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Total Synthesis of Iso- and Bongkrekic Acids: Natural Antibiotics Displaying Potent Antiapoptotic Properties

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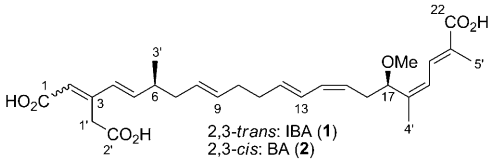
Abstract: For over five decades, owing to their antiapoptotic activities, bongkrekic and isobongkrekic acids have generated interest from the scientific community. Here, we disclose full details of our investigation into the synthesis of isobongkrekic acid, which culminated in its first preparation and features various palladium-catalysed cross-couplings and Takai olefination reactions. Access to bongkrekic acid is also reported by this route. These syntheses involve the preparation and use of new general building blocks which could find wider applications.

Keywords: anti-apoptotic · natural products · palladium cross-couplings · total synthesis

Introduction

Isobongkrekic acid (IBA) (**1**) and its more well known isomer bongkrekic acid (BA) (**2**) (Scheme 1) are poisonous antibiotics produced by *Pseudomonas cocovenenans* (or also called *Burkholderia gladioli*). Their names come from an Indonesian equivalent of tofu called tempeh bongkrèk. When prepared from contaminated coconuts this dish can cause food poisoning, and from 1951 to 1990 these intoxications caused nearly 1000 deaths in central Java.[1] The origin of this fatal response has been attributed to the presence of bongkrekic derivatives and toxoflavin.[2] The sale of tempeh bongkrèk is now prohibited by law in Indonesia.

BA and IBA were isolated in 1934[3] and 1976,[4] and the structure of BA elucidated between 1970 and 1973.[5] BA was determined to be an inhibitor of adenine nucleotide translocase (ANT), which mediates the ADP/ATP exchange in mitochondria.[6] IBA showed the same properties, albeit to a lesser extent.[7] These particular effects on mitochondria have been shown to delay the programmed cell death.[8] As a result, bongkrekic derivatives have become general tools in the elucidation of apoptosis mechanisms, appearing in more than 700 publications.[9] Still a contemporary topic, earlier this year, biosynthetic studies revealed that BA was a polyketide-derived with β-branches and terminal carboxylates both derived from acetate.[10]



Scheme 1. Isobongkrekic (**1**) and bongkrekic (**2**) acids.

To date, there have been four reported total syntheses of BA, the first by Corey and Tramontano in 1984.[11] Some 20 years later, Shindo, Shishido and co-workers devised a second route which was not without its problems.[12] Dissatisfied by this approach, these two authors recently published two different second generation syntheses in considerably improved overall yields reaching 6.5[13] and 13.7%.[14] We too became interested in this area and recently described the first total synthesis of IBA as well as the shortest route to BA reported so far.[15] Here, we describe our full investigations into the syntheses of these two natural products.

Synthetic plan: Our main objective, which distinguished our synthesis from others, was to directly target the trimethylester of IBA [IBAMe$_3$ (**3**)]; the advantage being the presumed stability of the intermediate esters which would avoid laborious sequences of protection/deprotection along the route. The risk of this strategy lies in the final saponification which might result in a loss of stereogenic integrity.

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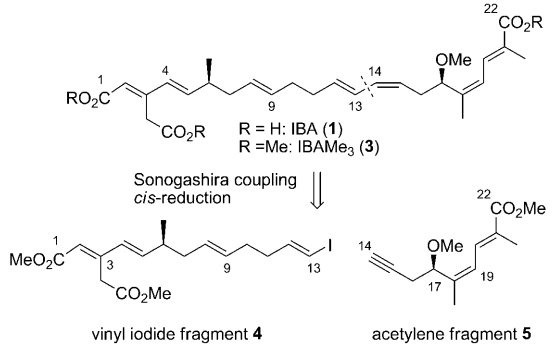
Based on this approach, it was expected that Sonogashira coupling[16] between vinyl iodide **4** and alkyne **5** and subsequent *cis*-reduction of the acetylenic bond would provide efficient access to IBAMe$_3$ (**3**) (Scheme 2). Several routes to these two fragments were investigated.



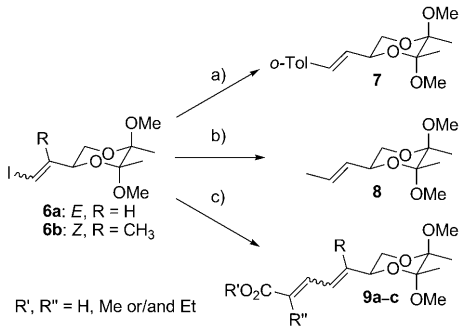
Scheme 2. Central disconnection of IBA **1**.

Results and Discussion

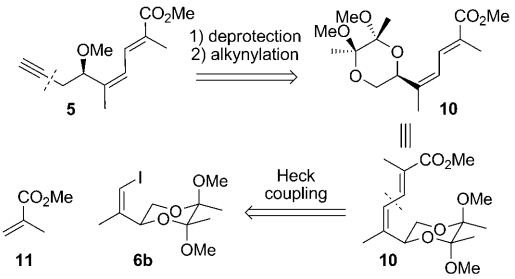
Synthesis of the acetylene fragment 5

Plan A: The initial approach to acetylene **5** was to use functionalised butanediacetal (BDA)-protected 1,2-diols **6**[17] that could be further elaborated by palladium-catalysed cross-coupling reactions. This method has been previously developed within our group (Scheme 3)[18] and exemplified in the synthesis of (−)-*epi*-pyriculol.[19] Thus, we sought to construct the *Z,E*-diene **10** through the Heck cross-coupling of partners **11** and **6b** (Scheme 4). Fragment **5** would arise from diene **10** following BDA deprotection and an appropriate alkynylation process.

Following our previously published procedures,[17,18] D-mannitol (**12**) was converted to the ketone **13** in 25% yield

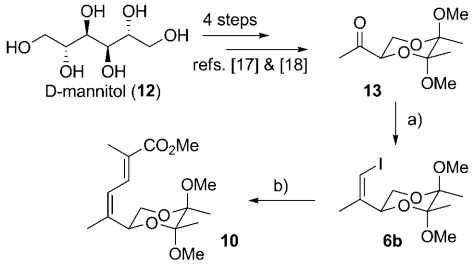


Scheme 3. Pd-catalysed cross-coupling reactions performed on two different vinyl iodide BDA-protected 1,2-diols **6a** and **6b**. a) *o*-TolB(OH)$_2$, Pd(OAc)$_2$, S-Phos, K$_3$PO$_4$, toluene, 110 °C, 4 h, 70%; b) Me$_3$B$_3$O$_3$, [PdCl$_2$(dppf)]·CH$_2$Cl$_2$, K$_2$CO$_3$, 1,4-dioxane, 110 °C, 48 h, 95%; c) R′O$_2$C(R″)C=CH$_2$, [Pd$_2$dba$_3$]/P(*t*Bu)$_3$, Cy$_2$NMe, toluene, 80–120 °C, 80–99% (yield determined by GC-MS). S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, dba = dibenzylideneacetone.



Scheme 4. Initial retrosynthesis for fragment **5**.

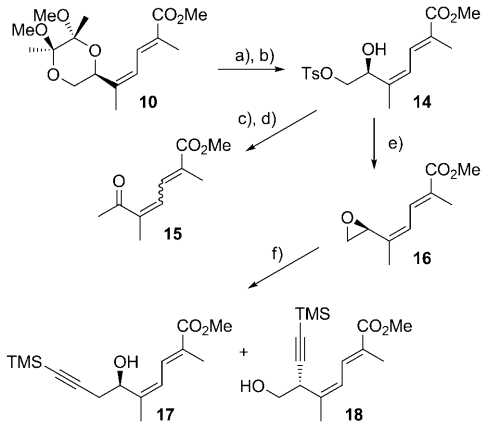
over four steps on 10 g scale (Scheme 5). Using Wittig–Stork conditions,[20] ketone **13** was converted selectively to vinyl iodide **6b**, which participated in the anticipated Heck reaction. Although undesired minor isomers were also obtained, column chromatography provided good quality *Z,E*-diene **10** but in moderate overall yield.



