Stereoselective Total Synthesis of Etnangien and Etnangien Methyl Ester

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Received ...

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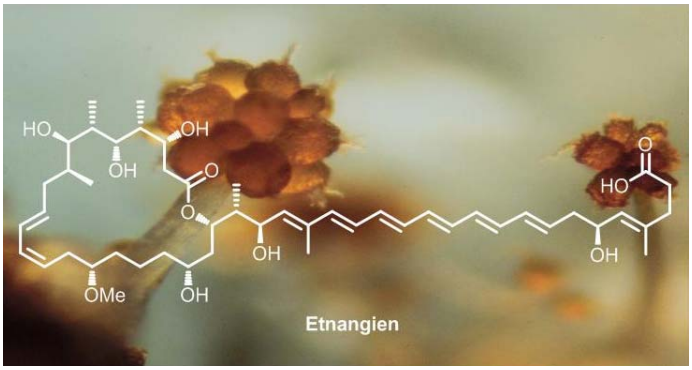


ABSTRACT**.** A highly stereoselective joint total synthesis of the potent polyketide macrolide antibiotics etnangien and etnangien methyl ester was accomplished by a convergent strategy and proceeds in 23 steps (longest linear sequence). Notable synthetic features include a sequence of highly stereoselective substrate-controlled aldol reactions to set the characteristic assembly of methyl- and hydroxyl-bearing stereogenic centers of the propionate portions, an efficient diastereoselective Heck macrocyclization of a deliberately conformationally-biased precursor, and a late-stage introduction of the labile side chain by means of a high-yielding Stille coupling of protective-group free precursors. Along the way, an improved, reliable protocol for a *Z*-selective Stork-Zhao-Wittig olefination of aldehydes was developed and an effective protocol for a 1,3-*syn* reduction of sterically particularly hindered *β*-hydroxy ketones was devised. Within the synthetic campaign, a more detailed understanding of the intrinsic isomerisation pathways of these labile natural products was elaborated. The expedient and flexible strategy of the etnangiens should be amenable to designed analogues of these RNA-polymerase inhibitors, thus enabling further exploration of the promising biological potential of these macrolide antibiotics.

Introduction

The polyketide natural product etnangien (**1**, Figure 1) was originally isolated from the myxobacterium *Sorangium cellulosum*, strain So ce750 and later from So ce1045, by the groups of

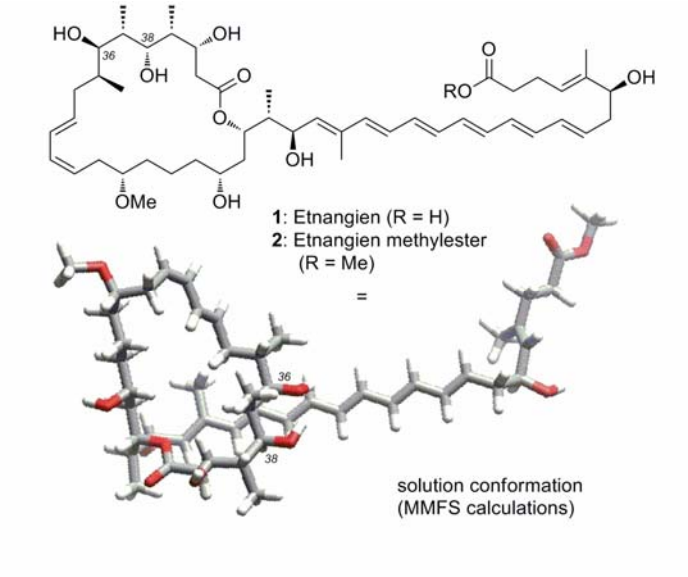
Höfle and Reichenbach.[1,2] Etnangien together with the more readily available methyl ester **2**,[3] present highly potent antibiotics, with average IC_{50} values in the submicromolar range, both *in vitro* and *in vivo*.[1-3] They are effective against a broad panel of Gram-positive bacteria, especially those belonging to the actinomycetes.[1] On a molecular level, they constitute inhibitors of RNA-polymerase. To date, the rifamycins are the sole class of clinically used RNA-polymerase inhibitors which qualifies RNA polymerase as one of the rare validated — but underexploited — targets for broad-spectrum antibacterial therapy.[4] However, resistance to the rifamycins has been increasingly spreading, which renders the development of structurally novel inhibitors an important research goal. Importantly, the etnangiens appear to exhibit no cross-resistance to rifampicin.[1,3] Furthermore, they also retain activity against retroviral DNA polymerase and show only low cytotoxicity against mammalian cell cultures, which adds with their attractiveness for further development. However, preclinical advancement is severely hampered by the notorious instability of etnangien (**1**), which has been associated to the polyene side chain.[1,3]

The unique architecture of the etnangiens is characterized by a 22-membered macrolactone ring with two alkenes and a polyunsaturated side chain with seven *E*-configured double bonds. In total, they contain twelve methyl and hydroxyl-bearing stereogenic centers. Although originally reported as a planar structure, the absolute and relative stereochemistry has been determined in our group in cooperation with the group of Rolf Müller by a combination of *J*-based configurational analysis with molecular modeling, chemical derivatization and an innovative method based on gene-cluster analysis.[3] First SAR data suggest that a free acid is not essential for biological activity and that it is possible to modify and stabilize the etnangien structure, yet still retain activity. Truncation of the side chain, however, leads to significant loss of activity, which suggests this region to be part of the pharmacophore region.[5]

The important biological properties of etnangien together with its natural scarcity and unique and challenging structure render it an attractive synthetic target, to support further biological evaluation, as well as to enable more elaborate structure–activity relationship (SAR) studies. Recently, the first total

synthesis of etnangien was accomplished in our group,[6] which also unambiguously confirmed our stereochemical assignment. Herein, we provide a full account of the development and execution of our synthetic strategy, which culminated in the first and joint total synthesis of etnangien (**1**) and its methyl ester (**2**).

Figure 1. The etnangiens: Potent macrolide antibiotics of myxobacterial origin.

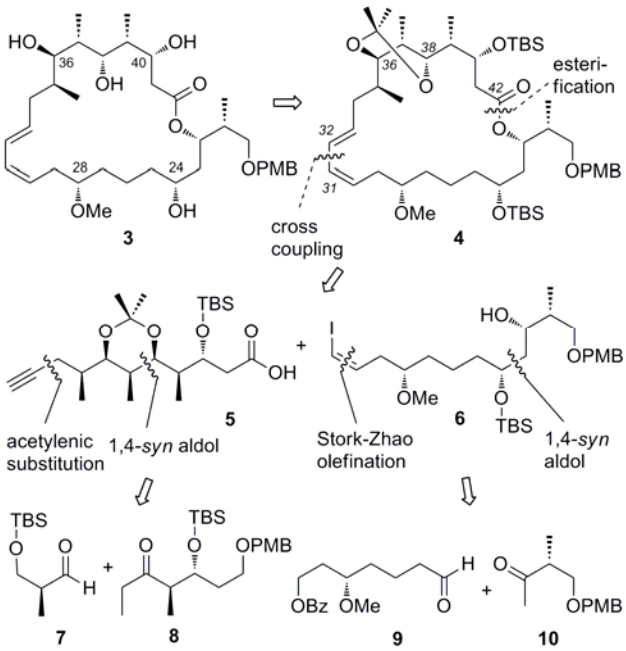


Results and Discussion

In a rationale to confirm the stereochemistry of the natural product as well as to enable access to simplified analogues lacking the labile polyene side chain for SAR-studies, we initiated our synthetic campaign with an effort to first target the macrocyclic core **3** of etnangien. As outlined in Scheme 1, the fully protected precursor **4** may be disconnected at the lactone bond and the (31,32)-diene-moiety, revealing two fragments **5** and **6** of similar complexity. For cyclization, various cross-coupling strategies to set the characteristic (*Z*,*E*)-diene may be envisioned, as an alternative to a more conventional[7] macrolactonization strategy. While a terminal *Z*-vinyl iodide was planned for the southern

fragment **6**, a terminal alkyne on the northern part **5** should serve as a flexible precursor to vinyl stannanes, boronates or alkenes, allowing for a very high degree of flexibility in our synthetic plan. In order to mimic the solution structure of the natural product,[3] which is characterized by a hydrogen bond between OH-36 and OH-38, an acetonide protection group was chosen for these two hydroxyls, in a rationale to potentially facilitate macrocyclization. Acid **5** may be further disconnected by a 1,4-*syn*-aldol reaction to ethyl ketone **8** and Roche ester derived aldehyde **7**, while the southern fragment **6**, may likewise be derived by an aldol disconnection, here from methyl ketone **10** and aldehyde **9**. Introduction of the presumably labile vinyl iodide would then be effected by means of a Stork-Zhao-Wittig olefination.

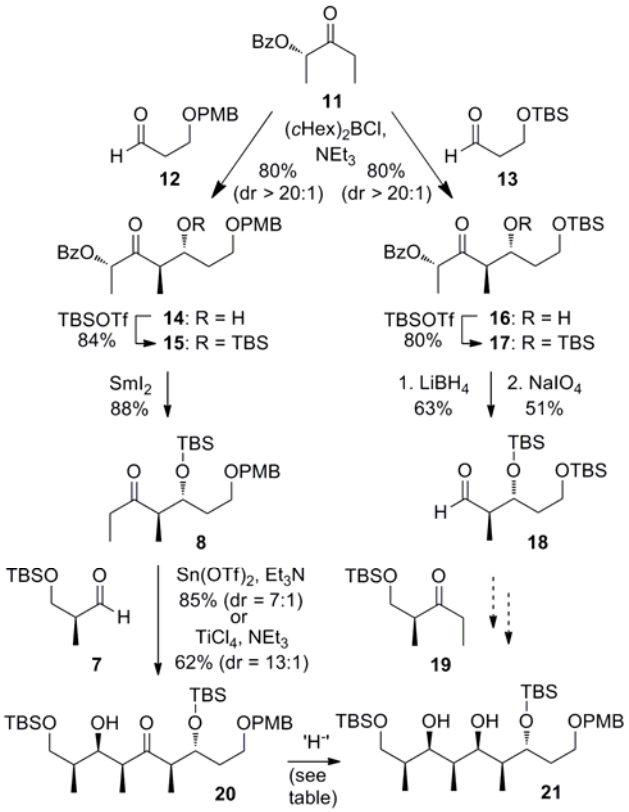
Scheme 1



As shown in Scheme 2, two main strategies for construction of the polypropionate C32-C42 fragment were evaluated.[8] Both routes were based on a boron-mediated aldol reaction of lactate-derived methyl ketone **11**[9] with aldehydes **12** and **13**, which proceeded with high stereoselectivity and yield to give the *anti*-propionates **14** and **16**, respectively. The derived TBS ether **15** was then further elaborated to ethyl ketone **8**, by cleavage of the benzoyloxy group with samarium diiodide, while **17** was

transformed to aldehyde **18** by a two step-procedure involving reductive removal of the benzoate and subsequent diol cleavage. Best results in the pivotal 1,4-*syn* aldol coupling of ketone **8** with aldehyde **7** were obtained with a tin(II) triflate-mediated coupling following a slightly modified procedure of Paterson,[10] to afford the desired *β*-hydroxy-ketone **20** in good stereoselectivity (dr 7:1) and yield. This procedure proved to be more robust and reliable also on large scale as compared to a likewise evaluated titanium mediated aldol coupling.[11] The likewise tested alternative on an inverse aldol coupling of ethyl ketone **19** with aldehyde **18**, proceeded with much lower yields and selectivities. Accordingly, this route was no longer pursued.

Scheme 2



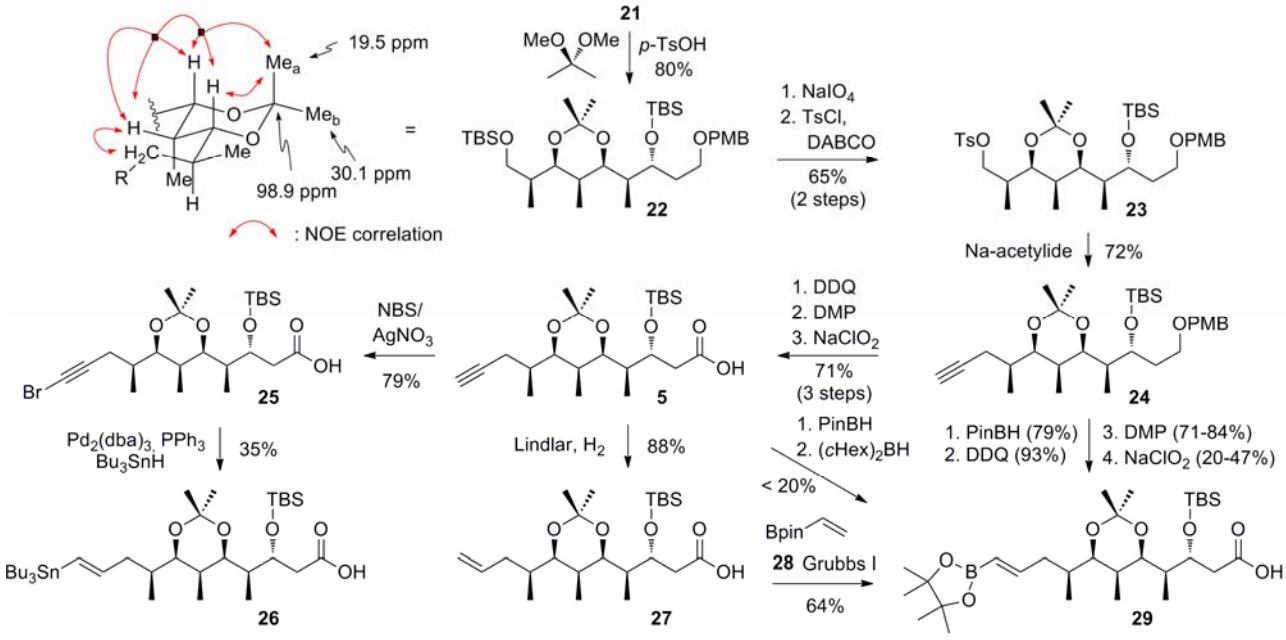
entry	reducing agent	yield (%)	*syn*/*anti*
1	Et_2BOMe; $NaBH_4$ (3 equiv)	< 5	-
2	Et_2BOMe; $LiBH_4$ (3 equiv)	24	2:1
3	DIBAL-H	48	1:4
4	$LiEt_3BH$	< 5	-
5	L-Selectride	< 5	-
6	Catecholboran	< 5	-
7	$LiBH_4$	35	1:1
8	$NaBH_4$	< 5	-
9	$Zn(BH_4)_2$ (1 equiv)	22	20:1
10	$Zn(BH_4)_2$ (20 equiv)	57	19:1
11	$(cHex)_2BCl$ (1.5 equiv); $LiBH_4$ (1 equiv)	87	19:1 ⇐

Unexpected difficulties were then encountered in the hydroxyl-directed 1,3-*syn* reduction of **20**. As shown in Scheme 2, a wide variety of commonly used reagents failed almost completely, resulting in either very low conversion and/or low degrees of selectivity, suggesting a very high degree of steric hindrance of propionate **20**. Initially, useful levels of 1,3-*syn* induction could only be obtained with $Zn(BH_4)_2$ as reducing agent. However, yields remained moderate and variable, particularly on large scale. After considerable optimization, a two step procedure was developed, which firstly involved chelation of *β*-hydroxy-ketone with (c-Hex)$_2$BCl (1.5 equiv) and NEt_3 (1.5 equiv) at -30 °C in Et_2O and

subsequent reduction with $LiBH_4$, (1 equiv) at -78 °C, resulting in the formation of **21** with high yield and selectivity, allowing for a large scale access to this fragment.

