with the chosen protecting groups, moderate stereoselectivity was observed (for instance, see Scheme 7). Faced with these disappointing results, our attention turned towards the more demanding zirconium chemistry[50] (Scheme 5).



Scheme 7. Hydrostannylation of terminal alkyne **18**. AIBN = azobisisobutyronitrile.

As expected in the presence of the Schwartz reagent, the terminal alkyne **16** underwent a highly regio- and stereoselective hydrozirconation. Upon iodination of the *E*-alkenylzirconium intermediate, the resulting vinyl iodide **21** was subjected to a Sonogashira cross-coupling reaction[51] in the presence of trimethylsilylacetylene, [$PdCl_2(PPh_3)_2$], CuI in DIPA and THF. The desired TMS-protected enyne **22** was isolated in excellent yield (82%, Scheme 5).

Selective deprotection of the TMS group was nicely achieved (99%) thanks to K_2CO_3 in a methanol/dichloromethane (1/1 *v*/*v*) mixture, whereas TBAF-mediated procedures at cold temperatures resulted in only partial deprotection, affording the terminal *E*-enyne **23** in a moderate yield only (67%), as a mixture contaminated with the starting material **22**. If the temperature is raised, the reaction is not selective anymore.

Subsequently, hydrozirconation of enyne **23** with the Schwartz reagent (resulting $J_{olefin} = 18.0$ Hz) followed by trapping with NIS gave the expected *E,E*-iododiene **24** in moderate yields ranging from 30 to 70%. The coupling constants of the olefinic protons ($J_{1,2} = 14.4$, and $J_{3,4} = 15.1$ Hz) were consistent with the formation of the *E,E*-diene. Unfortunately, the sample was most-often contaminated with diene **25** and/or starting enyne **23**, highlighting that the main downside of the use of the Schwartz reagent is a lack of reproducibility in the yields, probably due to its poor stability in storage. A dramatic improvement was achieved with in situ prepared[52] Schwartz reagent followed by trapping with I_2 at −78 °C. Yields were quantitative and reproducible. Notably, *E,E*-iododiene **24** is highly sensitive and prone to decomposition, requiring careful handling, and was best used without further purification.

An alternative sequence (Scheme 5) for obtaining the *E,E*-iododiene **24** was investigated. Wittig homologation of aldehyde **15** with 2-(triphenylphosphoranylidene)acetaldehyde proceeded smoothly in CH_3CN to give the α,β-unsaturated aldehyde **26** which, in turn, underwent Colvin rearrangement[53] with trimethylsilyldiazomethane and a lithiated base, affording the terminal enyne **23** in good yield. Then, quantitative hydrozirconation as described above furnished the desired *E,E*-iododiene **24**. This sequence by Colvin homologation is two steps shorter and much more convenient than the one featuring Bestmann–Ohira alkynylation and two hydrozirconation–iodination sequences.