Scheme 5. Synthesis of intermediate **10**. a) Ph$_3$P$^+$CH$_2$I·I$^-$, NaHMDS, THF, −78 to 0 °C, 3 h, 68% (*Z*/*E* 8:1); b) H$_2$CC(Me)CO$_2$Me **11a**, [Pd$_2$dba$_3$]/P(*t*Bu)$_3$, Cy$_2$NMe, toluene, 90 °C, 15 min, 100% (*Z*/*E* 70:30). NaHMDS = sodium bis(trimethylsilyl) amide, THF = tetrahydrofuran.

Next, the BDA protecting group was removed under acidic conditions and the primary alcohol of the corresponding diol was selectively tosylated to give **14** (Scheme 6).[21] To avoid any racemisation, the free secondary hydroxyl was methylated under non-basic conditions using Meerwein's salt.[22] Subsequent nucleophilic displacement of the tosylate by lithium acetylide ethylenediamine complex was attempted under typical conditions.[23] Unfortunately, all attempts failed and only isomers of ketone **15** were isolated, presumably as a result of an elimination process transiting through the corresponding enol methyl ether. Alternatively, secondary alcohol **14** was transformed to epoxide **16**[24] and then rapidly submitted to modified Yamaguchi ring-opening conditions using BF$_3$·THF.[25] Although complete addition was achieved, the regioselectivity of the reaction was again disappointingly low favouring undesired primary alcohol **18** over compound **17** in a ratio of 2.5:1.

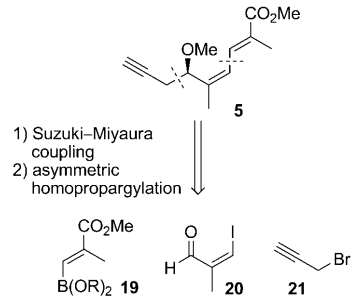
At this point therefore two clear difficulties had arisen namely the synthesis of the *Z,E*-diene and installation of the homopropargylic alcohol in **17**. Further issues arose when scaling up the Heck reaction where a poorer 1:1 ratio of *E,Z* isomers was obtained. We therefore concluded that



Scheme 6. Alkynylation issues. a) HCl (2 N), H_2O, THF, reflux, 2 h, quant.; b) TsCl, 2,4,6-collidine, CH_2Cl_2, RT, 24 h, 69%; c) Proton Sponge, Meerwein's salt, CH_2Cl_2, RT, 24 h, 60%; d) HCCLi/ethylenediamine, DMSO, RT, 1 h, 75%; e) iPr_2NEt, CH_3CN, 65 °C, 15 h, 55%; f) Me_3SiCCH, nBuLi, BF_3·THF, THF, −78 °C, 30 min, 85% conv. (**17**/**18** 1:2.5). DMSO = dimethylsulfoxide.

route was not robust enough to deliver the quantities of material necessary to progress the synthesis further.

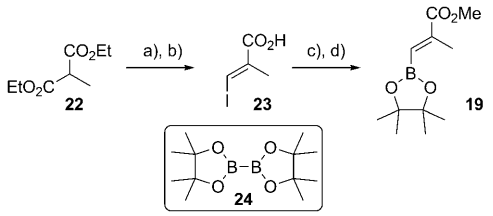
Plan B: A new strategy was investigated based upon two critical bond construction events: a) the formation of the *Z*,*E*-diene using a Suzuki–Miyaura coupling was expected to be more selective, and b) a direct asymmetric homopropargylation reaction would install the required stereogenic centre (Scheme 7). Accordingly the two coupling partners, boronic ester **19** and a synthetic equivalent for vinyl iodide **20**, were prepared by straightforward methods.



Scheme 7. Revised retrosynthesis for fragment **5**.

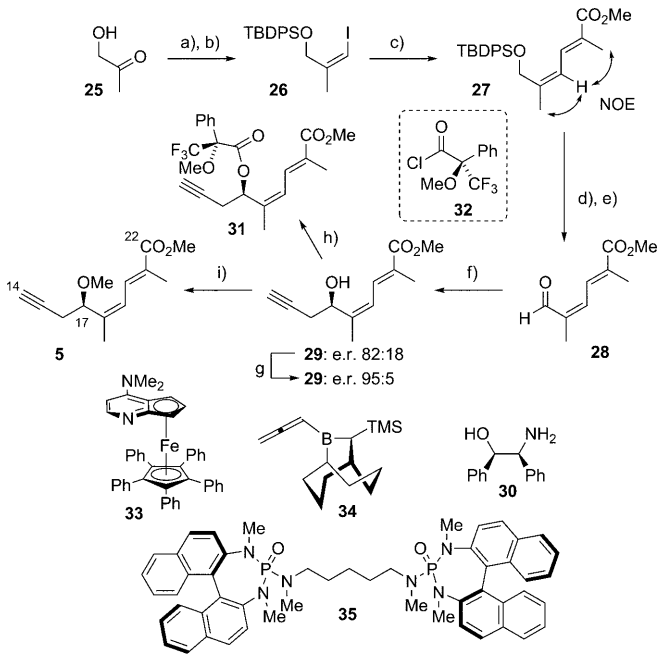
Diethyl 2-methylmalonate (**22**) was transformed via a known sequence of iodination and elimination/decarboxylation into vinyl iodide **23**.[26] After formation of the corresponding methyl ester under acidic conditions, a palladium-catalysed iodine/boronic ester exchange was performed in 84% yield (Scheme 8). This route was reproducible on larger scale and gave access to several grams of the stable boronic ester **19**.[27]

The next component was obtained from hydroxyacetone **25**, which was protected as its TBDPS ether and then converted selectively to *Z*-vinyl iodide **26** again using the Wittig–Stork conditions[20] in multigram quantities and in 69% yield over the two steps (Scheme 9). With the two fragments in hand, we turned our attention to finding suitable conditions for the proposed Suzuki–Miyaura coupling.[28] As reported in several syntheses, including those containing highly substituted dienes,[29] Kishi's modified conditions using thallous ethoxide would provide our best chance of success.[30] In the event, the reaction was stereospecific with complete formation of the desired *Z*,*E*-diene **27** in good yield (geometry confirmed by NOE studies). Moreover, by comparison to the previous Heck strategy, this reaction was reliable and reproducible on gram scale affording significant quantities of pure diene **27**. Subsequent TBDPS deprotection with TBAF[31] and Dess–Martin oxidation[32] gave the fully conjugated aldehyde **28** (Scheme 9).

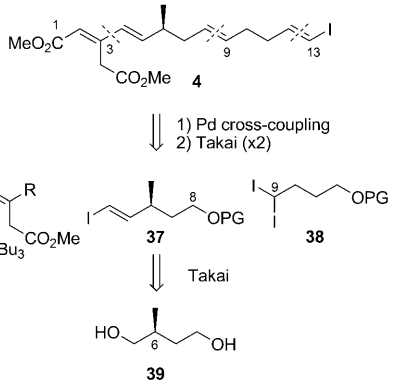


Scheme 8. Synthesis of boronic ester **19**. a) NaH, CHI_3, Et_2O, 45 °C, 24 h; b) KOH, EtOH/H_2O 4:1, reflux, 24 h, 58% over 2 steps; c) H_2SO_4 (conc.), MeOH, reflux, 15 h, 94%; d) **24**, $[PdCl_2(dppf)]$·CH_2Cl_2, KOAc, DMSO, 80 °C, 2.5 h, 84%.