As shown in Scheme 3, the diol **21** was then protected as the acetonide **22**. At this stage the relative configuration of the stereohexad was rigorously confirmed by NMR methods.[12] Selective cleavage of the primary TBS-ether with $NaIO_4$ using a procedure recently developed in our group[13] and attachment of the tosylate by a method of Hünig and Hartung[14] proceeded in good yields. For homologation to alkyne **24** by substitution of tosylate **23**, the use of sodium acetylide proved beneficial as compared to the more conventional lithium salt, giving the desired alkyne **24** in useful yields (72%). The carboxylic acid was then introduced by deprotection of the PMB group with DDQ and two-step oxidation (3 steps, 71%). In total, the sequence to **5** proceeded in 12 steps from **11** and 12% yield and allowed access to multi-gram quantities of the key northern building block.

Scheme 3



For further functionalization of alkyne **5**, we firstly targeted *E*-vinyl stannane **26**. Based on unfavorable precedents of direct *E*-selective hydrostannylation of terminal alkynes,[15] a two step method was applied,[16] which firstly involves generation of acetylenic bromide **25**, by a silver nitrate mediated bromination, which proceeded in good yield. The derived bromoalkyne was then directly

hydrostannylated with $Pd_2(dba)_3/PPh_3/Bu_3SnH$ according to the published procedure.[16] Although *E*-selection was almost complete (dr > 19:1), the yield remained low (30~35%) and not reproducible. The destannylated analogue was obtained as the main side product, possibly due to an unfavorable influence of the carboxylic acid group. Furthermore, model Stille coupling reactions of stannane **26** with simple vinyl iodides were not successful, under various catalytic conditions.

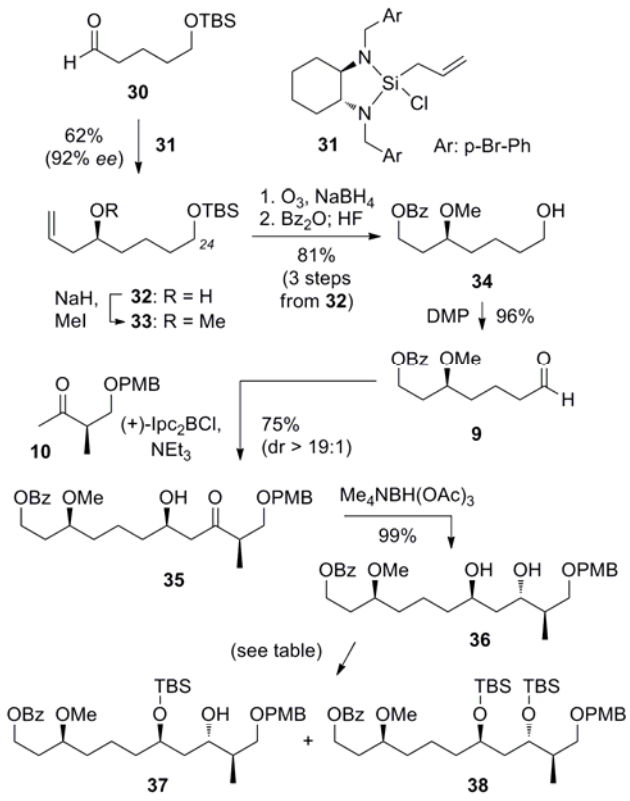
Consequently, we turned our attention to alternatives. Firstly, Lindlar hydrogenation of **5** was applied to give the terminal alkene **27**. The reaction proceeded in good yields, based on careful monitoring of the conversion, to avoid overreduction to the alkane. Alternatively, hydroboration of the terminal alkyne was studied. Since *in situ* hydroboration with catechol borane and immediate Suzuki macrocyclization failed to afford the macrocyclic core (Scheme 6, *vide infra*), a potentially more robust and more easily-handable pinacol borane was used to target the presumably more stable[17] boronate **29**. Firstly, the direct hydroboration of alkyne **5** was studied. Interestingly, to the best of our knowledge there appears to be no precedence of such a hydroboration with pinacol borane in the presence of a free carboxylic acid group. Recently, Shirakawa *et al.* have developed an efficient hydroboration method with pinacol borane in the presence of catalytic amounts of dicyclohexylborane.[18] Presumably, the reaction involves initial hydroboration by dicyclohexylborane, followed by an alkenyl B-to-B transfer to pinacolborane. In our case a slight modification of the original procedure was applied, due to the presence of a free acid group leading to rapid protonation of dicyclohexylborane. Accordingly, the substrate was first treated with 3.0 equiv of pinacol borane for 15 min at 0 ^{o}C to consume the acidic proton of the terminal carboxylic acid, followed by addition of dicyclohexylborane. However, only very low degrees of conversion could be observed for substrate **5** under conventional conditions and extended reaction times or elevated temperatures led to complex mixtures. Consequently, introduction of the boronate prior to the acid group formation was studied. Hydroboration of alkyne **24** with pinacolborane and removal of the PMB group with DDQ proceeded in good yields. Despite initial concerns of the known lability of boron compounds to oxidations,[19] oxidation of the derived primary alcohol with Dess-Martin periodinane proceeded smoothly to the corresponding aldehyde in good, albeit to a certain degree

variable yields (71% to 84%). The final oxidation to the desired acid **29**, however, proved very capricious. Best results were obtained with the Pinnick protocol,[20] giving the acid **29** in low and variable yields (20-47%), presumably due to oxidative decomposition pathways of the boronate.[21]

Accordingly, a more efficient approach was required, which was finally devised by a cross metathesis [22] of alkene **27** with commercially available vinyl boronate **28**. After considerable optimization, it was found that preparatively useful yields (64%) may be obtained, with the first generation catalyst of Grubbs, involving high catalyst loading (30 mol %) and a large excess of **28** (20 equiv).

As in Scheme 4, our synthetic approach for the southern fragment **6** was based on an asymmetric allylation of 1,5-pentanediol-derived aldehyde **30**.[23,24,25] which was initially studied using Brown's methodology.[26] However, even under low reaction temperatures (-100 ^{o}C), the enantioselectivity, as determined by advanced Mosher esters analysis,[27] remained low (<80% *ee*). In conjunction with the tedious isolation procedure due to coelution of the reagent-derived byproducts during column chromatography, we turned our attention to Leighton's reagent **31**.[28,29] Gratifyingly, a solution of aldehyde **30** and (*S,S*)-**31** afforded at -10 ^{o}C the homoallylic alcohol **32** in high enantioselectivity (92% *ee*), albeit moderate yields (62%), presumably due to gradual decomposition of the material under the Lewis acidic conditions over the required prolonged reaction times (48 h). Isolation of the allylation product **32** was straightforward by chromatography and the reaction proved well-scalable, without deterioration of efficiency. The corresponding methyl ether **33** was then prepared with NaH/MeI. Initial attempts to directly homologate the corresponding C24-aldehyde of alkene **33**, readily obtained by deprotection of the primary TBS group (HF/CH_3CN) and subsequent oxidation using Swern conditions by aldol coupling[30] with methyl ketone **10**[31] resulted however in only low yields (< 10%), presumably due to practical difficulties associated with the high volatility of the aldehyde.

Scheme 4



entry	conditions	**36** (%)	**37** (%)	**38** (%)
1	TBSOTf (1.2 equiv), 2,6-lutidine (2.2 equiv), DCM, -78 °C, 1 h	10	< 2	64
2	Bu_2SnCl_2 (1.1 equiv), DIPEA (5.0 equiv), toluene, 100 °C; then TBSCl (1.2 equiv), rt	-[a]	0	0
3	Bu_2SnO (1.05 equiv), MeOH, reflux 4h; then TBSCl (1.2 equiv), $CHCl_3$	-[a]	0	0
4	TBSCl (3.0 equiv), imidazole (6.0 equiv), DMAP (0.1 equiv), DMF, 0 °C to rt, 2 h	32	47	10

[a] no recovery of starting material

Accordingly, the corresponding Bz-protected aldehyde **9** was prepared in good yields (81%) from **32**, by methylation, ozonolysis with reductive workup, Bz-protection, subsequent TBS deprotection and DMP oxidation of intermediate alcohol **34**. Notably, it was found that Bz protection and TBS deprotection could be done in one-pot fashion, *i.e.* after disappearance of the starting material, as monitored by TLC analysis, 40% aqueous HF was directly added dropwise to the reaction mixture. The Dess-Martin oxidation of alcohol **34** proceeded straightforward in the presence of sodium bicarbonate, giving aldehyde **9** essentially in quantitative yield after flash chromatography.

For the pivotal aldol coupling, we followed a slightly modified procedure of Paterson,[32] which involved conversion of the methyl ketone into the corresponding enol borinate with (+)-Ipc_2BCl and triethylamine (TEA). *In situ* reaction with aldehyde **9** afforded the desired 1,4-*syn* aldol product **35** in 75% yield and high stereoselectivity (dr > 19:1).[33]

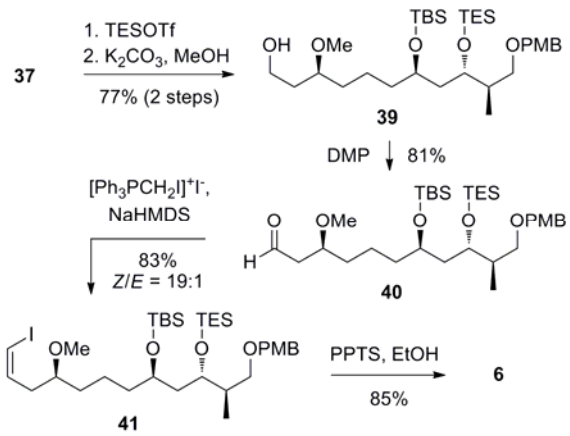
For construction of the C-22 stereocenter by means of a 1,3-*anti* reduction of *β*-hydroxy ketone **35**, the Evans protocol [34] using tetramethylammonium triacetoxyborohydride [$Me_4NBH(OAc)_3$] in acetonitrile and anhydrous acetic acid (1:1 v/v) was efficiently applied, proceeding with excellent diastereoselectivity (dr > 19:1) and yield (99%) at -40 °C (20 h).

For further advancement towards the etnangien macrocycle, a differentiation of the two hydroxyl groups of diol **36** was required. We anticipated that the steric environments might be sufficiently different to allow for selective protection of the less hindered 24-OH. However, treatment with 1.2 equivalent of TBSOTf at -78 ^oC for 1 h gave almost exclusively the bisprotected product (64% isolated yield), suggesting little steric bias towards selective monoprotection. No product formation was observed when substrate **36** was pre-treated with organotin reagents,[35] *i.e.* Bu_2SnCl_2[36] or Bu_2SnO[37] (entries 2, 3), presumably because both complexed hydroxyl groups were not reactive enough. In both cases, only decomposition was observed. Finally, use of TBSCl / Imidazole / DMAP in DMF proved relatively effective (entry 4). At 0 ^oC to room temperature a certain degree of regioselection was observed, giving the desired TBS ether **37** as the main product (47%), together with 32% reisolated starting material and 10% bis-protected diol. The diol could easily be recycled. At this stage the configuration of the stereocenter at C-22 was confirmed by Mosher ester analysis, which also confirmed the regioselective protection at C-24.

As shown in Scheme 5, protection of the remaining free hydroxyl at C-22 proceeded smoothly with triethylsilyl triflate in the presence of 2,6-lutidine. Subsequent treatment of the derived TES ether[38] with potassium carbonate in methanol removed the benzoyl group cleanly. The good but not excellent overall yield (77%, two steps) may be attributed to partial removal of the labile TES group in the Bz

deprotection step. The primary alcohol **39** was then oxidized by Dess-Martin periodinane in the presence of sodium bicarbonate to aldehyde **40** uneventfully.