Aldehyde 30 and flexibility of the strategy for tail-chain installation

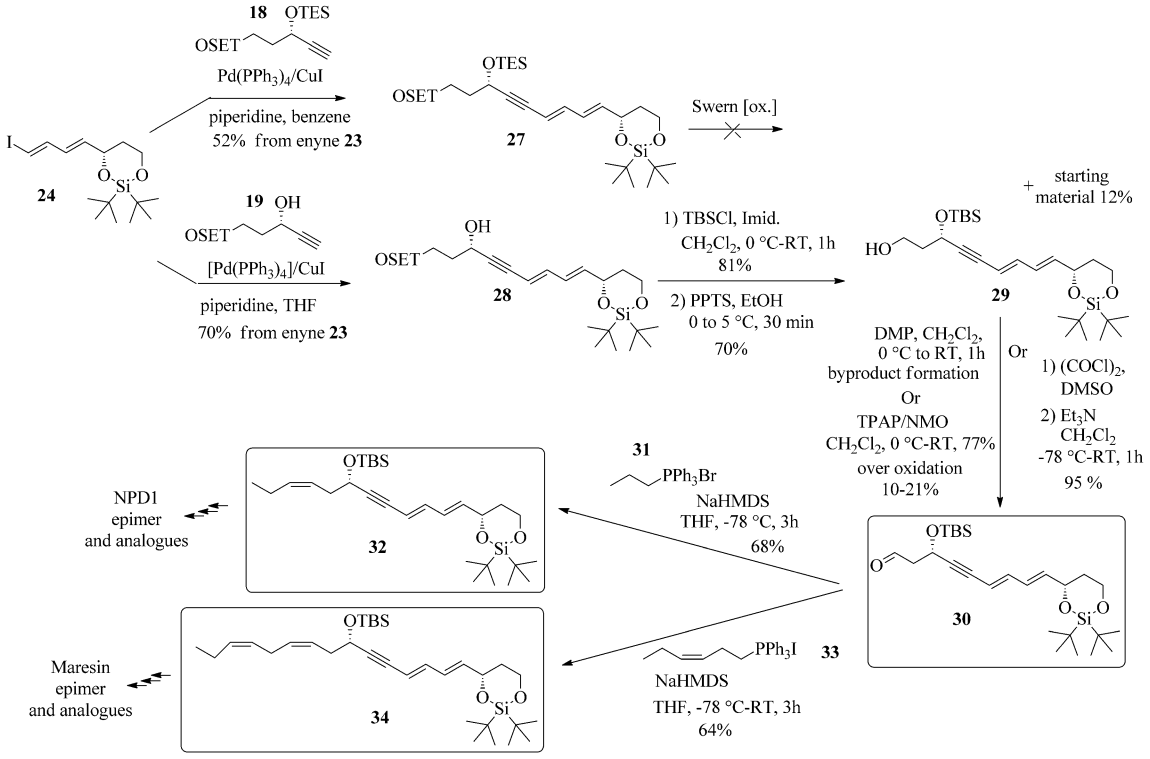
With pure *E,E*-iododiene **24** in hand, the next hurdle to overcome in the synthesis was the elaboration of the β-hydroxy-aldehyde **30** through the protected primary alcohol **24** and the installation of tail chains by Wittig extension (Scheme 8). The seemingly trivial oxidation–Wittig sequence appears rather challenging in the context of the present strategy since the basic conditions required for the Wittig reaction can lead to epimerization of the β-hydroxyaldehyde or α,β-elimination of the (protected) activated allylic or propargylic hydroxyl group.

First, alkyne **17** was protected as its bis(TES) ether **18** by treatment with TESCl and imidazole (Scheme 6), since it is known[54] that primary TES-ethers can be cleaved and oxidized under Swern oxidation conditions. Then, after a Sonogashira reaction[51,55] in good yield, treatment of the bis(TES)ynediene **27** with the Swern reagent was unfortunately unsuccessful, leading to the desired aldehyde in a complex mixture along with many byproducts (Scheme 8).

To circumvent this problem, the secondary alcohol of alkyne **19** (Scheme 6) was protected as a TBS-ether (alkyne **20**). Subsequent Sonogashira reaction with *E,E*-iododiene **24** provided the desired ynediene in moderate yield along with a great amount of the Glaser byproduct (dimer of alkyne **20**). The later could be easily avoided by means of slow additions of the terminal alkyne **20** with a syringe pump. Many reaction conditions were tested, without producing significant improvement of the yields. Interestingly, protection of the secondary alcohol was found to be unnecessary (Scheme 8). On the contrary, by using the terminal alkyne **19** with a free hydroxyl group, the desired *E,E*-ynediene **28** was obtained in a much better yield (84%; 70% from enyne **23**) without formation of the Glaser byproduct.

After TBS-protection then selective PPTS-mediated TES-cleavage, the resulting primary alcohol **29** was converted to the pivotal key aldehyde **30**. While the Dess–Martin oxidation conditions resulted in a sample of aldehyde **30** contaminated with many byproducts, about 21% of over-oxidation to carboxylic acid also occurred in the milder Ley oxidation conditions (Scheme 8). Finally, the pure aldehyde **30** was successfully obtained in quantitative yield by using the standard Swern oxidation procedure.

Subsequently, *Z*-selective Wittig olefination was performed with the commercially available *n*-propyltriphenylphosphonium bromide **31**. With its terminal omega-3 homoallylic *Z*-



Scheme 8. Flexibility for introduction of various tail chains from aldehyde **30**. DMP = Dess–Martin Periodinane; NaHMDS = sodium hexamethyldisilazane; TPAP = tetrapropylammonium perruthenate.

double bond, the resulting *E,E*-ynediene **32** is an advanced precursor of NPD1 epimer (or AT-NPD1 enantiomer).