At this stage, several options were available to append the homopropargylic side chain in an enantioselective fashion. We were initially attracted by the impressive yields and enantiomeric ratios described with Soderquist's asymmetric allenyl borane **34**[33] and by Denmark's allenyl stannane procedure using chiral phosphoramide ligand **35**.[34] Unfortunately, neither of these worked well in our particular situation owing to the instability of aldehyde **28**. Nevertheless, applying the mild conditions reported by Singaram,[35] using indium metal to mediate reactivity in the presence of chiral aminoalcohol **30**, the homopropargylation occurs to give **29** in good yield (91%) and an acceptable 82:18 enantiomeric ratio (e.r.) in favour of the desired product. We expected that we could improve this ratio by a variety of methods however in the end we opted to use the chemical kinetic resolution method reported by Fu et al.[36] Selective acylation of the unwanted enantiomer using acetic anhydride in the presence of the appropriate chiral iron 4-dimethylaminopyridine complex (in this case **33**)[37] provided **29** in an upgraded ratio of 95:5, which was deemed acceptable for the next steps. All enantiomeric ratios were determined by ^1H and ^{19}F NMR analysis of the corresponding Mosher ester **31** (Scheme 9).[33] At this stage, we faced the task of methylating secondary alcohol **29** without epimerising the C17 stereocentre or isomerising the *Z*,*E*-diene. Several procedures were investigated without success, including Ag_2O/MeI,[38] diazomethane derivatives[39] or Meerwein's salt in the presence of excess of Proton Sponge.[22] Ultimately, we found



Scheme 9. Synthesis of fragment **5**. a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT, 15 h; b) $Ph_3P^+CH_2I\ I^-$, NaHMDS, THF, −78 °C to RT, 4 h, 69% over 2 steps; c) **19**, $[Pd(PPh_3)_4]$, TlOEt, THF/H_2O 3:1, RT, 1 h, 91%; d) TBAF, THF, RT, 1 h, 99%; e) Dess–Martin periodinane, CH_2Cl_2, 0 °C to RT, 1 h, quant.; f) **21**, **30**, In, THF, −78 °C to RT, 24 h, 93%, e.r. 82:18; g) Ac_2O, **33** (cat.), Et_3N, *tert*-amyl alcohol, 0 °C, 48 h, 81%, e.r. 95:5; h) **32**, DMAP, THF, RT, 16 h, 82%; i) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 60 °C, 15 h, 88%. TBDPSCl = *tert*-butyldiphenylsilyl chloride, DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride, MeOTf = methyl trifluoromethanesulfonate.



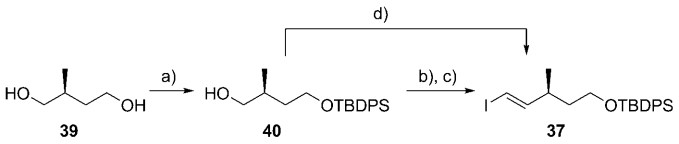
Scheme 10. Initial retrosynthesis for fragment **4**.

that treatment of alcohol **29** with methyl triflate and a hindered base[40] cleanly afforded methyl ether **5** in 88% yield without any isomerisation. In conclusion, acetylenic coupling partner **5** was obtained in 12 steps overall (Scheme 9).

Synthesis of the vinyl iodide fragment 4

First challenge: The elaboration of the 1,3-diene: We first considered a chiral pool approach to install the chiral centre at C6 using the commercially available diol **39** (Scheme 10). Vinyl iodide fragment **4** should then be obtained from the logical assembly of fragments **36a** (or **36b**), **37** and **38** via a palladium-catalysed cross-coupling, a Takai reaction and subsequent elaboration.

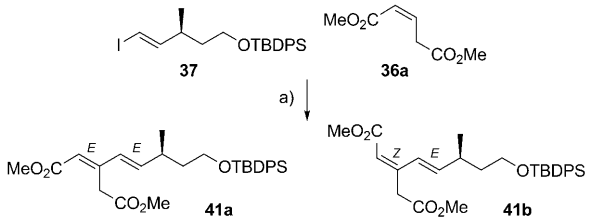
Synthesis of the central vinyl iodide **37** commenced with the low-temperature monosilylation of chiral diol **39** (Scheme 11).[41] Oxidation of alcohol **40** to the corresponding aldehyde under Parikh–Doering conditions[42] followed by Takai olefination[43] afforded vinyl iodide **37** in moderate yield. Unfortunately, this procedure was irreproducible on larger scale due to instability of the intermediate aldehyde. Drawing inspiration from our work describing a one-pot TPAP oxidation–Wittig olefination sequence,[44] a related one-pot oxidation–Takai homologation was studied. After minimal experimentation, alcohol **40** was successfully converted in good yield and in one-pot to vinyl iodide **37**. This procedure was scalable and afforded multigram quantities of the desired product.



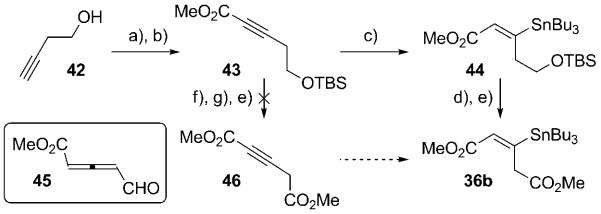
Scheme 11. Synthesis of fragment **37**. a) TBDPSCl, DBU, DMF, −50 °C, 30 min, 70%; b) SO_3·pyridine, iPr_2NEt, CH_2Cl_2, DMSO, 0 °C, 1 h, quant.; c) $CrCl_2$, CHI_3, THF, 0 °C to RT, 3 h, 45%; d) TPAP, NMO, CH_2Cl_2, 4 Å MS, RT, 15 min, then $CrCl_2$, CHI_3, THF, RT, 1.5 h, 65%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves.

We now reached the crucial stage of how best to install the geometry of the terminal 1,3-diene which distinguishes IBA **1** from BA **2**. The first and most straightforward option was a Heck coupling reaction. Few examples in the literature have described the formation of hindered 1,3-dienes via Heck reactions,[45] and coupling vinyl iodides with non-activated 1,2-substituted alkenes, such as diester **36a**, appeared to be particularly challenging. Several conditions, including those detailed by Fu,[46] Jung[47] and Roglans,[48] were unsuccessfully screened to couple dimethyl glutaconate **36a** and vinyl iodide **37**. Eventually, conditions described by Buchwald[49] proved to be the most suitable for our substrate giving a separable mixture of isomers **41a** and **41b** (4:1 ratio) in 30% yield (Scheme 12). Unfortunately, the yield for this transformation dropped to 18% on scaling to quantities greater than one gram.

Dissatisfied by these results, we elected to investigate the Stille–Migita coupling.[50] Consequently, a stereoselective synthesis of stannane **36b** was achieved based on Piers hydrostannylation process (Scheme 13).[51] 3-Butyn-1-ol (**42**) was protected as its TBS ether and the corresponding lithium acetylide added to methyl chloroformate giving multigram quantities of ester **43**.[52] At this stage, it was planned



Scheme 12. Heck cross-coupling. a) $Pd(OAc)_2$, Bu_4NBr, Cy_2NMe, DMF, 140 °C, 1 h, 24 % of **41a**, 6 % of **41b**.



Scheme 13. Synthesis of stannane **36b**. a) TBSCl, imidazole, CH_2Cl_2, 0 °C to RT, 3 h; b) $ClCO_2Me$, *n*BuLi (in hexanes), THF, −40 °C to 0 °C, 2 h, 80 % over 2 steps; c) iPr_2NH, Bu_3SnH, *n*BuLi, CuSPh, THF/MeOH, 0 °C to −100 °C to 0 °C, 4 h, 85 %; d) H_2CrO_4, acetone, 0 °C, 10 min, 68 %; e) $TMSCHN_2$, CH_2Cl_2/MeOH, 40 min, quant.; f) PPTS, MeOH, RT, 15 h, 92 %; g) several oxidation methods, failed. TBSCl = *tert*-butyldimethylsilyl chloride, $TMSCHN_2$ = trimethylsilyldiazomethane, PPTS = pyridinium *para*-toluenesulfonate.