Scheme 5



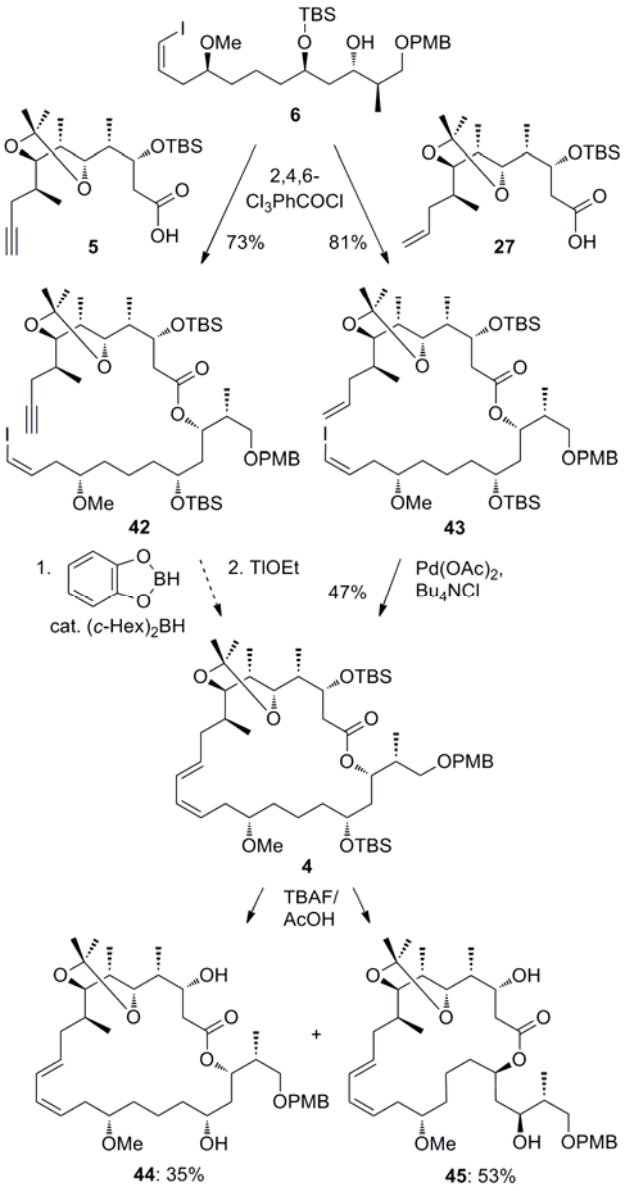
For introduction of the required *Z*-vinyl iodide, a Stork-Zhao-Wittig olefination[39] was envisioned. The required phosphonium reagent $[Ph_3PCH_2I]^+I^-$ was prepared by a modified procedure,[40] which involved heating a solution of triphenylphosphine and methylene iodide in dry toluene to 50 ^oC and stirring at this temperature for 96 h in the dark. After washing with diethyl ether and drying under vacuum, the desired phosphonium salt was obtained in 56% yield. Importantly, following these conditions, ^{1}H-NMR and ^{13}C-NMR analysis indicated the presence of a single compound and not mixtures as claimed in the literature.[39] The olefination step was then conducted under "salt-free" conditions.[41] Accordingly, the required phosphor ylide was firstly prepared by deprotonation of the phosphonium salt with KHMDS. After standing for 30 min, the yellow supernatant solution of the "salt-free" ylide was cannulated into the other flask containing the aldehyde. The reaction was complete within 30 min at -78 ^oC and produced the desired vinyl iodide **41** in excellent selectivity (*Z/E* = 50:1), however only moderate yield (52%). After considerable experimentation, an improved protocol was applied (compare discussions Scheme 8, *vide infra*), giving the desired iodide in 83% yield and *Z/E* = 19:1 selectivity. Finally, selective deprotection of the TES protecting group in the presence of a less hindered but more bulky

TBS group, was best achieved by catalytic amount of PPTS (0.25 equiv) in ethanol giving alcohol **6** in 85% yield. In total, the southern fragment **6** was prepared in 7.4% overall yield (9.8% with recycling once diol **36** during the regioselective protection step) and 12 steps from **12** in the longest linear sequence from aldehyde **30**.

As shown in Scheme 6, two main strategies were then pursued for advancing to the macrocyclic core of etnangien. Initial attempts relying on a Stille coupling of **26** resulted in only low and not reproducible yields on model compounds, giving mainly destannylated product, possibly due to the presence of the free carboxylate. Attempts were then directed towards an esterification, hydroboration and Suzuki macrocyclization approach. Thus, under standard Yamaguchi esterification condition (2,4,6-trichlorobenzoyl chloride, TEA and DMAP in toluene), ester **42** was prepared from **5** and **6** in 73% yield. Subsequently, an *in situ* procedure for hydroboration and Suzuki macrocyclization without intermediate isolation of the boronate was evaluated.[42] Accordingly, after complete hydroboration of alkyne **42** with catechol borane (10.0 equiv) in the presence of catalytic amount of dicyclohexylborane (0.2 equiv), the crude product was directly submitted to catalytic amounts of $Pd(PPh_3)_4$ and a slight excess of TlOEt. However, only complex product mixtures could be obtained. The successful strategy finally involved an intermolecular esterification between alkene **27** and alcohol **6**, followed by a Heck macrocyclization. Again, the Yamaguchi protocol was effectively employed, giving ester **43** in 81% yield. For complete conversion and ease of separation, it proved beneficial to use a slight excess of acid **27** (1.2 equiv), which was easily recovered after the reaction. Subsequently, the Heck macrocyclization reaction could be effected under slightly modified Jeffery condition,[43] involving a degassed mixture (3.9 mM) of the substrate, tetrabutylammonium chloride (3.0 equiv), anhydrous potassium carbonate (8.0 equiv) and palladium acetate (1.2 equiv) in DMF at 60 ^{o}C, giving the desired macrolactone in 47% yield, with complete *E*-selectivity. Presumably, this remarkable diastereoselectivity[44] may be caused by a favored conformation controlled by the rigid acetonide protection group. For further elaboration of **4**, removal of the protecting groups was studied. In agreement with more elaborate experiments (*vide infra*, Scheme 17), the TBS groups were completely removed by a freshly prepared DMF solution of

TBAF (2.0 M) and acetic acid (0.2 M) at 0 °C. The expected product **44** could be isolated by preparative normal phase HPLC in 35% together with the contracted analogue **45** in 53% yield.

Scheme 6

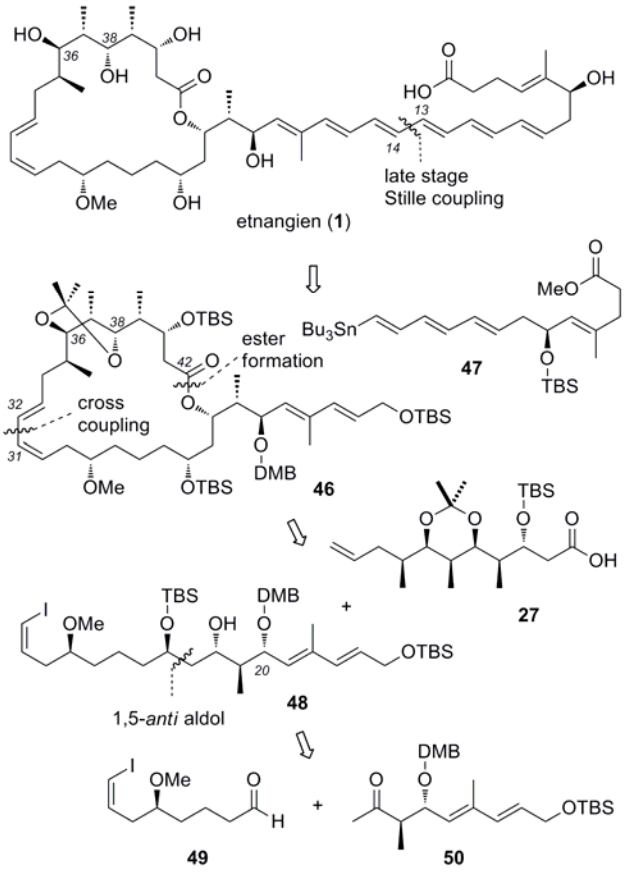


In summary, the synthesis of **44** was accomplished in 16 steps from ketone **11** with 1.4% overall yield. A sequence of highly stereoselective aldol reactions was developed to set the characteristic sequence of hydroxyl- and methyl-bearing stereogenic centers with high degrees of efficiency and convergence while a Heck macrocyclization was effectively used for closing the macrocyclic core. Importantly, at this stage, the close similarity of the NMR data of **44** and the corresponding etnangien

acetonide[3] allowed to confirm the relative stereochemistry of the macrocyclic core of the natural product.

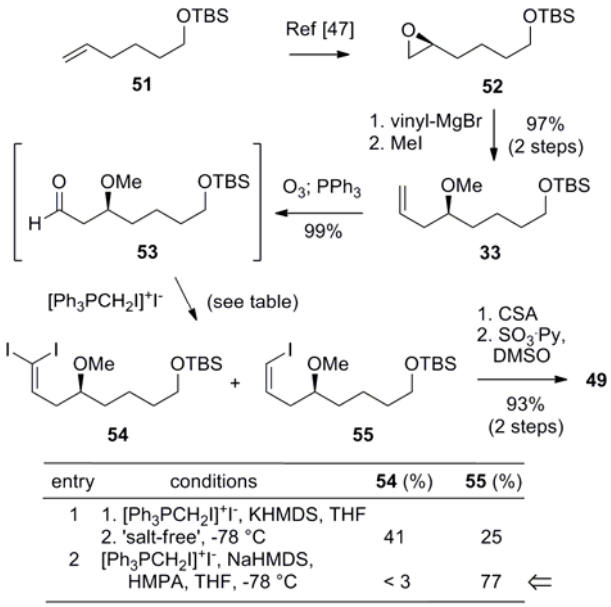
With these findings in hand, a synthetic strategy towards the authentic natural product was devised. As shown in Scheme 7, critical disconnections in the macrocyclic part were chosen in an analogous fashion to the model system, *i.e.* an ester formation and a cross coupling to forge the diene system. However, in contrast to the model system, the side chain was dissected in the middle of the conjugate hexaene subunit in a rationale to set the labile hexaene-system at a late stage of the synthesis. Accordingly, a base free Stille coupling[45] was envisioned for a late stage attachment of the side chain, revealing the trienyl stannane building block **47** (C1-C13 fragment). The macrocycle would be disconnected into the same northern fragment **27** (C32-C42) and a homologated southern fragment **48** (C15-C31), in a rationale to increase the overall convergence. Furthermore, it was hoped that the more elaborate macrocycle **46** might be less prone to isomerisation processes, which have not been reported for the authentic natural products.[1] Compound **48** was planned to arise from an aldol connection along the C23-C24 bond. Notably, a 3,4-dimethoxybenzyl(DMB)-protection group was chosen for the 20-OH to allow for useful levels of a favorable 1,5-*anti* induction.[46] Based on the observed stability of vinyl iodide **6**, introduction of the vinyl iodide portion was planned before the aldol coupling to render the strategy more convergent, which revealed the coupling partners **49** and **50**.

Scheme 7



As shown in Scheme 8, the synthesis of vinyl iodide fragment **49** involved the same intermediate **33** as used before (see Scheme 4). However, in contrast to the route above, a revised synthetic plan based on a Jacobsen hydrolytic kinetic resolution (HKR) of epoxide **52**[47] was implemented, due to the high expense of the chiral reagent **31** and the requirements for even larger amounts of **33**. Accordingly, the chiral epoxide was obtained in two steps from readily available TBS ether **51** following a published procedure,[47a] which proved well-scalable. Regioselective ring opening, methylation and ozonolysis of **33** gave aldehyde **53** in essentially quantitative yield. Stork-Zhao-Wittig olefination was first tested under the "salt-free" condition, as evaluated above (see Scheme 5).[32] However, in contrast to the observations with substrate **40**, here a mixture of the expected *Z*-vinyl iodide **55** (25% yield), together with the geminal diiodide **54** was obtained which could only be separated by normal phase preparative HPLC.

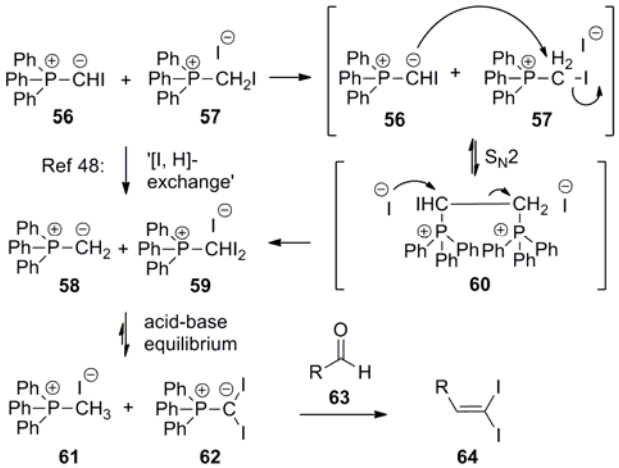
Scheme 8



entry	conditions	**54** (%)	**55** (%)	
1	1. $[Ph_3PCH_2I]^+I^-$, KHMDS, THF 2. 'salt-free', -78 °C	41	25	
2	$[Ph_3PCH_2I]^+I^-$, NaHMDS, HMPA, THF, -78 °C	< 3	77	⇐

A similar observation has only been reported by the group of Bestmann.[48] To explain the generation of the unwanted diiodide, they suggested an iodine-hydrogen exchange process, as shown in Scheme 9. According to their model, the normal ylide **56** and the undeprotonated salt **57** might exchange a hydrogen and iodide, leading to an iodine-free ylide **58** and a new salt (**59**) with two covalently attached geminal iodine atoms (*i.e.* H to I exchange). The resulting two species may then further undergo proton transfer, leading to phosphor ylide **62**, resulting in the formation of the geminal diiodide **64**.

Scheme 9



In order to understand the side reaction and ultimately improve the reaction outcome, a possible mechanism of this exchange process may be proposed as shown in Scheme 9 (right part). Accordingly, the salt **57** might be attacked by ylide **56** in a nucleophilic-substitution fashion to give a hetereodimerized salt (**60**) as an intermediate. A second substitution, now by an iodide, might then lead to C-C bond cleavage forming the neutral ylide **58**.[49] Possibly, such an I-H exchange process might be useful for the synthesis of 1,1-diiodoalkenes in a HWE variant.[50] However, to the best of our knowledge, a detailed study and mechanistic explanation for this process appear not to have been reported.

Based on this proposal, the I-H exchange is initiated by two species, **56** and **57**, which are present in the deprotonation stage. We hypothesized that if there is little undeprotonated salt **57** present, formation of the diiodide side product should be avoided. As the deprotonation process with strong bases such as NaHMDS should be a rapid process, slow addition of the salt to a solution of the base would be critical to ensure the all-over excessive presence of NaHMDS. On the other hand, excess of base might be detrimental to the following reaction with the aldehyde **63**. Accordingly, exactly a 1:1 molar ratio of the phosphonium salt and the base was considered to be ideal.