Replacement of the phosphonium salt **31** with the *Z*-hex-3-enyltriphenylphosphonium iodide **33** (prepared as previously described)[56] nicely afforded the desired bis-allylic system **34**.

With its terminal omega-3 homoallylic and conjugated *Z,Z*-pentadiene subunit, the resulting *E,E*-ynediene **34** is an advanced precursor of Maresin epimer.

We observed that the β-hydroxyaldehyde **30** suffers from β-elimination of the OTBS group in competition with the Wittig reaction. However, although the current yields are moderate (not yet optimized), the production of both sensitive *E,E*-ynedienes **32** and **34** exemplifies the useful flexibility of the reported strategy. This successful result with the highly sensitive bis-allylic system makes us confident that this sequence may be applied to various other phosphonium salts, and may thus lead to many other analogues.

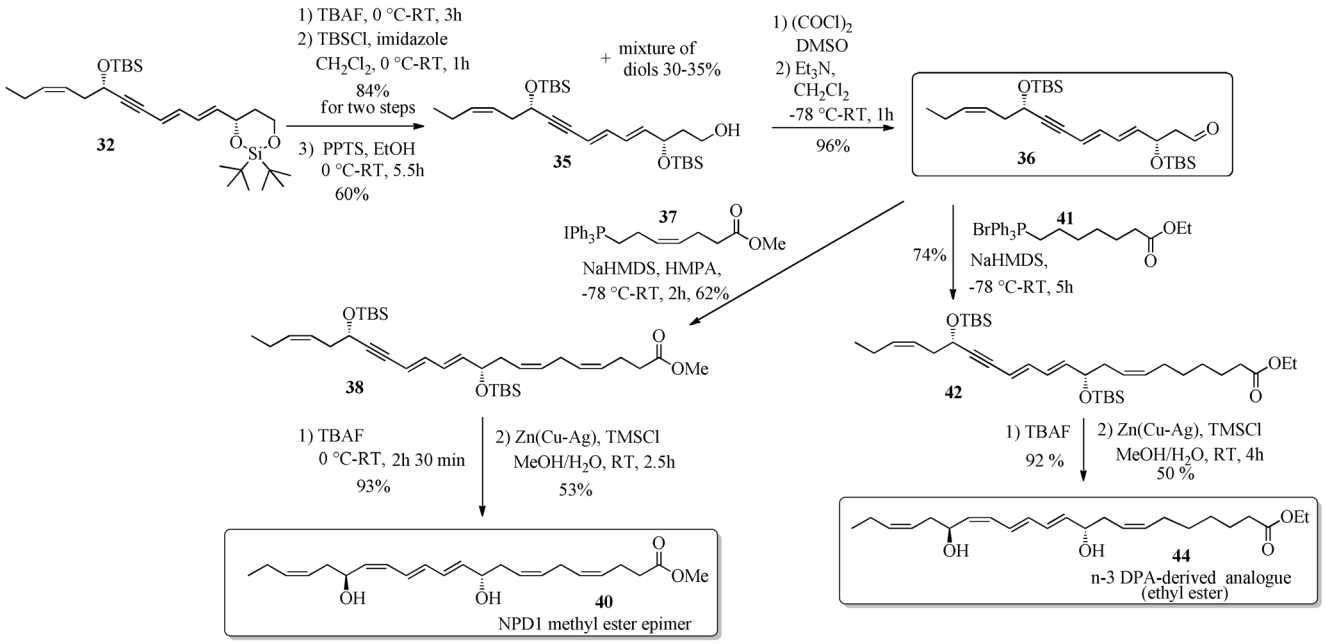
Aldehyde 36 and flexibility of the strategy for head-chain installation

Next, the remaining tasks were the challenging preparation of the aldehyde **36** from the silylene protected diol **32**, and the installation of a second chain (Scheme 9).