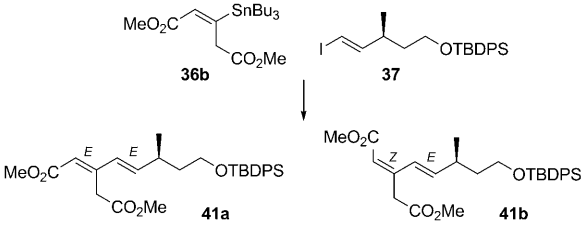
to perform the key hydrostannylation with diester **46** in order to minimize the hazardous manipulation of the stannane derivatives. After a successful deprotection, the corresponding alcohol was subjected to many different oxidation procedures: Swern,[53] TPAP/NMO,[54] TEMPO,[55] Dess–Martin,[32] PCC,[56] and Jones[57] oxidation. None of these afforded the desired oxidised product and led to degradation or to the corresponding allenyl aldehyde **45**. Consequently, the stereo- and regioselective hydrostannylation was performed on the alkyne **43**. Again, several methods of silyl deprotection and oxidation were screened. Surprisingly, this was eventually and smoothly achieved in one step under Jones' conditions affording the corresponding carboxylic acid[58] which was subsequently esterified with trimethylsilyldiazomethane.[59] Stannane **36b** was then obtained on a gram scale by this reliable five-step sequence in an overall yield of 46 %.

The coupling of fragments **37** and **36b** via the Stille–Migita reaction for hindered dienes was investigated using three different procedures (Table 1, entries 1–3).[60,61] Fürstner's conditions,[61] which employ a phosphonate salt as a tin scavenger, were the most promising (entry 3). Modification of the catalyst loading (entry 4) and reaction time (entry 5) allowed the coupling to proceed in an encouraging 75 % yield. Unfortunately, the reaction always delivered a 3:2 mixture of isomers **41a** and **41b**; however, these could be readily separated by conventional chromatography. Surprisingly, the *E*,*E*-diene was less thermodynamically stable than expected (this might also account for the stability and geometry of BA found in the nature). On larger scale, the addition of triethylamine at the end of the reaction (entry 6) proved to be the most efficient and convenient way to obtain an equilibrium 3:1 mixture. By this method *E*,*E*-diene **41a** could be isolated in an acceptable 60 % yield.

With effective access to the *E*,*E*-diene secured it was necessary to verify the stereochemical integrity of the methyl group. Diene **41a** was deprotected with methanolic HCl[31] (TBAF led to decomposition) and the resulting alcohol **47** was converted to Mosher ester **48**.[33] Based on ^1H and ^{19}F NMR analysis, an e.r. of >95:5 was determined. Comforted by this observation, alcohol **47** was quantitatively oxidised under Dess–Martin conditions[32] to the corresponding aldehyde **49**, ready for further homologation (Scheme 14).

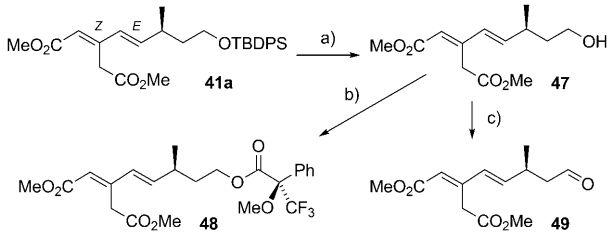
Second challenge: a long elongation: In compliance with our initial strategy (Scheme 10), the partner **38** for the Takai coupling was obtained from butanediol **50** by a sequence of a monoprotection, TPAP oxidation and transformation of the aldehyde **25** to *gem*-diiodide **38** using Sternhell's proto-

Table 1. Results of the Stille–Migita coupling between fragments **37** and **36b**.



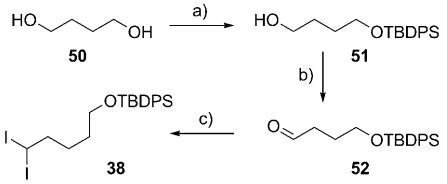
Entry	Pd cat. [mol %]	Additives	Conditions	Yield [%] **41a** and **41b**	**41a**/**41b** ratio[a]
1[60a]	$[(CH_3CN)_2PdCl_2]$ (10 mol %)	–	RT, 16 h	<10[b]	–
2[60b]	–	CuTC	0 °C→RT, 1 h	50[b]	1:1
3[61]	$[Pd(PPh_3)_4]$ (0.6 mol %)	CuTC $Ph_2PO_2NBu_4$	RT, 2 h	50[b]	3:2
4	$[Pd(PPh_3)_4]$ (5 mol %)	CuTC $Ph_2PO_2NBu_4$	RT, 2 h	62[b]	3:2
5	$[Pd(PPh_3)_4]$ (5 mol %)	CuTC $Ph_2PO_2NBu_4$	RT, 1 h	75[b]	3:2
6	$[Pd(PPh_3)_4]$ (5 mol %)	CuTC $Ph_2PO_2NBu_4$	RT, 1 h	80[c]	3:1

[a] Calculated from isolated yields of the two products. [b] Performed on 0.3 mmol. [c] Performed on 1.3 mmol and subsequent treatment with Et_3N, RT, 30 min. CuTC = copper thiophene-2-carboxylate



Scheme 14. Synthesis of aldehyde **49**. a) HCl 1.25 M in MeOH, RT, quant.; b) **32**, DMAP, THF, RT, 16 h, 86%; c) Dess–Martin periodinane, 0°C to RT, CH_2Cl_2, quant.

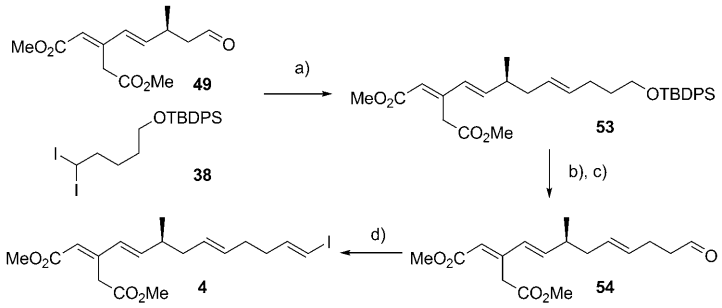
col (Scheme 15).[62] The low yield obtained in the last step was consistent with those previously reported.[62] It is noteworthy that the yield for the oxidation was significantly improved (63 to 97%) by employing freshly prepared TPAP.[63]



Scheme 15. Synthesis of *gem*-diodide **38**. a) TBDPSCl, *i*Pr_2NEt, CH_2Cl_2, RT, 2 h, quant.; b) TPAP (cat), NMO, CH_2Cl_2, RT, 1 h, 97%; c) H_2NNH_2, H_2O, 0°C, 45 min, then I_2, Et_3N, CH_2Cl_2, 5 min, 36%.

Next, the Takai reaction[64] between aldehyde **49** and *gem*-diiodide **38** was performed in a highly stereoselective fashion with relative ease. Triene **53** was TBDPS deprotected and oxidised under Dess–Martin conditions. Aldehyde **54** was converted to *E*-vinyl iodide **4** using a second Takai reaction (Scheme 16).[43] In summary, the coupling fragment **4** was obtained in 17 steps (12 steps longest linear sequence) and 8.5% overall yield.

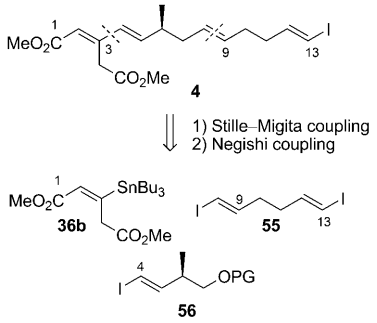
Although this result was acceptable, a shorter route based on a $C(sp^2)$–$C(sp^3)$ Negishi coupling[65] using bis(vininyl iodide) **55**[66] was also investigated (Scheme 17). When used



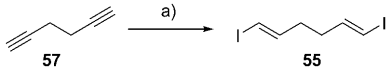
Scheme 16. Synthesis of vinyl iodide fragment **4**. a) $CrCl_2$, THF, RT, 15 h, 61%; b) HCl 1.25 M in MeOH, RT, 85%; c) Dess–Martin periodinane, CH_2Cl_2, RT, 4 h; d) $CrCl_2$, CHI_3, THF, 0°C to RT, 3 h, 69% over 2 steps.

in excess, this linker allows direct elongation of both termini.