Conventionally, the phosphonium salt is added to the reaction flask before addition of the base, presumably due to the insolubility of the salt in most solvents and due to ease of conduction. Surprisingly, however, in many cases, I-H exchanges appear not to have been observed. One possible explanation could be that normally the base is rapidly added to the suspension of the salt and the deprotonation processes is much faster than the I-H exchange process. In our case, however, we could not add large amount of the base in a few seconds, due to reasons of reproducibility and scalability, whereas prolonging exposal of the salt **57** to ylide **56** might lead to unfavorable I-H exchange processes.

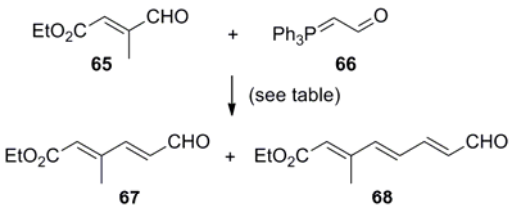
Based on these thoughts, we adopted the following procedure for our preparation of the *Z*-vinyl iodide. In the absence of light, a suspension of a fine powder of the phosphonium iodide (1.5 equiv) in anhydrous HMPA was slowly added to a solution of NaHMDS (1.5 equiv) in dry THF at 10-15 ^{o}C.

After 1 min, the mixture was cooled to -78 ^{o}C and a solution of the aldehyde (1.0 equiv) in THF was added dropwise. After 20 min at -78 ^{o}C, the reaction was stopped and a usual aqueous workup procedure produced the *Z*-vinyl iodide. Following this procedure, the *Z*-vinyl iodide was reproducibly obtained in good yield (70-77%) and high *Z/E* selectivity (15:1 to 27:1), without any observable formation of the vinyl diiodide (see Table, Scheme 8). Notably, when the insoluble salt was added in solid form batch wise and in otherwise identical condition, small amount of the diiodide was still formed (*Z*-**55**/*E*-**55**/diiodide **54** = 10:1.0:1.3), presumably as the adding rate could not be rigorously controlled under these conditions.

Subsequently, the primary TBS protecting group was removed with catalytic amount of 10-camphorsulfonic acid (0.3 equiv) in methanol, giving the derived alcohol in essentially quantitative yields. The subsequent oxidation was most effectively performed with the Parikh-Doering procedure.[51]

As shown in Scheme 10, construction of the desired methyl ketone **50** was initiated by a previously described Wittig reaction of commercial aldehyde **65** with ylide **66**.[52] In our hands, however, the reported procedure in toluene resulted in only moderate degrees of conversion and yields. In contrast, it was observed that the reaction proceeds much faster in DCM, resulting in higher degrees of conversion and yields. Optimum results were obtained with 1.0 equivalents of the Wittig reagent and 3.0 equivalents of the aldehyde at room temperature, giving the desired aldehyde **67** in 80% yield. The homologated compound **68** was observed as the main side product.[53]

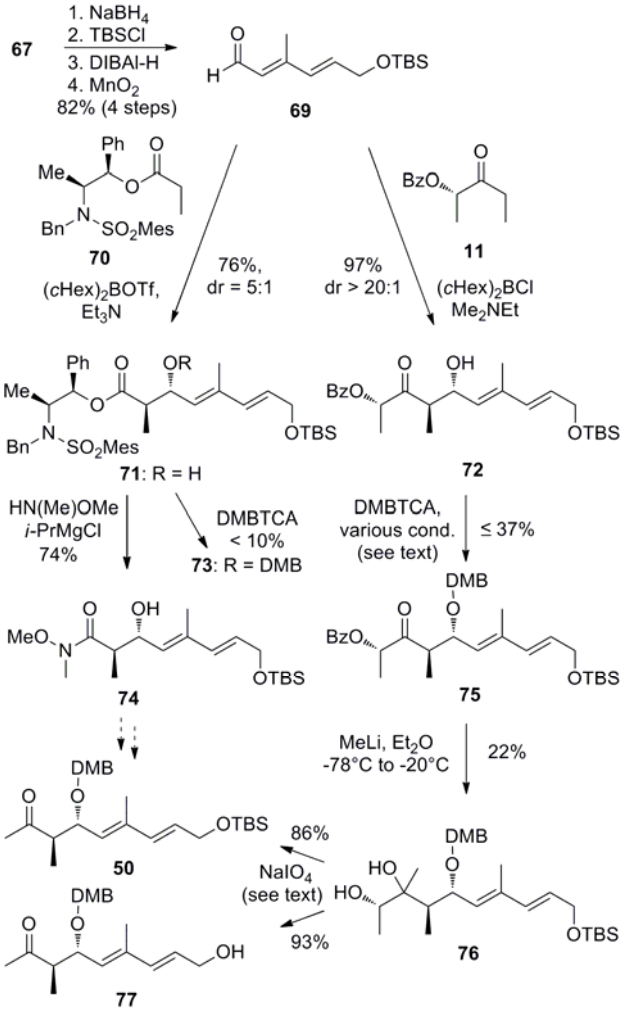
Scheme 10



entry	solvent	**65** (equiv)	**66** (equiv)	T (°C)	t (h)	yield (%) **67**	**68**	**65**	
1	toluene	1.0	1.1	110	24	57 (ref 52)			
2	DCM	1.0	1.1	rt	24	65	13	11	
3	DCM	1.0	1.5	rt	24	70	9	16	
4	DCM	3.0	1.0	rt	24	80	-	2.7	⇐

With **67** in hand, a series of functional group operations, involving reduction of the aldehyde, TBS protection of the derived primary alcohol, DIBAL reduction of the ester and MnO_2 oxidation of the derived allylic alcohol gave aldehyde **69** in high yield (82%) over these four steps, as shown in Scheme 11. Unexpectedly,[8] the subsequent Abiko-Masamune aldol reaction with propionate **70** proceeded in only moderate selectivity and yield (76%, dr > 5:1). Also, conversion of aldol adduct **71** to Weinreb amide **74** using our previously developed method with a slight excess of *i*-PrMgCl and *O*,*N*-dimethylhydroxylamine hydrochloride[54] was accompanied with variable degrees of elimination and protection of the newly generated hydroxyl of **71** as a DMB-ether failed to provide the desired ether **73**.[55]

Scheme 11

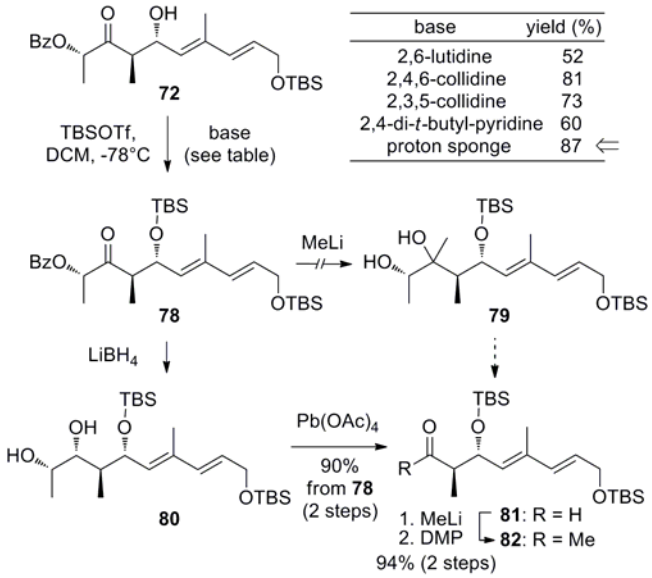


Due to theses unsatisfactory results, we turned our attention to a Paterson *anti*-aldol reaction with lactate-derived ethyl ketone **11**,[9] which proceeded with excellent selectivity and yield (97%, dr > 20:1). However, again DMB protection of the generated hydroxyketone **72** proved capricious. Despite considerable experimentation, yields remained low. Best results were obtained with PPTS giving **75** with 37% yield. Also, subsequent addition of MeLi to the ketone functionality with concomitant benzoyl cleavage provided the desired 1,2-diol **76** also only in low yield (22%). Finally, conversion to the desired methyl ketone **50** by oxidative cleavage with $NaIO_4$ in THF/H_2O also proved difficult to control, giving variable degrees of methyl ketones **50** and **77**.[56]

On the basis of these unsatisfactory results, an alternative protective group strategy had to be implemented. For convenience, a TBS group was chosen, despite expected unfavorable effects on the envisioned 1,5-*anti* induction in the subsequent aldol coupling with aldehyde **49**. As shown in Scheme

12, TBS protection of aldol product **72** was best carried out with TBSOTf in the presence of proton-sponge, while alternative bases (2,6-lutidine, 2,4,6- collidine, 2,3,5-collidin, 2,4-di-*t*-butyl pyridine) resulted in lower yields and were accompanied with various degrees of elimination. Presumably, the increased steric hindrance of the base suppresses these unwanted side reactions. For conversion of **78** to the desired methyl ketone **82**, it proved beneficial to firstly remove the benzoate reductively ($LiBH_4$), followed by oxidative cleavage of the derived diol **80**, which was best carried out with $Pb(OAc)_4$ in toluene to avoid removal of the allylic TBS ether, as observed before (see Scheme 11). Aldehyde **81** was then converted in two steps and high yields (94%) to the desired methyl ketone **82**, by addition of MeLi and oxidation of the derived alcohol. This strategy proved to be superior to a likewise tested alternative of direct addition of methyl lithium to benzoate **78**, leading to extensive decomposition, presumably by direct nucleophilic attack to the electron rich allylic TBS ethers.[57] In summary, ketone **82** was prepared in 11 steps and 47% yield.

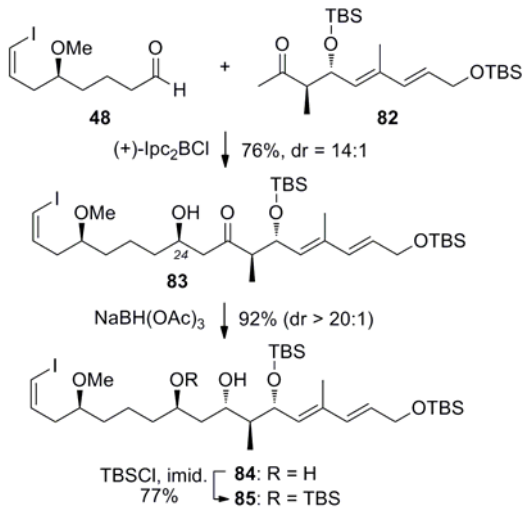
Scheme 12



Gratifyingly, the pivotal coupling of ketone **82** with aldehyde **48**, proceeded with high stereoselectivity and yield following an Ipc-boron mediated aldol reaction (76%, dr > 14:1). As shown

in Scheme 13, optimum conditions involved enolization of methyl ketone with (+)-DIPCl and Et_3N in Et_2O at 0 °C, which was allowed to react with aldehyde **48** at -78 °C for 1 h and then at -20 °C for 14 h. Subsequent 1,3-*anti* reduction of the aldol product was straightforward following the procedure as established above, giving **84** in high yield (92%) and stereoselectivity (dr > 19:1). In agreement with the results for the model compound, selective protection of diol **84** was optimal with TBSCl/imidazole in dichloromethane, giving the desired monoprotected TBS ether **85** in 77% yield. The slightly improved result as compared to the previous substrate might be attributed to the increased steric hindrance around the C22 hydroxyl group.

Scheme 13



As shown in Scheme 14, efforts to advance to the elaborated macrocyclic core **87** of etnangien were initiated by a Suzuki coupling strategy. Since hydroboration with catechol borane and immediate Suzuki macrocyclization failed to afford the macrocyclic core before (compare Scheme 6), we turned our attention to first implement the cross coupling. However, coupling of vinyl iodide **85** with **29** proceeded in only low yield (21%), giving *seco*-acid **86**, which was further carried on to the macrocycle uneventfully under standard Yamaguchi esterification condition in 51% yield.

Scheme 14

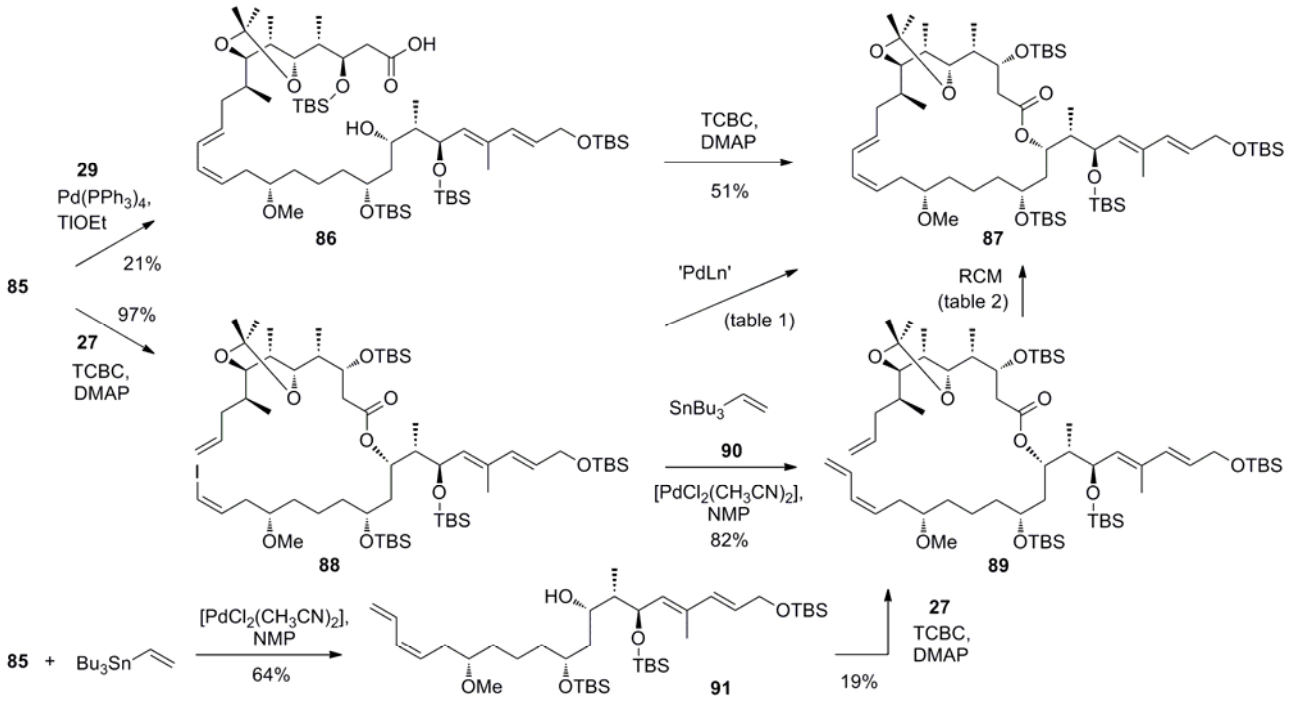


Table 1

entry	catalyst	conditions	yield (%)	
1	$PdCl_2(MeCN)_2$	Et_3N, HOCO, MeCN, rt, 22h	-[a]	
2	$PdCl_2(MeCN)_2$	Et_3N, HOCO, DMF, rt, 3h	-[a]	
3	$Pd(PPh_3)_4$	Et_3N, K_2CO_3, MeCN, 50 °C, 1h	-[a]	
4	$PdCl_2(PPh_3)_2$	K_2CO_3, Bu_4NCl, DMF, 80 °C, 0.5 h	12	
5	$Pd(OAc)_2$	K_2CO_3, Bu_4NCl, DMF, 70 °C, 1h	70	⇐