Full deprotection of the silylated triol **32** with TBAF, followed by full reprotection of the three hydroxyl groups as TBS ethers, then selective deprotection in mild acidic (PPTS) conditions delivered the primary alcohol **35** as a major product. Prolonged reaction times were detrimental. However, in an iterative process, the over-deprotected molecule can be reprotected as its full TBS ethers. Treatment of the newly unmasked primary alcohol **35** with the Swern reagent smoothly yielded the expected pivotal key aldehyde **36**, which was subjected to Wittig elongation with the phosphonium **37** (the preparation of which is discussed below). Thus, the strategy successfully led to the targeted *Z,Z*-bis-allylic C1–C8 chain **38**, required for NPD1.

Subsequently, TBAF-mediated deprotection of the TBS ethers occurred uneventfully to give desired diol **39** (93% yield).

The next critical step in the synthesis was the chemoselective reduction of the triple bond in ynediene **39** to the *cis*-double bond **40** in the presence of the additional conjugated and isolated double bonds avoiding over-reduction.[57] According to Boland[58] and Spur,[59] partial reduction of the ynediene **39** without reducing the other olefins was achieved by using the recent Hansen procedure[60] with addition of TMSCl (10 equiv) together with copper/silver activated zinc in aqueous methanol, thereby affording the conjugated triene **40** (Scheme 9) in 53% yield (not optimized; Notably, a better 60% yield without the use of TMSCl was reported by Petasis[27] for the C10-epimer). The semireduction reaction produced a single pure product, which showed high instability during the workup and purification process. In addition, according to previously described NMR spectroscopic analyses of conjugated *E,E,Z*-trienes,[27,28] the coupling constant of the newly created olefinic protons ($J_{15,16}$ = 10.9 Hz) was consistent with the formation of a *Z*-olefin.



Scheme 9. Flexibility for introduction of various polar head chains from aldehyde **36**. HMPA = hexamethylphosphoramide.

Synthesis of a n-3 DPA-derived analogue (compound 44)

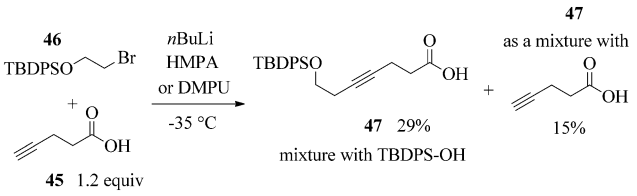
After having successfully achieved the conversion of the pivotal key *E,E*-ynediene intermediate **36** to the desired NPD1 methyl ester epimer **40**, we applied the same Wittig olefination–TBS deprotection—Hansen reduction sequence to the synthesis of a n-3 DPA-derived analogue by replacing the phosphonium salt **37** with (7-ethoxy-7-oxoheptyl)triphenylphosphonium **41** (prepared as previously reported[56]). This synthesis is depicted in Scheme 9. Thus, aldehyde **36** was successfully converted to polyunsaturated ynediene **42** (74% yield). After removal of the TBS groups with TBAF, the resulting diol **43** was subjected to Zn/Cu reduction by using the modified Boland procedure,[60] affording the desired n-3 DPA-derived analogue **44** in good yield. Assignment of the stereochemistry of the double bonds has been established by NMR spectroscopic techniques, notably the constant $J_{15,16} = 11.3$ Hz is in good agreement with the formation of a *Z*-olefin in conjugated *E,E,Z*-trienes.

We have thus demonstrated the feasibility of using the late advanced intermediate **36** as a key pivotal intermediate. Since good results were obtained with the sensitive ylide derived from phosphonium **37**, we are confident that the strategy may be applied to the total synthesis of many other analogues.

Phosphonium 37

Phosphonium **37**, required for our targeted NPD1 synthesis, was first prepared by Delorme et al.,[61] starting from ethylene oxide. However, a several months stock outage of this toxic and inconvenient gas from chemical providers urged us to devise a new approach. Its synthesis and the difficulties encountered are outlined in schemes **10** and **11**.