Linker fragment **55** was obtained efficiently following the double Schwartz dihydrozirconation and in situ iodinolysis[67] of 1,5-hexadiyne **57** (Scheme 18).



Scheme 17. Second retrosynthesis for fragment **4**.

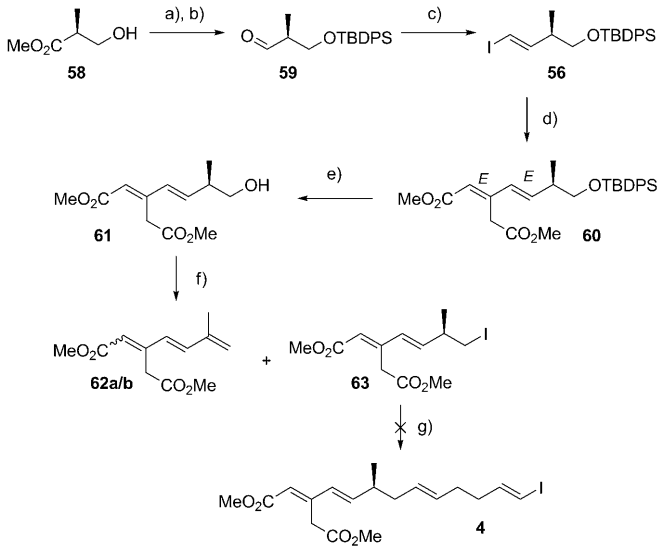


Scheme 18. Synthesis of linker **55**. a) Cp_2ZrHCl, I_2, THF, 40°C, 10 min, 84%.

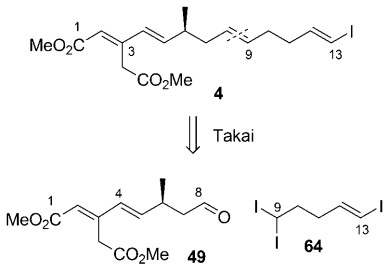
Next, the synthesis of alkyl iodide **63** commenced with the TBDPS protection of Roche ester **58** followed by DIBAL-H reduction of the ester to aldehyde **59** (Scheme 19). Aldehyde **59** was then converted to *E*-vinyl iodide **56** using a Takai olefination. Under the Stille–Migita coupling conditions developed during our first approach, *E*,*E*-diene **60** was isolated in a similar 61% yield. Surprisingly, and in contrast to our initial route, TBDPS deprotection proceeded smoothly and without any degradation using TBAF.[31] However, subsequent iodination of the resulting alcohol[68] gave the alkyl iodide **63** in only 30% yield. This disappointing result was partly explained by a side reaction which resulted in the formation of the two conjugated 1,3,5-trienes **62a** and **62b**. Despite this problem and with alkyl iodide **63** in hand, the Negishi coupling with *bis*-vinyl iodide **55** was attempted. Unfortunately, none of the conditions[69] screened provided the desired vinyl iodide fragment **4**. We were therefore forced to consider a new route, which also necessitated the preparation of a new linker fragment.

The bidirectional coupling partner **64** was designed in order to overcome the synthetic issues of the previous route (Scheme 20). This promising new triiodide coupling unit, with its orthogonal reactivity, should allow us to install the unsymmetrical hexa-1,5-diene fragment (a common subunit to a number of natural products)[70] in an efficient and interesting manner and was expected to find application in other syntheses.

Pentynyl alcohol **65** was transformed selectively into the corresponding *E*-vinyl iodide (Scheme 21).[71] Following unsuccessful attempts with TPAP/NMO[54] and Swern[53] condi-



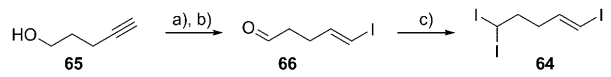
Scheme 19. Attempted synthesis of vinyl iodide fragment **4** via Negishi coupling. a) TBDPSCl, imidazole, 0°C to RT, 1 h, 99%; b) DIBAL-H, Et_2O, −78°C, 1 h, 70%; c) $CrCl_2$, CHI_3, THF, 0°C to RT, 2 h, 80%; d) **36b**, $[Pd(PPh_3)_4]$, CuTC, $Ph_2PO_2NBu_4$, DMF, RT, 30 min, then Et_3N, RT, 1 h, 61%; e) TBAF, THF, 0°C to RT, 1 h, 96%; f) PPh_3, I_2, imidazole, CH_2Cl_2, 50°C, 15 h, **62a/b**: 50% and **63**: 37%; g) **55**, $ZnCl_2$, *t*BuLi, $[Pd(PPh_3)_4]$, Et_2O, −78°C to RT, 15 h, failed. DIBAL-H = diisobutylaluminium hydride.



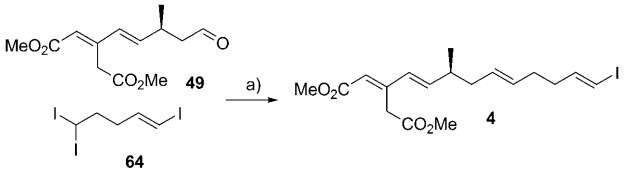
Scheme 20. Final retrosynthesis for fragment **4**.

tions, the primary alcohol was efficiently oxidised with PCC.[56] Then, aldehyde **66** was converted to triiodide **64** under the Sternhell conditions.[62] Importantly, this sequence was reproducible on gram scale and afforded reasonably clean and stable material to proceed the synthesis.

At last, the Takai coupling[64] between fragments **49** and **64** gave *E*-vinyl iodide **4** selectively and in good yield (Scheme 22). In summary, this final route afforded key coupling fragment **4** in a scalable and reliable fashion with an overall yield of 20.8% after 14 steps (9 steps longest linear sequence).



Scheme 21. Synthesis of triiodide **64**. a) DIBAL-H, THF, −20°C to RT, 15 h then I_2, −78°C to RT, 30 min, 56%; b) PCC, CH_2Cl_2, 0°C, 6 h, 95%; c) $NH_2NH_2{\cdot}H_2O$, RT, 1 h then Et_3N, I_2, RT, 10 min, 40%. PCC = pyridinium chlorochromate.



Scheme 22. Completion of vinyl iodide fragment **4**. a) $CrCl_2$, THF, RT, 4.5 h, 79%.

Completion of the synthesis

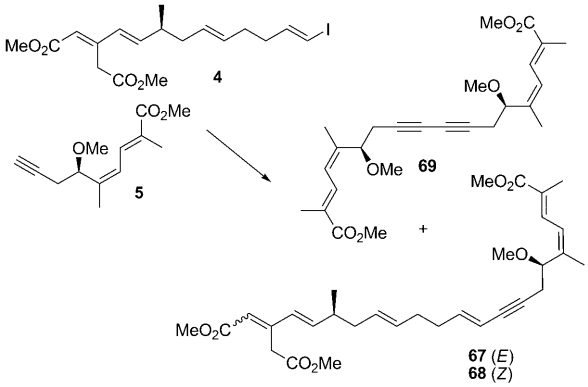
We hoped now that the effort invested in the preparation of fragments **4** and **5** would be rewarded by their successful union via Sonogashira coupling[16] (Table 2). Firstly, application of Hoye conditions[72] employing $[Pd(PPh_3)_4]$ resulted in only 18% of the desired coupled products with 50% recovery of vinyl iodide **4** (entry 1). By increasing the stoichiometry of the catalyst, copper source and base, total conversion was achieved and the desired enynes **67**/**68** could be isolated in a 53% yield (entry 2). Unfortunately, the reaction was accompanied by the significant formation of dimer **69** resulting from a Glaser coupling.[73] This type of side reaction normally occurs in presence of O_2 and consequently, the reaction was performed in degassed THF with $[PdCl_2(PPh_3)_2]$ as catalyst. The yield in Glaser product was decreased as was the conversion to Sonogashira product **67**/**68** (entry 3). Finally, by using the base as solvent[74] the dimer product was significantly decreased from the product mixture (entry 4). This resulted in a reliable 74% yield of eneynes **67**/**68**. Furthermore, the ratio between the two separable isomers was 3:1 in favour of the desired **67**. Unfortunately, the Glaser dimer **69** was inseparable from **67**. As a result, the global mixture of **67**, **68** and **69** was carried through the next synthesis step.