Table 2

entry	catalyst (mol%)	conditions	conversion	ratio[a]
1	Hoveyda-Grubbs II (10%)	1,2-DCE, rt, 24h	< 40%	< 1:50[b]
2	Grubbs II (10%)	1,2-DCE, rt, 72h	> 80%	< 1:50[b]
3	Grubbs II (10%)	toluene, 100 °C, 20 min	> 80%	< 1:50[b]
4	Grubbs I (50%)	1,2-DCE, 80 °C, 4h	> 80%	2:1[b]
5	Grubbs I (5x40%)	1,2-DCE, 80 °C, 5h	45%[b]	1:0.7[c]

[a]: Ring contraction (expulsion of ethylene) was mainly observed;
[b]: ratio determined by LC-MS analysis; [c]: ratio determined after isolation

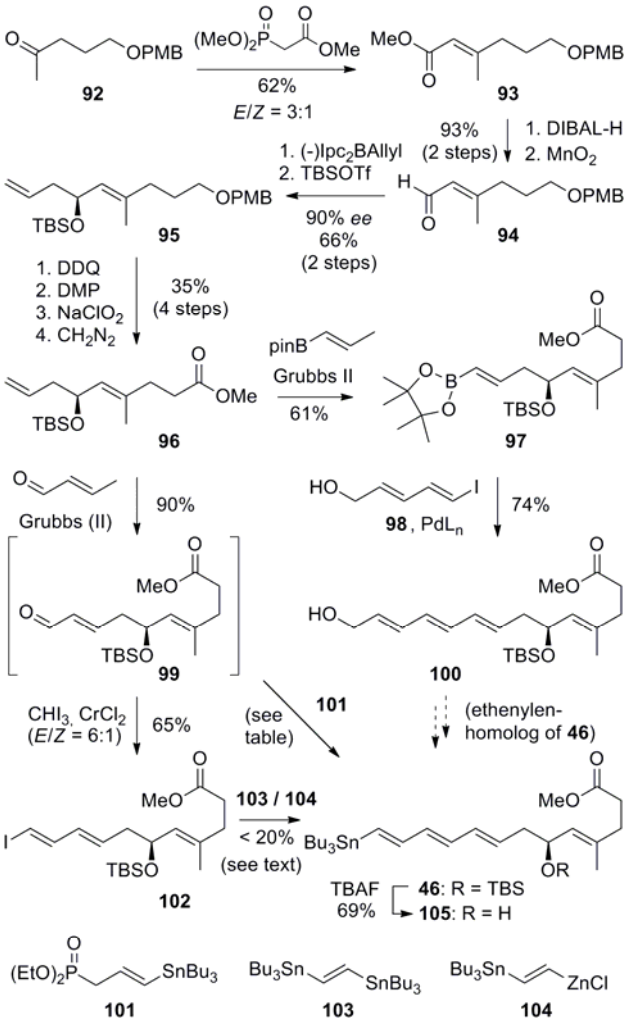
As an alternative, a ring closing metathesis (RCM)[58] of precursor **89** was evaluated. Initially, the required terminal diene subunit was synthesized by C2-homologation of iodide **85** by Stille coupling with commercially available tributyl vinylstannane giving diene **91** in high yield (64%). Surprisingly, however,[59] upon storage even at 0 °C, this (*Z*)-diene gradually isomerized to a mixture of (*E*)- and (*Z*)-isomers, presumably because of the presence of trace of palladium species even after column purification. Therefore, diene **91** had to be used immediately for the next transformation. However, esterification with **27** was unexpectedly inefficient under Yamaguchi conditions. Possibly, traces of residual palladium species led again to decomposition during solvent evaporation after chromatography, mainly by scrambling of olefin geometry. Consequently, the esterification was conducted prior to Stille homologation. Accordingly, Yamaguchi coupling of alcohol **85** and acid **27** produced the ester in good yield (97%). At this stage, Stille coupling with vinyl stannane **90** was straightforward (rt, 40 min, 82%).

The corresponding diene product **89** was then immediately used for RCM reactions, in order to prevent decomposition processes due to any residual palladium species. However, as shown in Table 2, reaction conditions could not be optimized to allow for an effective access to the desired macrolactone **87**. Main side product proved to be the contracted 20-membered ring. Furthermore, a mixture of **89** and the smaller congener could not be resolved by various chromatographic methods.

In a parallel fashion, Heck macrocyclization of alkene **88**, readily available from **85** and **27** by esterification, was studied.[60,61] Accordingly, ester **88** was subjected to various Heck condition to close the 22-membered ring, as shown in Table 1. After some optimizations, it was found that the reagent combination $Pd(OAc)_2/Bu_4NCl/K_2CO_3$/DMF (70 °C, 50 min)[62] provided the desired macrocycle **87** in high yield (70%), as the only isolable product with exclusively C32-C33 *E*-configuration.

With the fully protected macrocyclic core in hand, efforts could then be directed towards construction of the side chain. As shown in Scheme 15, its preparation starts from PMB-protected hydroxyl-pentanone **92**, which was homologated by an HWE reaction with trimethyl phosphonoacetate to provide the *α,β*-unsaturated ester **93** in preparatively useful yields (62%) as an *E*/*Z* mixture of 3:1, following a procedure, recently developed in our group on a related substrate.[44b] Reduction of this ester to the corresponding alcohol with DIBAL-H and reoxidation of the allylic alcohol with MnO_2 gave aldehyde **94** in a straightforward fashion. Brown allylation under "salt-free" conditions at -100 ^oC afforded the homoallylic alcohol **95** in 80% yield and good enantioselectivity (90% ee). After protection with TBSOTf, the *E*/*Z* isomers could be separated by ordinary column chromatography with silica gel. Finally, the *E* isomer was transformed to methyl ester **96** over 4 steps by PMB deprotection, Dess-Martin oxidation, Pinnick oxidation and methyl esterification with diazomethane.

Scheme 15



entry	base	conditions	yield **46** (%)
1	NaHMDS	THF, -78 °C, 20 min	20[a]
2	LiHMDS	DME, 0 °C, 10 min	0
3	*n*-BuLi	DME, 0 °C, 2h,	7[a]
4	NaH	THF, 0 °C to rt, 6h	5[a]
5	KHMDS /18-c-6	THF, -78 °C, 1h	38[b] ⇐

[a] yield based on ^{1}H-NMR analysis of crude product.
[b] isolated yield after prep. HPLC

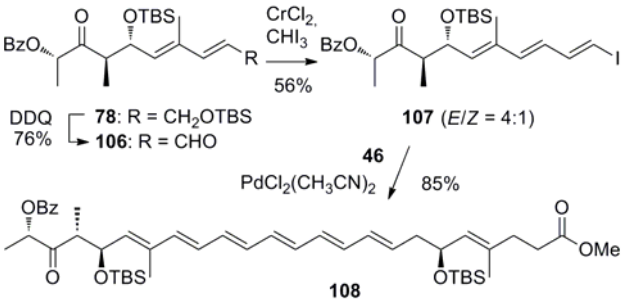
For introduction of the stannane, we initially conceived an approach *via* iodide **102** by mono-Stille coupling with *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene **103**.[63] Accordingly, the required iodide **102** was prepared by cross metathesis, Takai olefination and TBS deprotection from the terminal alkene **96**. Cross coupling was best performed with Grubbs II catalyst (5% mol) and an excess of crotonaldehyde (10 equiv) at 60 °C in dry toluene, giving desired aldehyde **99** in high yields (90%). Subsequently, Takai olefination[64,65] with iodoform (8.8 equiv) and chromium (II) chloride (14.0 equiv) in a mixed

solvent system (dioxane/THF = 6:1)[66] gave dienyl iodide **102** in 65% yield and acceptable selectivity (*E*/*Z* = 6:1), which proved to be highly labile to light (*E*/*Z* isomerization) and traces of iodoform.[67]

The final critical step, the Stille mono-coupling with *trans*-1,2-Bis(tri-*n*-butylstannyl)ethylene (**103**) was firstly tried under standard Stille conditions.[68] However, treatment of iodide **102** with $PdCl_2(CH_3CN)_2$ (10% mol) and 10 equivalents of *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene in degassed DMF, resulted in complex mixtures. Also, with $Pd(PPh_3)_4$ as catalyst, formation of complex mixtures was observed, and the deiodinated congener was observed as the main product (40%). We therefore resorted to an alternative protocol utilizing a one-pot Sn-Li-Zn transmetallation and subsequent Negishi coupling.[69] Accordingly, the required reagent **104** was prepared *in situ* from **103**, as previously described,[69a] and directly added to a cooled (0 ^oC) THF solution of iodide **102** and catalyst $Pd(PPh_3)_4$. However, only low degrees of conversions were observed under conventional conditions and after extended reaction times formation of various side products was observed. Moreover, the low and similar polarity of starting material and product and slow decomposition of stannane **46** on silica gel in the absence of triethylamine, rendered isolation of the desired stannane **46** extremely challenging, resulting in very low yields in all cases. After a series of further unsuccessful attempts including a tin-Takai olefination,[70] we turned our attention to the introduction of the stannane by a HWE olefination with stannylated phosphonate **101**, a related work of which had previously been used by the Smith group with limited success.[71,72] As shown in the Table in Scheme 15, various reaction conditions were applied, resulting however initially only in very low yields of the right product which was also contaminated by a few other side products. It seemed that sodium as counter ion and lower temperatures appeared to be beneficial (entries 1-4), suggesting the size (K^+(18-c-6) > K^+ > Na^+ > Li^+) or coordinative capability (K^+(18-c-6) < K^+ < Na+ < Li^+) of the counter ion to be important for the reaction outcome. Indeed, deprotonation of phosphonate **101** with KHMDS in the presence of 18-crown-6 followed by addition of the aldehyde **99** at -78 ^oC resulted in the formation of the expected triene **46** in 38% yield after preparative HPLC (Entry 5). Subsequent removal of the secondary TBS was cleanly effected by TBAF, giving the desired alcohol **105** in useful yields (69%).[73]

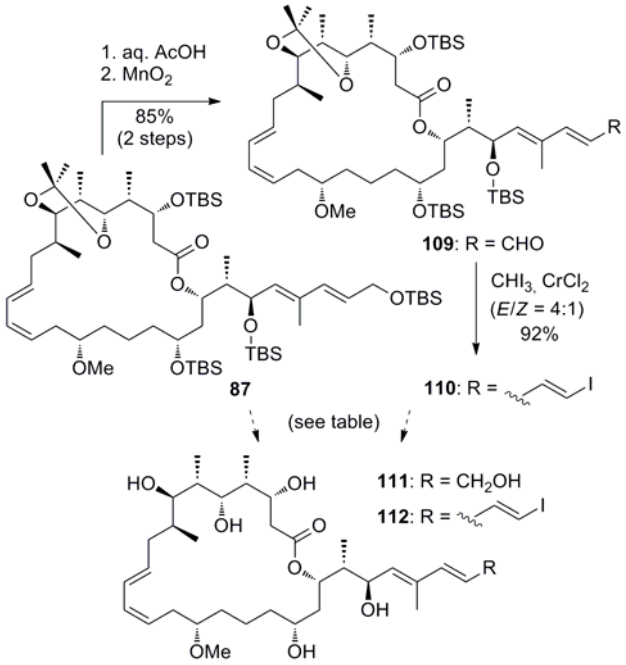
To test the projected late-stage generation of the all-(*E*) hexaene subunit of etnangien, the Stille-coupling of **46** was subsequently attempted with simplified model vinyl iodide **107**, which was prepared from **78** by allylic oxidative deprotection with DDQ.[74] Notably, the secondary allylic TBS ether remained untouched. Takai olefination of aldehyde **106** gave the labile trienyl iodide **107** (56% yield, *E*/*Z* = 4:1). Gratifyingly, the subsequent Stille coupling between iodide **107** and stannane **46** proceeded smoothly using $PdCl_2(CH_3CN)_2$ in DMF system, giving the desired product in high yield (85%).