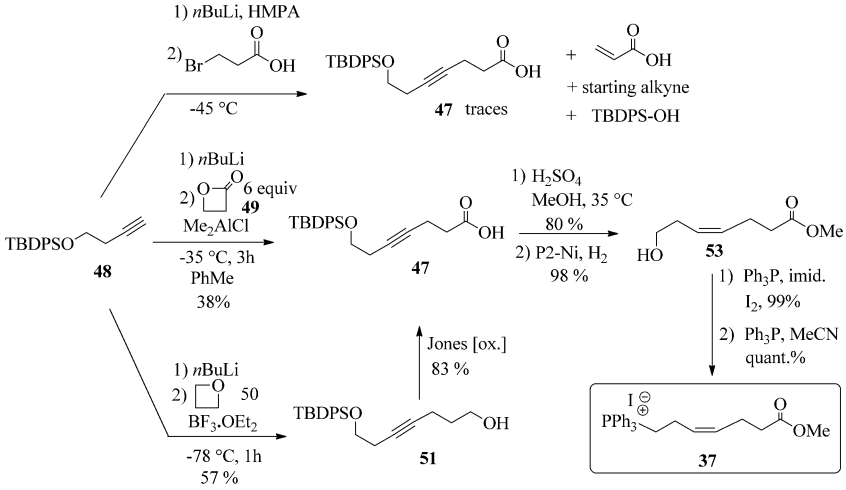
Nucleophilic substitution of bromide by a metal acetylide is one of many useful synthetic tools in organic chemistry. Addition of doubly deprotonated 4-pentynoic acid **45** to bromide **46** would result in the most direct route to alkyne **47** (Scheme 10). In our hands, all attempts yielded the expected



Scheme 10. Alkynylation of bromide **46**.

disubstituted alkyne **47** only in poor yield as a mixture. We tested several conditions in an attempt to achieve nucleophilic substitution of bromides with various acetylide anions (**48** into **47** for instance), but all of these attempts failed to produce the desired transformation in useful yields while the previously reported[62] ring opening of β-propiolactone **49** proved costly and difficult (Scheme 11).

Frustrated by weeks of fruitless effort, we turned to opening the oxetane **50** with the monoanion of TBDPS-butynol **48** by using Yamaguchi's alkynylation procedure (Scheme 11).[63] The best yield for obtaining alkyne **51** was 57%. After Jones oxidation, Fisher esterification conditions converted the carboxylic acid group to its methyl ester along with the in-situ deprotection of the TBDPS group. Upon semihydrogenation of the triple bond **52** by using Brown's catalyst (98% yield), the primary alcohol **53** was converted to the homoallylic iodide **54** in one step by using Appel's halogenation reaction[64] (99%



Scheme 11. Synthesis of phosphonium **37**.

yield). Subsequent treatment with triphenylphosphine provided the desired phosphonium **37** in quantitative yield. Gratifyingly, this route is two steps shorter, with a higher yield (34.8% overall yield for seven steps) than the one previously described[61] by Delorme et al. (24% overall yield for nine steps).

Conclusion

A versatile strategy featuring Colvin rearrangement, hydrozirconation, Sonogashira cross-coupling reaction, and *Z*-selective Wittig olefination, was successfully developed for the construction of a conjugated *E,E,Z*-triene subunit flanked, on both sides, by two allylic hydroxyl groups. This chemical pattern is found in many lipid metabolites and analogues with appealing biological applications.

Unlike previous approaches, the present strategy has the advantage of flexibility, as it allows us to modify the omega-end, the carboxylated head or both ends of the molecule without repeating the whole synthetic sequence.

The total synthesis of NPD1 methyl ester epimer (which can also be considered as enantiomer of AT-NPD1) was completed in a total of 27 steps and 1.967% overall yield from commercially available (*S*)-1,2,4-butanetriol **5** with a longest linear sequence (i.e., without considering the preparation of the phosphonium salt **37**) of 17 steps. Regarding the number of steps, the strategy presented herein nicely competes with the previously reported strategies for NPD1 synthesis (26 steps run by Petasis et al.,[27] 37 steps carried out by the Kobayashi team).[28]

In addition, using the same pivotal late advanced key aldehyde **36** as the one developed for the NPD1 epimer, the first total synthesis of a n-3 DPA-derived analogue (ethyl ester, compound **44**) was achieved in a total of 20 steps and 2.190% overall yield from commercially available (*S*)-1,2,4-butanetriol **5** with a longest linear sequence of 17 steps.

Progress toward the total synthesis of maresins from their advanced intermediate **34** will be reported in due course.

The present innovative route may be easily adapted to gain access to other dihydroxylated metabolites and analogues of polyunsaturated fatty acids containing a conjugated *E,E,Z*-triene subunit. Different epimers/diastereoisomers may be obtained by purchasing the suitable optically pure (*S*)- and/or (*R*)-1,2,4-butanetriol(s).

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