In their synthesis of BA (**2**), Corey and Tramontano[11] reported the chemoselective *cis*-reduction of the alkyne function by Lindlar hydrogenation.[75] However, in our hands, the reaction required high catalyst loading and H_2 pressures, which frequently led to unpredictable and significant over-reduction. We therefore choose the Avignon–Tropis–Bolland[76] method, as this had successfully been applied to our synthesis of (−)-valilactone.[77] Pleasingly, the reaction proceeded in almost quantitative yield and the two isomers $IBAMe_3$ (**3**) and $BAMe_3$ (**70**) were readily separated for analytical purposes (Scheme 23). However, the 4:1 mixture was used directly in the final hydrolysis experiments as some double bond isomerisation was also expected under these conditions.

For this final hydrolysis of the trimethylester substrates we screened various hydroxide sources (Table 3).

Firstly, and following the work of Corey,[11] the use of nBu_4NOH was investigated. Unfortunately, a very complex and inseparable mixture was obtained and no IBA (**1**) or BA (**2**) could be detected (entry 1). Next, we used LiOH in a H_2O/THF mixture (entries 2 and 3)[78] and promisingly, traces of the desired products were observed. Further investigation of LiOH in another biphasic H_2O/DME mixture[79]

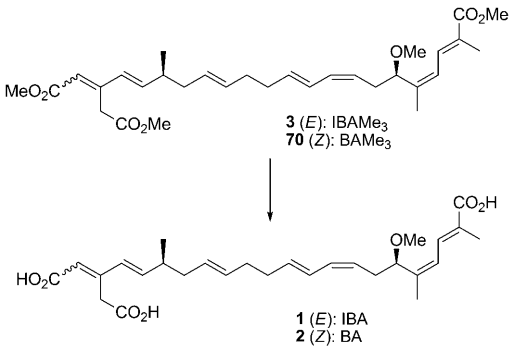
Table 2. Results of the Sonogashira coupling between fragments **4** and **5**.



Entry	Pd cat. [mol%]	Additives	Conditions[a]	Yield [%] **67**/**68**[b] (% of recov. **4**)
1[72]	$[Pd(PPh_3)_4]$ (10 mol%)	CuI (0.2 equiv) Et_3N (5 equiv)	THF, RT, 16 h	18 (SM: 50)
2	$[Pd(PPh_3)_4]$ (20 mol%)	CuI (1.2 equiv) Et_3N (10 equiv)	THF, RT, 5 h	53
3	$[PdCl_2(PPh_3)_2]$ (20 mol%)	CuI (1.2 equiv) Et_3N (5 equiv)	THF,[c] RT, 5 h	38 (SM: 20)
4[74]	$[PdCl_2(PPh_3)_2]$ (10 mol%)	CuI (0.2 equiv) Et_3N (solvent)	Et_3N, RT, 2.5 h	74

[a] Performed on 0.07 mmol of **4** with 1.5 equiv of **5**. [b] Estimated by ^{1}H NMR from the mixture with dimer **69** [c] Degassed THF. SM = starting vinyl iodide **4**.

Table 3. Results towards IBA (**1**) and BA (**2**).



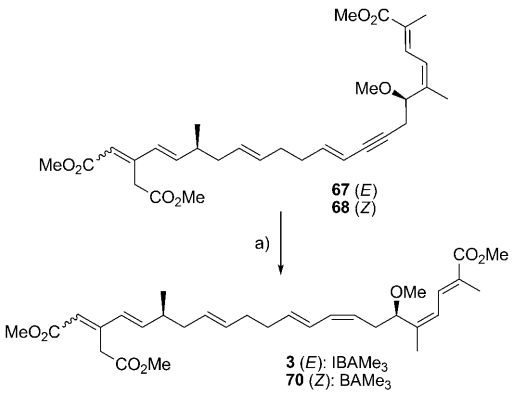
Entry	Base	Conditions[a]	Yield [%] **1**/**2**[b]
1[11]	nBu_4NOH (5 equiv) 0.5 M	H_2O/MeOH 1:1, 0 °C → RT, 24 h	–
2[78]	LiOH (5 equiv) 1 M	H_2O/THF 1:1, 0 °C → RT, 24 h	incomplete
3	LiOH (45 equiv) 1 M	H_2O/THF 1:1, 0 °C → RT, 24 h	traces
4[79]	LiOH (100 equiv) 1 M	H_2O/DME 1:4, RT, 1 h	31:23
5[4]	KOH (100 equiv) 2 M	H_2O, 100 °C, 48 h	31:12
6	LiOH (100 equiv) 2 M	H_2O, 100 °C, 5 h	24:14
7	KOH (100 equiv) 0.2 M	H_2O/DME 1:4 RT, 8 h	35:17

[a] Performed on 0.4 mmol of starting 4:1 mixture. [b] Calculated from isolated yields of the two products. DME = 1,2-dimethoxyethane.

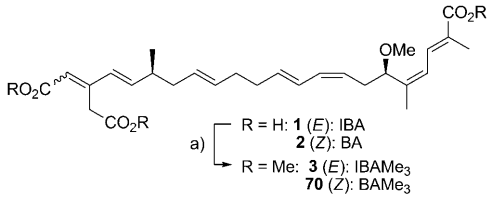
provided **1** and **2** in a combined 54% yield (entry 4). Regrettably, the initial 4:1 mixture degraded under these conditions to a 3:2 mixture of **1**/**2**; however, a 23% yield of BA (**2**) was deemed acceptable in comparison to previous results and when considering the sensitivity of the substrate. During the isolation of IBA, Vignais and co-workers[4] achieved interconversion between the two natural products **1** and **2** using aqueous KOH at 100 °C. In our hands, **1** and **2** resisted isomerisation even under these drastic conditions. They were isolated in acceptable yields and better ratios using either aqueous KOH (entry 5) or aqueous LiOH (entry 6). Revisiting the promising biphasic H_2O/DME conditions but with KOH as a base afforded pure IBA (**1**) and BA (**2**) in 35 and 17% yield, respectively, our best result so far (entry 7).

Fortunately, also, separation of the isomers was achievable using preparative TLC. Finally, however, it was important to check for any epimerization of the C6 and C17 stereocentres arising from these harsh conditions. Both IBA (**1**) and BA (**2**) were reconverted separately and quantitatively to their corresponding trimethylester $IBAMe_3$ (**3**) and $BAMe_3$ (**70**) (Scheme 24),[59] and both gave analytical data including optical rotation in accord with the original substrates prior to their saponification.

Whilst our synthetic materials are in complete accordance with the spectroscopic data presented in the literature, data discrepancies do occur in the optical rotational measurements for IBA (**1**). For completeness, we have summarised this data in Table 4. Firstly, we observe that all optical rotation data arising from synthetic materials match for the BA (**2**) series. However, significant deviation (both in sign and magnitude) is evident when comparing these data to that of the isolation chemists.[80] In the original isolation publications key analyses were performed at very low concentrations and in aqueous or partially alcoholic solvents. We suggest that this is both unnecessary and inappropriate[81] and leads us to believe that the natural products might have been isolated as various carboxylate salts. This could explain the differences between our measured optical rotation values and those presented in the literature.



Scheme 23. Synthesis of $IBAMe_3$ **3**. a) Zn(CuAg), $MeOH/H_2O$ 1:1, 65 °C, **3** + **70**: 99 %, ratio **3**/**70**: 4:1.



Scheme 24. Re-esterification of IBA and BA. a) $TMSCHN_2$, CH_2Cl_2/MeOH 5:1, quant.

Table 4. Specific rotation values $[\alpha]_D^{25}$.