Scheme 16



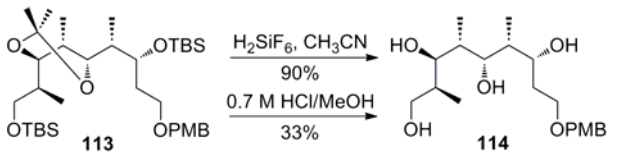
With the introduction of the side chain established, efforts were then directed to access the macrocyclic vinyl iodide **110**. Initially, a similar sequence as before was applied, involving allylic oxidation and Takai reaction. However, direct treatment of **87** with DDQ/pH7 buffer gave only low yields (36%) of the expected aldehyde **109**. Alternatively, a two-step process, involving first liberation of the primary allylic alcohol, best done with aqueous 65% acetic acid in THF,[75] and subsequent allylic oxidation with manganese(IV) dioxide, proved beneficial giving aldehyde **109** which was directly used for the Takai olefination, which proceeded in excellent yield and acceptable stereoselectivity (92% over 2 steps, *E*/*Z* = 4:1).[76]

Scheme 17



entry	substrate	conditions	yield
1	**110**	3.0 M HCl / MeOH, THF, 0 °C, 30 min	-[a]
2	**110**	1) CSA, MeOH, rt, 2h; 2) HF . Py, THF, 0 °C, 1h	-[a]
3	**110**	CSA, MeOH, rt, 1h	-[a]
4	**110**	0.5 M HCl / MeOH, rt, 15 h	-[a]
5	**110**	1.25 M HCl / MeOH, 0 °C, 100 min	-[a]
6	**87**	0.7 M HCl / MeOH, 0 °C, 1h	-[a]
7	**87**	aq. H_2SiF_6, CH_3CN, 0 °C, 1h	-[a]
8	**87**	1% conc HCl in EtOH/THF, 0 °C, 2h	-[a]
9	**87**	aq. 40% HF aq. H_2SiF_6, CH_3CN, 0 °C, 1h	-[a,b]
10	**87**	TMSOTf, DCM, -78 °C, 30 min	-[a]
11	**87**	BF_3-Et_2O/Me_2S, DCM/CH_3CN, 0 °C, 1h	-[a]
12	**87**	TASF, DMF, 0 °C, 40h	-[c]
13	**87**	1.0 M TBAF, THF, rt, 4.5h, aq. workup	-[a,d]
14	**87**	1.0 M TBAF, THF, rt, 4.5h,[e]	-[a]
15	**87**	HCO_2H/H_2O/THF 65:35:100, rt, 4.5h	-[a]
16	**87**	AcOH/H_2O/THF 65:35:100, 50 °C, 4h	-[c]
17	**87**	$FeCl_3$ on SiO_2, $CHCl_3$, rt, 1h	-[a]
18	**87**	BF_3-OEt_2/1,3-propanedithiol, DCM, 0 °C, 6h	-[a]
19	**87**	$Zn(NO_3)_2$-$6H_2O$ in CH_3CN, 50 °C, 20h	-[c]
20	**87**	TBSOTf/2,6-lutidine, DCM, -78-0 °C, 2 h	-[a]
21	**87**	0.5 M TBAF/AcOH, THF, 0 °C-rt, 40h,[e]	-[d,f]
22	**87**	2.0 M TBAF/0.2 M AcOH, DMF, 0 °C-rt, 3h	-[f] ⇐

[a] complex product mixture; [b] dehydration was observed
[c] only deprotection of primary allylic alcohol
[d] seco-acid formation
[e] workup according to ref. 77 with Dowex 50w, $CaCO_3$ and MeOH
[f] formation of isomers **115**, **116**, **117** (see scheme 18)



For deprotection, we initially planed to remove both the acetonide as well as the TBS groups of **110** in a one-pot fashion under acidic conditions. However, as shown in the Table in Scheme 17, only complex

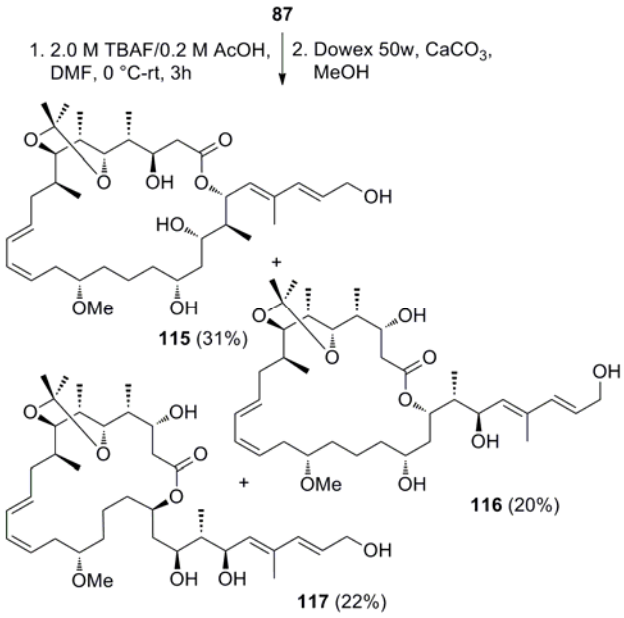
product mixtures could be obtained using a variety of conditions, including CSA, HF and HCl in various concentrations and solvents and no traces of the desired compound could be detected by LC-MS analysis (entries 1-5).

Due to these difficulties, we turned our attention to the macrocycle **87**. Furthermore, to understand the difficulties of the deprotection process, we firstly evaluated concomitant removal of the acetonide and TBS groups with the northern fragment **113**. For this compound, both hydrochloric acid and hexafluorosilicic acid (H_2SiF_6) proved effective with complete removal, resulting in selective formation of the desired tetraol **114**. However, when these or related conditions were transplanted onto macrocycle **87** (entries 6-9), again only complex mixtures were obtained, and no traces of the desired product were found. Similar results were obtained with various Lewis acids, including TMSOTf or BF_3-OEt_2 (entries 10, 11).

At this stage we decided to apply non-acidic conditions and attempted to firstly remove the TBS groups. While some reagents [TASF, $Zn(NO_3)_2$], entries 12, 19] were too unreactive giving mainly removal of the primary TBS group, other likewise mild reagents resulted in extensive decomposition (Silica gel supported $FeCl_3$, BF_3-OEt_2/1,3-propanedithiol, BF_3-OEt_2, TBSOTf, entries 11, 17, 18, 20). Finally, TBAF (1.0 M in THF) emerged as a promising reagent, resulting in a limited number of products. However by conventional aqueous workup, the corresponding open-chain seco-acid was obtained as the main product. Accordingly, to avoid potential saponification during workup, which may be caused by basic fluorides, we applied an alternative workup procedure, recently developed by the Kishi group, by means of Dowex 50w, $CaCO_3$ and MeOH.[77] Indeed, applying this procedure (entry 14) resulted in the formation of three distinct compounds, which were eventually confirmed to be **116** together with translactonized **115** and **117** (see Scheme 18), together with smaller amounts of the corresponding seco-acid. After further optimization (entries 20-22), optimum results were obtained with use of TBAF buffered with HOAc in combination with short reaction times, in combination with the Kishi workup, resulted in the formation of three distinct isomers **115**, **116** and **117** with complete loss of

TBS groups, which were isolated after preparative HPLC separation on silica gel (DCM/*i*-PrOH = 91:9) in preparatively acceptable yields, with only negligible traces of the *seco*-acid.

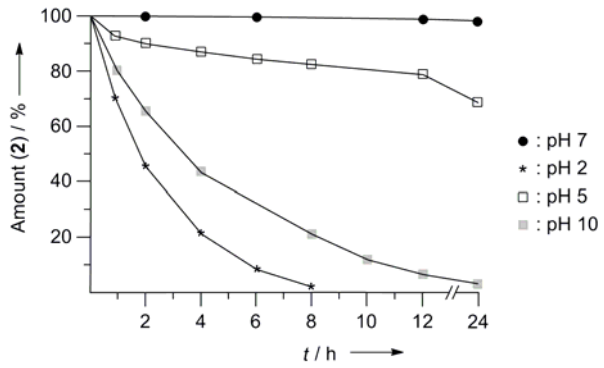
Scheme 18



With these TBS deprotected macrocycles in hand, we again studied removal of the acetonide. No reaction was observed, when lactone **115** was subjected to a suspension of Dowex 50w in methanol for 8 h or PPTS in methanol, suggesting a high degree of steric hindrance exerted by the adjacent methyl groups. While acetonide removal may be effected by treatment of **116** with CSA/MeOH or HCl/MeOH, in both cases several products were obtained. Furthermore LC-MS analysis suggested the incorporation of an additional methylene-unit, presumably by addition of methanol, suggesting alternative solvents to be more appropriate. Acetonide removal was possible with 65% aqueous acetic acid, however again a number of side products were concomitantly formed. Other methods which were evaluated included silica gel supported $FeCl_3$, leading to dehydration or $PdCl_2(CH_3CN)_2$, which resulted in a complex mixture. We also wondered if the ring size makes difference upon deprotection of the acetonide. These results suggested that also the primary allylic C-15 alcohol might be too labile under these acidic conditions. Together with the propensity of isomerisation of the terminal vinyl iodide **110**, we re-evaluated the endgame strategy and decided to remove the acetonide after the Stille coupling.

To further evaluate the endgame strategy, the stability of a solution of etnangien methyl ester (**2**)[78] in methanol under various pH-values was studied, as shown in Figure 2. While, as expected[3] the methyl ester was stable under neutral conditions and can be conveniently stored at pH 7 in dark vessels in solution, considerable degrees of decomposition was observed at very low (pH < 3) or high pH-values (pH > 10), in agreement with the observed lability of **87**, **111** and **115-118** in acidic media. However, despite this pronounced tendency for decomposition, it was observed that even at pH 2, around 60% of the initial product could be retained after two hours. Accordingly, it was envisioned that final acetonide removal might be possible within this pH-range and short reaction times, in agreement with promising results obtained above with HOAc.

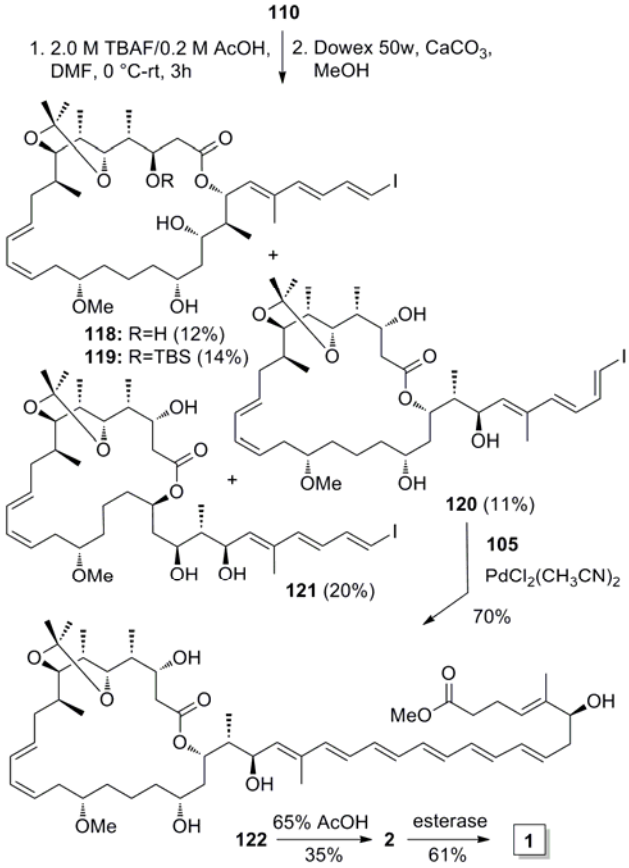
Figure 2. Stability of etnangien methyl ester at various pH-values.



Accordingly, as shown in Scheme 19, the macrocyclic vinyl iodide **110** was submitted to the previously established conditions (TBAF/AcOH) for complete removal of all TBS groups giving the expected three isomers **118**, **120**, **121** together with partially deprotected **119** as the major products, after purification by prep. HPLC on silica gel. Subsequent Stille coupling of **120** with iodide **105** proceeded smoothly using our previously established conditions, giving the desired coupling product **122** in good yields (70%), which was then submitted to 65% acetic acid at 0 ^{o}C. Gratifyingly, the desired etnangien methyl ester could then be obtained in acceptable yield (35%) after 80 min. Finally, cleavage of the methyl ester was effectuated with porcine liver esterase following our previously

established procedure,[3] giving etnangien, which was identical in all aspects (^{1}H and ^{13}C NMR, HRMS, R_f and optical rotation) to an authentic sample.

Scheme 19



Conclusions

In conclusion, a highly stereoselective total synthesis of etnangien was accomplished by a convergent strategy. It proceeds in 23 steps (longest linear sequence) and 0.25% yield starting from commercially available aldehyde **65**. This work establishes unambiguously the relative and absolute configuration. Notable synthetic features include an array of highly stereoselective aldol reactions to set the characteristic methyl and hydroxyl bearing stereogenic centers, an efficient conformation controlled Heck macrocyclization, by use of an acetonide protecting group, mimicking solution structure of the

natural products and a late-stage introduction of the labile side chain by an efficient Stille coupling reaction, in the presence of four nonprotected hydroxyls.

Along this synthesis, considerable time and efforts had to be invested in a few critical steps. The best method to construct the macrocyclic core proved to be the most direct approach, a Heck reaction involving a non-functionalized alkene. With regard the side chain stannane **105**, after several unsuccessful attempts to introduce the stannane from a terminal alkene, an effective approach involving a HWE reaction with a metallated allylic phosphonate (**101**) was developed. However, the most demanding part appeared very late. Global deprotection of all TBS groups and the acetonide was extremely demanding, resulting in a plethora of unexpected side reactions, reminding us many times that a much deeper understanding of this kind of natural products and related chemistry is vital. Ultimately, a two-step method (TBAF/AcOH removal of all TBS groups and 65% AcOH deprotection of the acetonide), enabled us to attain the goal, however in only very low yield. This problem should be addressed in future synthetic studies towards the etnangiens.

The presented modular synthesis of etnangien should be instructive and amenable to designed analogues of this novel RNA-polymerase inhibitor, thus enabling further exploration of the promising biological potential of this macrolide antibiotic.