References	BA (**2**)	$BAMe_3$ (**70**)	IBA (**1**)	$IBAMe_3$ (**3**)
Corey[11]	–	+80	–	–
Shindo[13]	−51.3	+81.5	–	–
Shishido[14]	−51.9	+87.1	–	–
natural products[4b,82]	+105	–	+93.8	+27.8
this work	−47.2	+81.2	+55.5	+110

Conclusion

The first total synthesis of isobongkrekic acid (**1**) has been completed. This highly convergent route required only 13 steps from commercially available materials in the longest linear sequence, required only 29 steps in total and afforded (**1**) in 7.0 % yield. We have also accessed bongkrekic acid (**2**) in 4.7 % yield, which compares favourably to recently published syntheses.[83] Furthermore, the triiodide **64** has been developed as a new and effective bidirectional coupling partner that is of particular interest owing to its orthogonal reactivity. This linchpin component should find application in other complex molecule syntheses where bis skipped diene components appear as structural motifs.

Experimental Section

General methods: Solvents were freshly distilled before use. All non-aqueous reactions were performed under an atmosphere of argon and carried out using oven-dried glassware. PE = petroleum ether b.p. 40–60 °C. Optical rotations were measured using a Perkin–Elmer model 343 polarimeter with the sample temperature maintained at 25 °C. Concentration of the sample is quoted in units of 0.01 g cm^{-3}. ^{1}H NMR spectra were recorded at room temperature on Bruker Avance TXI-700 cryoprobe (700 MHz), DRX-600 (600 MHz), and DPX-400 (400 MHz, $CDCl_3$) spectrometers as solution in deuterated chloroform. The chemical shift δ are reported in ppm relative to tetramethylsilane. Residual $CHCl_3$ (δ_H = 7.26 ppm, singlet) was used as an internal standard. The multiplicity of signals is designated by the following abbreviations: s, singlet, brs, broad singlet, d, doublet, bd, broad doublet, t, triplet, q, quartet, quint, quintet, sex, sextet, m, multiplet. Coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were recorded at 100 or 125 MHz on Bruker DPX-400 or Bruker Avance DPX-500 cryoprobe instruments, respectively. Spectra were recorded as dilute solution in deuterated chloroform, with chemical shifts reported relative to residual $CHCl_3$ (δ_C = 77 ppm, triplet). NMR spectra were assigned using information ascertained from DEPT, COSY, HMBC, HMQC and NOE experiments. In order to facilitate a straightforward comparison between data, NMR assignments follow the standard numbering of the natural product (cf. Scheme 1). IR spectra were recorded on a Perkin–Elmer Spectrum I FTIR spectrometer. The samples were prepared as thin films. Only selected absorbances (ν_{max}) are reported in cm^{-1}. High resolution mass spectra (HRMS) were obtained on a Water LCT Premier spectrometer with micromass MS software using electrospray ionisation (ESI). Flash chromatography was carried out using silica gel Breckland 60 (0.040–0.063). Florisil refers to 200–300 mesh Florisil (BDH). Celite refers to Fluka Celite 545 coarse. Analytical and preparative TLCs were performed on a 0.25 mm thickness plates pre-coated with Merck Kieselgel 60 F_{254} silica gel. TLC were visualised under UV (254 nm) and by oxidative staining with aqueous acidic ammonium molybdate(VII) solution. All intermediates and final compounds were stored under argon at −20 °C.

Boronic ester 19: To a solution of carboxylic acid **23**[26] (8.0 g, 37.7 mmol) in MeOH (24 mL) at RT was added concentrated H_2SO_4 (0.8 mL). The reaction was stirred for 15 h at 100 °C before removal of volatiles under vacuum. Crude was dissolved in CH_2Cl_2 (30 mL) and reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum to give the corresponding methyl ester as a brown oil (8 g, 94 %). R_f = 0.8 (PE/Et_2O 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 1.0 Hz, 1H, H20), 3.76 (s, 3H, OCH_3 ester), 2.07 ppm (d, *J* = 1.0 Hz, 1H, H5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (C22), 139.5 (C21), 98.6 (C20), 52.4 (OCH_3 ester), 20.3 ppm (C5′); IR (film): ν_{max} = 2952, 2923, 2854, 1717, 1601, 1435, 1380, 1289, 1215, 1098, 948, 836, 726, 683 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_5H_7O_2INa$: 248.9388; found: 248.9391 $[M+Na]^+$.

To a solution of this methyl ester (2.96 g, 13.1 mmol, 1 equiv), bis(pinacolato)diboron (6.65 g, 26.2 mmol, 2 equiv) and KOAc (2.57 g, 26.2 mmol, 2 equiv) in DMSO (45 mL) under argon at RT was added $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (95 mg, 0.13 mmol, 10 mol %). The reaction was stirred for 2.5 h at 80 °C. Then H_2O (90 mL) was added and the aqueous layer was extracted with Et_2O (4 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude brown solid by flash chromatography (PE/Et_2O 95:5) gave the pure boronic ester **19** as a colourless oil (2.5 g, 84 %). R_f = 0.65 (PE/Et_2O 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (d, *J* = 0.7 Hz, 1H, H20), 3.70 (s, 3H, OCH_3 ester), 2.10 (d, *J* = 0.7 Hz, 1H, H5′), 1.24 ppm (s, 12H, CH_3 pinacol); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2 (C22), 147.0 (C21), 127.0 (small brs, C20), 83.5 (2C, Cq pinacol), 52.0 (OCH_3 ester), 24.8 (4C, CH_3 pinacol), 17.0 ppm (C5′); IR (film): ν_{max} = 2656, 2925, 2872, 2855, 1716, 1682, 16274, 1436, 1378, 1330, 1260, 1212, 1150, 1114, 1076, 1011, 962, 880, 831, 748, 673 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{11}H_{19}O_4BNa$: 249.1274; found: 248.9657 $[M+Na]^+$.

Vinyl iodide 26: To a solution of hydroxyacetone (2.8 mL, 36 mmol, 1 equiv), Et_3N (6.1 mL, 44 mmol, 1.2 equiv) and DMAP (30 mg, 0.25 mmol, 0.7 mol %) in CH_2Cl_2 (15 mL) under argon at RT was added dropwise TBDPSCl (9.4 mL, 36 mmol, 1 equiv). The reaction was stirred for 15 h at RT and quenched afterwards with a saturated aqueous solu-

tion of NH_4Cl. The aqueous layer was extracted with Et_2O (2×80 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum to give the expected silyl ether as a colourless oil (11.42 g) clean enough to proceed the next step.

To a solution of the Wittig–Stork salt[20,84] (23.2 g, 44 mmol, 1.2 equiv) in THF (105 mL) under argon at RT was added dropwise a 1 M solution of NaHMDS (44 mL, 44 mmol, 1.2 equiv) in THF. After the reaction mixture was stirred for 5 min to get complete solubilisation, the reaction was cooled at −78 °C and a solution of the silyl ether (11.4 g, ca. 36 mmol, 1 equiv) in THF (55 mL) was added slowly. Then reaction was stirred for 45 min at −78 °C, 3 h at RT and quenched afterwards with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with Et_2O (4×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude brown oil by flash chromatography (PE/Et_2O 100:0 → 95:5) gave vinyl iodide **26** as a yellow oil (10.78 g, 69% over 2 steps). R_f=0.85 (PE/Et_2O 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.60 (m, 4H, H_{ar}), 7.48–7.35 (m, 6H, H_{ar}), 5.87 (s, 1H, H19), 4.30 (s, 2H, H17), 2.00 (s, 3H, H4′), 1.07 ppm (s, 9H, CH_3 (*t*Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 135.6, 133.4, 127.8 (12C, C_{ar}), 129.7 (C18), 72.7 (C19), 69.3 (C17), 26.9 (3C, CH_3 (*t*Bu)), 21.7 (C4′), 19.3 ppm (Cq (*t*Bu)); IR (film): ν_{max} = 3071, 3050, 2957, 2930, 2856, 1472, 1427, 1376, 1283, 1261, 1188, 1139, 1106, 1087, 1051, 1021, 953, 819, 737, 999, 669; HRMS (ESI+): *m*/*z*: calcd for $C_{20}H_{25}OSiINa$;: 459.0617; found: 459.0604 $[M+Na]^+$.