Experimental Section

1,3-*syn* Reduction of 20 to 21. To a solution of chlorodicyclohexylborane (27 µL, 0.125 mmol) in 300 µL Et_2O was added Et_3N (18 µL, 0.125 mmol). The mixture was cooled to -20 °C before a solution of the keton **20** (50 mg, 0.083 mmol) in 50 µL Et_2O was added. The mixture was stirred at - 30 °C for 75 min and then cooled to -78 °C before 200 µL of a solution of $LiBH_4$ in THF (2 M, 0.415 mmol) was added. The mixture was stirred again for 60 min at -78 °C an then diluted with Et_2O (1 mL) and quenched with 1 mL satd. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with brine and concentrated in vacuo to an oil. The crude oil was dissolved in MeOH (330 µL), 10% NaOH solution

(100 μL), 30%H_2O_2 (150 μL) and stirred for 60 min at r.t before the reaction was diluted with 2 mL H_2O and 2 mL DCM. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic Phases were dried with $MgSO_4$ and concentrated to an oil. The reaction was purified by column chromatography (light petroleum ether /EtOAc 85:15) to afford the diol **21** (42.6 mg, 0.071 mmol, 87%, dr 19:1) of a clear oil. R_f = 0.28 (light petroleum ether /EtOAc 90:10); $[\alpha]^{22}_D$ = +2.5 (*c* = 1.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.02 (s, 3H), 0.03 (s, 3H), 0.05 (6H), 0.87 (s, 9H), 0.88 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.73 (m, 2H), 1.81 (m, 1H), 1.88 (m, 1H), 1.96 (m, 1H), 3.55 – 3.47 (m, 2H), 3.51 - 3.60 (m, 3H), 3.75 (s, 3H), 3.85 (dd, *J* = 6.7, 2.9 Hz, 1H), 3.87 (dd, *J* = 7.4, 2.4 Hz), 4.39 (d, *J* = 11.9 Hz), 4.40 (d, *J* = 11.9 Hz), 6.87 (dd, *J* = 8.7, 1.9 Hz, 2H), 7.24 (dd, *J* = 8.7, 1.9 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm -5.5, -5.4, -4.6, -4.5, 8.5, 11.4, 13.7, 17.9, 18.3, 23.8, 25.8, 25.9, 29.7, 34.2, 37.3, 37.9, 38.2, 55.5, 66.2, 66.7, 72.7, 73.8, 74.7, 75.9, 113.8, 129.5, 130.2, 159.9; HRMS calculated for $C_{32}H_{62}O_6NaSi_2$ [*M*+Na]$^+$: 621.3983, found: 621.3990.

Preparation of Stork-Zhao-Wittig reagent. A solution of PPh_3 (50.0 g, 0.19 mol, 1.00 eq) and diiodomethane (20.0 ml, 0.25 mmol, 1.30 eq) in 250 ml toluene was heated to 50 °C and stirred for 96 h in the absence of light. The mixture was cooled down to room temperature and filtered. The precipitate was washed with dry toluene and dry diethylether subsequently, then dried under vacuum to yield a colourless solid (56.8 g, 0.11 mol, 56%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ = 5.08 (d, *J* = 8.9 Hz, 2 H), 7.73-7.96 (m, 15 H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ = 117.9, 119.1, 130.4, 134.1, 135.5. MS calculated for $C_{19}H_{17}IP^+$ [M]$^+$ = 529.9; found 529.5.

Stork-Zhao-Wittig Reaction to Vinyl Iodide 55. In the absence of light, to a solution of NaHMDS (1.0 M in THF, 2.96 mL, 2.96 mmol, 1.5 equiv) in absolute THF (58 mL) was added a suspension of the phosphonium iodide (1.57 g, 2.96 mmol, 1.5 equiv) in anhydrous HMPA (dried over 4 Å molecular sieves, 4.0 mL and 2 x 2.5 mL washes) at 10-15 ^{o}C (ice-water bath). After 1 min, the mixture was cooled to -78 ^{o}C and a solution of aldehyde **53** (541 mg, 1.97 mmol, 1.0 equiv) in THF (1.0 mL and 2 x 0.5 mL washes) was added dropwise. After stirred at -78 ^{o}C for 20 min, the reaction was quenched by

addition of aqueous saturated NH_4Cl (25 mL) and water (10 mL). When warmed to room temperature, the insoluble solids were filtered off and the layers of the filtrate were separated. The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (80 g, hexanes / Et_2O = 35 : 1 to 12:1) afforded the vinyl iodide **55** (607 mg, 1.52 mmol, 77%, Z : E = 27 : 1). R_f = 0.68 (hexanes / EtOAc = 9 : 1); $[\alpha]^{23}_D$ = -9.9 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H), 0.90 (s, 9H), 1.36-1.60 (m, 6H), 2.30-2.43 (m, 2H), 3.30 (m, 1H), 3.36 (s, 3H), 3.61 (d, *J* = 6.6 Hz, 1H), 3.63 (d, *J* = 6.1 Hz, 1H), 6.24-6.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.2, 18.4, 21.8, 26.0, 32.9, 33.5, 38.6, 56.7, 63.1, 79.6, 84.1, 137.7; HRMS calculated for $C_{15}H_{31}IO_2SiNa$ $[M+Na]^+$: 421.1036, found: 421.1039.

Wittig reaction to Aldehyde 67. A flask containing $Ph_3PCHCHO$ (146 mg, 0.481 mmol, 1.0 equiv) was added a solution of (*E*)-Ehyl 3-methyl-4-oxobut-2-enoate (207 µL, 1.52 mmol, 3.0 equiv) in abs. DCM (100 µl). The reaction mixture was stirred for 15 h at room temperature and purified direct by flash chromatography (hexanes / Et_2O = 6:1 to 1:1) to give aldehyde **67** (64.6 mg, 0.384 mmol, 80%) and aldehyde **68** (2.5 mg, 13 µmol, 2.7%,) as amorphous solids. Aldehyde **67**: R_f = 0.37 (hexanes / EtOAc = 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.29 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.11 (s, 1H), 6.43 (dd, *J* = 15.6, 7.4 Hz, 1H), 7.08 (d, *J* = 15.6 Hz, 1H), 9.65 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.8, 14.2, 60.5, 127.0, 132.7, 148.6, 154.2, 165.8, 193.3; HRMS calculated for $C_9H_{12}O_3$ $[M]^+$: 168.0786, found: 168.0788. Aldehyde **68**: R_f = 0.37 (hexanes / EtOAc = 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.28 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 4.18 (q, *J* = 7.0 Hz, 2H), 6.94 (s, 1H), 6.26 (dd, *J* = 15.3, 7.7 Hz, 1H), 6.65 (d, *J* = 15.4, 1H), 6.74 (dd, *J* = 15.3, 10.4 Hz, 1H), 7.16 (dd, *J* = 15.3, 10.4 Hz, 1H), 9.60 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.6, 14.3, 60.2, 123.9, 131.1, 133.5, 144.8, 150.0, 150.4, 166.4, 193.3; HRMS calculated for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found: 194.0940.

Heck macrocyclization to 87. A solution of ester iodide **88** (88.0 mg, 71.2 µmol, 1.0 equiv), $Pd(OAc)_2$ (16.0 mg, 71.2 µmol, 1.0 equiv), Bu_4NCl (49.5 mg, 178 µmol, 2.5 equiv) and K_2CO_3 (78.5

mg, 569 μmol, 8.0 equiv) was added DMF (18.0 mL) at room temperature. The resulted yellow suspension was stirred at 70 °C for 50 min. The mixture was cooled to room temperature, diluted with Et_2O (40 mL) and filtered through a celite plug (3 × 10 mL Et_2O). After removing of the solvent, the residue was purificated by column chromatography (hexanes / Et_2O = 20:1) to give dien **87** (55.1 mg, 49.7 μmol, 70%) as a colorless oil. R_f = 0.55 (hexanes / Et_2O = 9:1); $[\alpha]^{20}_D$ = +6.3 (*c* = 0.57, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = -0.04 (s, 3H), 0.005 (s, 3H), 0.02 (s, 3H), 0.04 (s, 3H), 0.07 (s, 9H), 0.08 (s, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.84 (s, 9H), 0.87 (s, 9H), 0.89 (s, 9H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.34 (s, 3H), 1.37 (s, 3H), 1.39-1.53 (m, 6H), 1.61 (m, 1H), 1.68-1.75 (m, 2H), 1.73 (s, 3H), 1.80-1.85 (m, 2H), 1.89-1.93 (m, 2H), 2.11 (m, 1H), 2.20 (m, 2H), 2.34 (dd, *J* = 16.1, 8.8 Hz, 1H), 2.46 (m, 1H), 3.20 (m, 1H), 3.31 (s, 3H), 3.31-3.36 (m, 2H), 3.78 (m, 1H), 4.24-4.26 (m, 3H), 4.40 (dd, *J* = 9.2, 6.6 Hz, 1H), 5.17 (m, 1H), 5.36 (d, *J* = 9.5 Hz, 1H), 5.38 (m, 1H), 5.64 (m, 1H), 5.69 (dt, *J* = 15.8, 5.3 Hz, 1H), 6.04 (t, *J* = 10.8 Hz, 1H), 6.20 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 14.7, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.1, -4.7, -4.5, -4.4, -4.3, -4.1, -3.8, 5.8, 11.3, 13.3, 16.3, 18.0, 18.1, 18.5, 19.6, 25.9, 26.0, 26.1, 30.1, 31.1, 31.8, 35.0, 37.2, 38.3, 40.1, 44.1, 56.5, 64.1, 70.7, 71.0, 72.9, 80.3, 99.1, 126.0, 127.1, 127.9, 130.2, 132.2, 133.1, 133.6, 134.4, 171.0; HRMS calculated for $C_{61}H_{118}O_9Si_4Na$ $[M+Na]^+$: 1129.7751, found: 1129.7743.

Stannane 46. To a cooled (-78°C) solution of phosphonate **101** (74.9 mg, 160.3 μmol, 1.2 equiv) and 18-crown-6 (70.6 mg, 267.2 μmol, 1.2 equiv) in dry THF (0.8 mL) was added dropwise a solution of KHMDS (0.5 M in toluene, 320.6 μL, 1.2 equiv). After stirring for 5 min, a solution of aldehyde **99** (45.5 mg, 133.6 μmol, 1.0 equiv) in dry THF (0.2 mL and 0.2 mL washing) was added dropwise. The resulted mixture was stirred at -78°C for 1 h followed by dilution with n-hexane (5.0 mL) and quenching with pH7 phosphate buffer (4.0 mL). Warmed to room temperature, the layers were separated and the aqueous layer was extracted with n-hexane (2 x 2.0 mL). The combined organic phased were washed with brine (4.0 mL), dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The residue was chromatographed by preparative HPLC (Column:

LiChrospher® Si 60 (10 µm) 250x10 mm, n-hexane/EtOAc = 97:3, 6.0 mL/min, 254 nm) to produce the pure trienyl stannane (retention time = 8.08 min, 33.1 mg, 50.6 µmol, 38% yield).

Etnangien Methyl Ester 2. A cooled (0°C) solution of the acetonide **122** (0.3 mg, 0.34 µmol) in AcOH / water (65 / 35 v / v, 100 µL) was stirred at this temperature for 80 min. Aqueous saturated $NaHCO_3$ (1.5 mL) and EtOAc (1.5 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (9 x 2.0 mL). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was flash chromatographed (silica gel, dichloromethane / methanol = 15 : 1 to 10 : 1) to afford the product **2** (0.1 mg, 0.12 µmol, 35% yield). R_f = 0.31 (dichloromethane / methanol = 10 : 1): $[\square]^{22}_D$ = +17.0° (*c* = 0.20, MeOH); ^{1}H NMR (600 MHz, Acetone-d_6) δ ppm 0.84 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.31 (m, 2H), 1.41 (m, 1H), 1.42 (m, 1H), 1.46 (m, 1H), 1.65 (m, 1H), 1.66 (d, *J* = 0.7 Hz, 1H), 1.75 (m, 1H), 1.82 (d, *J* = 0.7 Hz, 1H), 1.84 (m, 1H), 1.87 (m, 1H), 1.95 (m, 1H), 1.98 (m, 1H), 2.22 (m, 1H), 2.23 (m, 1H), 2.27 (m, 1H), 2.33 (ddd, *J* = 14.9, 7.5, 6.8, 1H), 2.37 (m, 1H), 2.38 (m, 1H), 2.40 (d, *J* = 5.5 Hz, 1H), 2.44 (m, 1H), 3.25 (m, 1H), 3.29 (s, 3H), 3.44 (dd, *J* = 6.8, 3.8 Hz, 1H), 3.51 (m, 1H), 3.56 (m, 1H), 3.61 (s, 3H), 3.61 (dd, *J* = 7.9, 2.6 Hz, 1H), 3.72 (m, 1H), 3.81 (d, *J* = 2.6 Hz, 1H), 3.89 (m, 1H), 3.98 (d, *J* = 4.4 Hz, 1H), 4.17 (dt, *J* = 5.5, 5.5 Hz, 1H), 4.37 (ddd, *J* = 8.4, 6.8, 6.8 Hz, 1H), 4.39 (dd, *J* = 8.7, 8.3 Hz, 1H), 5.25 (d, *J* = 8.3 Hz, 1H), 5.35 (m, 1H), 5.44 (ddd, *J* = 8.5, 4.4, 4.4 Hz, 1H), 5.53 (d, *J* = 9.0 Hz, 1H), 5.71 (ddd, *J* = 14.9, 8.5, 6.2 Hz, 1H), 5.76 (ddd, *J* = 14.9, 6.8, 7.5 Hz, 1H), 6.06 (dd, *J* = 10.9, 10.9 Hz, 1H), 6.16 (dd, *J* = 14.9, 10.4 Hz, 1H), 6.24 (m, 1H), 6.25 (m, 1H), 6.31 (m, 2H), 6.33 (d, *J* = 17.9 Hz, 1H), 6.35 (m, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ ppm 7.2, 10.9, 11.1, 13.2, 15.1, 16.7, 22.2, 30.7, 33.0, 33.2, 35.2, 36.5, 37.3, 37.7, 38.6, 38.7, 39.2, 42.4, 42.8, 43.8, 51.7, 56.4, 67.9, 68.4, 69.0, 69.1, 73.5, 76.9, 79.4, 81.1, 126.0, 128.3, 129.5, 130.0, 130.9, 132.1, 132.6, 133.3, 133.6, 133.7, 133.9, 134.0, 134.1, 134.3, 135.5, 135.9, 136.2, 138.3, 173.6, 174.2; HRMS: calculated for $C_{50}H_{78}O_{11}Na$ $[M+Na]^+$: 877.5444, found 877.5442.

Etnangien 1. A solution of etnangien methyl ester **2** (1.00 mg, 1.17 µmol) in 500 µL DMSO/water = 1:3 was treated under argon at room temperature with 2 mg porcine liver esterase (obtained from

Sigma) and stirred for 24 h. The crude product was purificated by HPLC (Nucleosil 100-7 C18, 250/21; MeOH / H_2O, 0.01 M phosphate buffer = 75:25, flow: 18 mL/min; UV detection 355 nm) to give etnangien (**1**, 0.65 mg, 0.71 µmol, 61%) as a colorless oil. $[\alpha]_D^{20}$ = +16.2 (*c* = 0.65 mg/mL, MeOH) [Lit: $[\alpha]_D^{21}$ = +18.7 (*c* = 0.9, MeOH)][7];^{1}H NMR (600 MHz, Acetone-d_6) δ ppm 0.84 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.31 (m, 2H), 1.41 (m, 1H), 1.42 (m, 1H), 1.46 (m, 1H), 1.65 (m, 1H), 1.66 (d, *J* = 1.1 Hz, 1H), 1.75 (m, 1H), 1.82 (d, *J* = 0.7 Hz, 1H), 1.84 (m, 1H), 1.87 (m, 1H), 1.95 (m, 1H), 1.98 (m, 1H), 2.22 (m, 1H), 2.23 (m, 1H), 2.27 (m, 1H), 2.33 (ddd, *J* = 14.9, 7.5, 6.8, 1H), 2.37 (m, 1H), 2.38 (m, 1H), 2.40 (m, 2H), 2.44 (m, 1H), 3.25 (dddd, *J* = 6.0, 6.0, 5.6, 4.5 Hz, 1H), 3.29 (s, 3H), 3.44 (dd, *J* = 6.8, 3.8 Hz, 1H), 3.51 (tt, *J* = 8.3, 4.1 Hz, 1H), 3.56 (m, 1H), 3.61 (dd, *J* = 7.9, 2.6 Hz, 1H), 3.73 (m, 1H), 3.84 (d, *J* = 2.6 Hz, 1H), 3.89 (m, 1H), 3.98 (m, 1H), 4.17 (dt, *J* = 5.4, 6.2 Hz, 1H), 4.37 (ddd, *J* = 8.4, 6.4, 6.8 Hz, 1H), 4.39 (dd, 9.2, 7.8 Hz, 1H), 5.25 (d, *J* = 8.3 Hz, 1H), 5.35 (ddd, *J* = 10.7, 7.4, 7.4 Hz, 1H), 5.44 (m, 1H), 5.53 (m, 1H), 5.71 (ddd, *J* = 14.9, 8.5, 6.2 Hz, 1H), 5.76 (ddd, *J* = 14.9, 6.8, 7.5 Hz, 1H), 6.06 (dd, *J* = 11.2, 11.2 Hz, 1H), 6.16 (dd, *J* = 14.9, 10.4 Hz, 1H), 6.24 (m, 1H), 6.25 (m, 1H), 6.31 (m, 2H), 6.33 (d, *J* = 17.9 Hz, 1H), 6.35 (m, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ ppm 7.2, 10.9, 11.1, 13.2, 15.1, 16.7, 22.0, 30.7, 33.1, 33.2, 35.1, 36.5, 37.3, 37.8, 38.71, 38.72, 39.2, 42.3, 42.8, 43.9, 56.4, 68.1, 68.4, 69.0, 69.6, 73.5, 76.8, 79.4, 81.1, 126.0, 128.3, 129.5, 129.9, 130.9,132.1, 132.6, 133.4, 133.5, 133.7, 133.8, 134.0, 134.2, 134.3, 135.5, 135.9, 136.4, 138.6, 173.5, 174.3. HRMS: calculated for $C_{49}H_{75}O_{11}$ [M-H]: 839.5309, found: 839.5312. All data were identical to those previously reported for etnangien from *Sorangium cellulosum*.[1]

Acknowledgement. This work was supported by the 'Deutsche Forschungsgemeinschaft', the 'Wild-Stiftung' and the 'Fonds der Chemischen Industrie'. We thank Björn Wiegmann for support and Tanja Lau for early exploratory studies. Excellent NMR assistance by Markus Enders and Beate Termin is most gratefully acknowledged.

Supporting Information Available: Full experimental details and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge at http://pubs.acs.org.

References.

(1) (a) Höfle, G.; Reichenbach, H.; Irschik, H.; Schummer, D. German Patent DE 196 30 980 A1: 1-7 (5.2.1998). (b) Irschik, H.; Schummer, D.; Höfle, G.; Reichenbach, H.; Steinmetz, H.; Jansen, R. *J. Nat. Prod.* **2007**, *70*, 1060.

(2) For a recent review on polyketides from myxobacteria, see: Menche, D. *Nat. Prod. Rep.* **2008**, *25*, 905.

(3) Menche, D.; Arikan, F.; Perlova, O.; Horstmann, N.; Ahlbrecht, W.; Wenzel, S. C.; Jansen, R.; Irschik, H.; Müller, R. *J. Am. Chem. Soc.* **2008**, *130*, 14234.

(4) (a) Darst, S. *Trends Biochem. Sci.* **2004**, 29, 159. (b) Chopra, I. *Curr. Opin. Invest. Drugs* **2007**, *8*, 600. (c) Haebich D.; v. Nussbaum, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 3397.

(5) Menche, D.; Li, P.; Irschik, H. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 939.

(6) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Am. Chem. Soc.* **2009**, *131*, 11678.

(7) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911.

(8) For a review on polypropionate syntheses, see: Li, J.; Menche, D. *Synthesis* **2009**, 2293.

(9) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

(10) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.

(11) Arikan, F.; Li, J.; Menche, D. *Org. Lett.* **2008**, 3521.

(12) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Dale, L. R.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

(13) Li, J.; Menche, D. *Synthesis* **2009**, 1904.

(14) Hartung, J.; Hünig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis* **1997**, 1433.

(15) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853.

(16) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(17) Roy, C. D.; Brown, H. C. *Monatsh. Chem.* **2007**, *138*, 879.

(18) Shirakawa, K.; Arase, A.; Hoshi, M. *Synthesis* **2004**, 1814.

(19) Kabalka, G. W.; Hedgecock, H. C. *J. Org. Chem.* **1975**, *40*, 1776 and references therein.

(20) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(21) NMR-analysis of the crude product suggested the presence of formyl protons.

(22) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

(23) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, 52, 1236.

(24) Kozikowski, A. P.; Shum, P. W.; Basu, A.; Lazo, J. S. *J. Med. Chem.* **1991**, *34*, 2420.

(25) The corresponding homoallylic alcohol has previously been prepared in racemic form before: (a) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979. (b) Bonini, C.; Campaniello, M.; Chiummiento, L.; Videtta, V. *Tetrahedron* **2008**, *64*, 8766.

(26) Racherla, U. S.; Brown, H. C. *J. Org. Lett.* **1991**, *56*, 401.

(27) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (c) J. M. Seco, E. Quinoa, R. Riguera, *Chem. Rev.* **2004**, *104*, 17.

(28) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946.

(29) Zhang, X.; Houk, K. N.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 938.

(30) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(31) Ketone **10** was prepared by a slightly modified procedure of the literature: Smith III, A. B.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783. In our case, PMB-protection of (*R*)-(-)-D-Roche's ester with *p*-methoxybenzyl imidate was best done in the

presence of catalytic amount of 10-camphorsulphonic acid in dichloromethane. Notably, the reaction scale seems important for the outcome. While small-scale (86 μmol) reactions were slow (24 h for completion, ~ 60% yield), large scale (4.86 mmol) reactions proved fairly fast (< 4 h, 95% yield).

(32) Paterson, I.; Coster, M. J.; Chen, D. Y. K.; Oballa, R. M.; Wallace, D. J.; Norcross, R. D. *Org. Biomol. Chem.* **2005***, 3*, 2399.

(33) For practical purposes, it proved beneficial to rely on a stock solution of (+)-Ipc_2BCl in pentane. Prior to the reaction, the solvent was completely removed and the reagent dried for more than 2 h under high vacuum to remove any trace of HCl. The absolute configuration of the newly generated stereocenter and the degree of stereoselectivity were confirmed by Mosher ester analysis

(34) (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (b) Evans, D. A.; Chapman, K. T.; Carriera, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(35) For tin-based regioselective protections of hydroxyl groups in carbohydrate chemistry, see: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

(36) Pitsch, S.; Weiss, P. A.; Jenny, L. US Patent 5,986,084, **1999**.

(37) (a) Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun*. **1994**, 1373. (b) Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132.

(38) The TES-ether was so unpolar that removal of the byproduct Et3SiOH by flash chromatography was sometimes not complete. However, after Bz-deprotection, alcohol **39** was obtained in pure form after flash chromatography.

(39) Stork, G., Zhao, K. *Tetrahedron. Lett.* **1989***, 30*, 2173.

(40) Seyferth, D.; Heeren, J. K.; Singh, G.; Grim, S. O.; Hughes, W. B. *J. Orgnomet. Chem.* **1966**, *5*, 267.

(41) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. 1,* **2002**, 1494.

(42) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760.

(43) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(44)(a) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100. (b) Menche, D.; Hassfeld, J.; Li, J.; Mayer, K.; Rudolph, S. *J. Org. Chem.* **2009**, *74*, 7220.

(45) Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Asian J.* **2009**, *41*, 594.

(46) (a) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (c) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788. (d) Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

(47) (a) Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(48) Bestmann, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron Lett.* **1989**, *30*, 5261.

(49) An analogous Br-H exchange process has also been observed: (a) Fischer, H.; Fischer, H. *Chem. Ber.* **1966**, *99*, 658. (b) Bestmann, H. J. *Chem. Ber.* **1962**, *95*, 58.

(50) Bonnet, B.; Gallic, Y. L.; Ple, G.; Duhamel, L. *Synthesis* **1993**, 1071.

(51) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(52) Famer, L. J.; Marron, K. S.; Koch, S. S. C.; Hwang, C. K.; Kallel, E. A.; Zhi, L.; Nadzan, A. M.; Robertson, D. W.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2352.

(53) The amount of this side product may be further minimized by increasing the excess of the starting aldehyde, which may readily be recycled after the reaction.

(54) Li, J.; Li, P.; Menche, D. *Synlett* **2009**, 2417.

(55) While TBS protection was possible at this stage (TBSOTf, 2,6-Lutidine, DCM, 98%, see Supporting Information), conversion of the derived TBS ether to the Weinreb amide failed, possibly due to steric reasons.

(56) In one instance, 7 equivalents of $NaIO_4$ were added in three portions over a period of 3.5 h, giving the desired methyl ketone **49** in high yields as the main product (86%), while under similar conditions (6 equiv NaIO4, addition in one portion), the deprotected analogue **77** was obtained in high yields, see Supporting Information.

(57) Ahmed, M.; Atkinson, C. E.; Barrett, A. G. M.; Malagu, K.; Procopiou, P. A. *Org. Lett*. **2003**, *5*, 669.

(58) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Mulzer, J.; Öhler, E.; Enev. V. S.; Hanbauer, M. *Adv. Synth. Catal.* **2002**, *344*, 573. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. (d) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086.

(59) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem. Int. Ed.* **2000**, *39*, 377.

(60) There are only sporadic known successful examples of Heck macrocyclization in natural product synthesis, in particular the reaction between two simple double bonds (without electron withdrawing substituent on either alkene) appears nonexistent. In this context, our synthesis of etnangien macrocycle utilizing Heck macrocyclization here is remarkable with respect to the efficiency (yield, *E*/*Z* selectivity, atom- and step- efficiency), see also: (a) Yokoyama, H.; Satoh, T.; Furuhata, T.; Miyazawa, M.; Hirai, Y. *Synlett* **2006**, 2649. (b) Stocks, M. J.; Harrison, R. P.; Teague, S. J. *Tetrahedron Lett*. **1995**, *36*, 6555. (c) Geng, X.; Miller, M. L.; Lin, S.; Ojima, I. *Org. Lett*. **2003**, *5*, 3733.

(61) For intra-molecular Heck reactions for formation of medium size rings, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945. (b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.

(62) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(63) *trans*-1,2-Bis(tri-*n*-butylstannyl)ethylene was synthesized from commercially available tributylethynylstannane following a reported procedure: Renaldo, A. F.; Labadie, J. W.; Stille, J. K. *Org. Syn.* **1989**, *67*, 86.

(64) Takai, K .; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(65) Hodgson, D. M. *J. Organomet. Chem.* **1994**, *476*, 1.

(66) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

(67) Because of the low polarity of iodide **102**, complete removal of the excess of iodoform or its derivatives was not practical. Column-purified compound also decomposed upon storage even under argon atmosphere at -20 ^{o}C

(68) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(69) (a) Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966. (b) Sorg, A.; Brückner, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 4523.

(70) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Tetrahedron Lett.* **1998**, *39*, 6419.

(71) Smith, A. B.; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738.

(72) We slightly modified the preparation of **101**. Direct hydrostannylation of progargylic alcohol has been reported to produce a mixture of three possible isomers: *E*, *Z* and geminal bistannylated products and separation of *E*/*Z* mixture was not straightforward (see: Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851). In contrast, radical hydrostannylation of TBS protected propargyl alcohol gave little *Z* product (see: Hayes, M. P.; Hatala, P. J.; Sherer, B. A.; Tong, X.; Zanatta, N.; Borer, P. N.; Kallmerten, J. *Tetrahedron* **2001**, *57*, 1515). Therefore, propargyl alcohol was protected as TBS ether. The crude ether was directly mixed with tributyltin hydride (1.2 equiv) and catalytic amount of AIBN (3% mol) and heated at 80-85°C for 2 h and then diluted with THF and TBAF (2.0 equiv), to access pure (*E*)-stannane in 64% yield over 3 steps. Subsequent bromination under Appel reaction conditions with catalytic amounts of 2,6-lutidine (0.2 equiv) gave the corresponding allylic bromide which was used immediately for displacement by sodium salt of diethyl phosphate ($HPO(OEt)_2$, NaH), giving the required phosphonate **101** in 65% over 2 steps.

(73) At this stage, the all-(*E*) configuration of alcohol **105** was confirmed by 1H NMR (600 MHz, C6D6) analysis, revealing the characteristic coupling constants.

(74) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915.

(75) with TBAF in THF, the primary TBS could be removed in variable yields (50-85%) together with some over deprotected product even at 0 °C.

(76) The olefination product isomerizes rapidly to an *E*/*Z* = 1:1 mixture upon exposal to light.

(77) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723.

(78) Etnangien methyl ester was available from previous isolation procedures: see Ref. 3.