Diene 27: To a solution of vinyl iodide **26** (1.67 g, 3.84 mmol, 1 equiv) and boronic ester **19** (1.3 g, 5.76 mmol, 1.5 equiv) in THF/H_2O 3:1 (125 mL) under argon at RT was added $[Pd(PPh_3)_4]$ (444 mg, 0.38 mmol, 10 mol%). The reaction was stirred for 5 min in the dark before adding dropwise TlOEt (490 μL, 6.91 mmol, 1.8 equiv). After a 1 h stirring at RT, more $[Pd(PPh_3)_4]$ was added (222 mg, 0.19 mmol, 5 mol%) and reaction was stirred for an additional hour still in the dark. Then, the resulting suspension was filtered through a pad of celite and rinsed with Et_2O (300 mL). The aqueous layer was extracted with Et_2O (2×40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude dark brown oil by flash chromatography (PE/Et_2O 97:3) gave diene **27** as a yellow oil (1.44 g, 91%). R_f=0.3 (PE/Et_2O 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.65 (m, 4H, H_{ar}), 7.47–7.35 (m, 6H, H_{ar}), 7.32 (d, *J*=12.0 Hz, 1H, H20), 6.16 (d, *J*=12.0 Hz, 1H, H19), 4.40 (s, 2H, H17), 3.70 (s, 3H, OCH_3 ester), 2.00 (s, 3H, H5′), 1.92 (s, 3H, H4′), 1.07 ppm (s, 9H, CH_3 (*t*Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (C22), 145.5 (C18), 135.6, 135.5, 133.4, 129.8, 129.7, 127.8 (12C, C_{ar}), 133.1 (C20), 125.6 (C21), 121.8 (C19), 63.0 (C17), 51.6 (OCH_3 ester), 26.8 (3C, CH_3 (*t*Bu)), 22.4 (C4′), 19.3 (Cq (*t*Bu)), 12.3 ppm (C5′); IR (film): ν_{max} = 3051, 2931, 1894, 2857, 1706, 1640, 1604, 1428, 1377, 1325, 1254, 1199, 1109, 1073, 1027, 957, 941, 823, 807, 739, 700 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{25}H_{33}O_3Si$: 409.2193; found: 409.2190 $[M+H]^+$.

Aldehyde 28: To a solution of diene **27** (1.3 g, 3.19 mmol, 1 equiv) in THF (33 mL) under argon at 0 °C was added dropwise a 1 M solution of TBAF (6.4 mL, 6.37 mmol, 12 equiv) in THF. The reaction was stirred for 1 h at 0 °C and quenched afterwards with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with Et_2O (2×40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude yellow oil by flash chromatography (PE/Et_2O 1:1) gave the corresponding primary alcohol as a yellow oil (540 mg, 99%). R_f=0.2 (PE/Et_2O 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J*=12.0 Hz, 1H, H20), 6.21 (d, *J*=12.0 Hz, 1H, H19), 4.34 (brs, 2H, H17), 3.74 (s, 3H, OCH_3 ester), 1.98 (s, 3H, H5′), 1.92 ppm (s, 3H, H4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (C22), 145.3 (C18), 132.8 (C20), 126.3 (C21), 122.8 (C19), 61.5 (C17), 51.8 (OCH_3 ester), 22.3 (C4′), 12.6 ppm (C5′); HRMS (ESI+): *m*/*z*: calcd for $C_9H_{14}O_3Na$: 193.0841; found: 193.0839 $[M+Na]^+$.

To a solution of this alcohol (540 mg, 3.19 mmol, 1 equiv) in CH_2Cl_2 (23 mL) under argon at 0 °C was added Dess–Martin periodinane (1.62 g, 3.83 mmol, 1.2 equiv). The reaction was stirred for 1 h at RT and cooled at 0 °C before addition of PE (25 mL). The white suspension is then filtered through a pad of silica (PE/Et_2O 1:1 (300 mL)). The volatiles were removed under vacuum to give the expected aldehyde **28** as a yellow oil (536 mg, quant). R_f=0.6 (PE/Et_2O 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.40 (s, 1H, H17), 8.63 (d, *J*=12.6 Hz, 1H, H19), 7.20 (d, *J*=12.6 Hz, 1H, H20), 3.79 (s, 3H, OCH_3 ester), 2.04 (s, 3H, H5′), 1.94 ppm (s, 3H, H4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 190.4 (C17), 168.1 (C22), 139.8 (C18), 137.9 (C20), 133.2 (C21), 129.1 (C19), 52.3 (OCH_3 ester), 17.2 (C4′), 12.6 ppm (C5′); HRMS (ESI+): *m*/*z*: calcd for $C_9H_{12}O_3Na$: 191.0684; found: 191.6088 $[M+Na]^+$.

Alkyne 29: To a solution of indium (467 mg, 4.08 mmol, 2 equiv), chiral aminoalcohol **30** (868 mg, 4.08 mmol, 2 equiv) and pyridine (330 μL, 4.08 mmol, 2 equiv) in THF (24.5 mL) under argon at RT was slowly added propargyl bromide (450 μL, 4.08 mmol, 2 equiv). The cloudy suspension was stirred for 30 min with formation of a coin of indium. Then, more indium (233 mg, 2.04 mmol, 1 equiv) was added and the reaction was cooled to −78 °C. A solution of aldehyde **28** (342 mg, 2.04 mmol, 1 equiv) in THF (5 mL) was added dropwise and the reaction was stirred for 15 h at −78 °C then for 6 h during a slow warming to RT. The reaction was quenched with an aqueous 1 M solution of HCl (16 mL). The aqueous layer was extracted with PE/Et_2O 1:1 (2×60 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude yellow oil by flash chromatography (PE/Et_2O 2:1) gave a 82:18 mixture enriched in enantiomer **29** as a yellow oil (394 mg, 93%).

To a solution of this mixture of **29** (365 mg, 1.75 mmol, 1 equiv) and Et_3N (49 μL, 0.35 mmol, 0.2 equiv) in *tert*-amyl alcohol (3.5 mL) under air atmosphere at RT was added the DMAP iron catalyst **33** (58 mg, 0.09 mmol, 5 mol%). After sonication for 10 min to get a cloudy purple solution, Ac_2O was added slowly at 0 °C. Then, reaction was stirred for 48 h at 0 °C and finally quenched with MeOH (80 μL). Volatiles were removed under vacuum. Purification of the resulting crude purple oil by flash chromatography (PE/Et_2O 7:3) gave a 95:5 enriched mixture of the enantiomer **29** as a pale yellow oil (280 mg, 81%). R_f=0.4 (PE/Et_2O 1:1); $[\alpha]_D$=−36.4 (*c*=0.55, $CHCl_3$, 25 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J*=12.0 Hz, 1H, H20), 6.25 (d, *J*=12.0 Hz, 1H, H19), 5.01 (d, *J*=7.9, 5.7 Hz, 1H, H17), 3.77 (s, 3H, OCH_3 ester), 2.57 (ddd, *J*=16.6, 7.9, 2.6 Hz, 1H, H16a), 2.43 (ddd, *J*=16.6, 5.7, 2.6 Hz, 1H, H16b), 2.08 (t, *J*=2.6 Hz, 1H, H14), 1.94 ppm (s, 6H, H4′ and H5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0 (C22), 145.5 (C21), 131.9 (C20), 127.0 (C18), 123.4 (C19), 80.2 (C15), 71.3 (C14), 68.2 (C17), 51.9 (OCH_3 ester), 26.1 (C16), 18.8 (C4′), 12.4 ppm (C5′); IR (film): ν_{max} = 3447, 3306, 2951, 1697, 1635, 1603, 1436, 1389, 1322, 1255, 1209, 1112, 1044, 1012, 913, 752, 731 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{12}H_{16}O_3Na$: 231.0997; found: 231.1007 $[M+Na]^+$.

Mosher ester 31: To a solution of alkyne **29** (20 mg, 0.106 mmol, 1 equiv) in THF (0.8 mL) under argon at RT were added DMAP (16 mg, 0.122 mmol, 1.1 equiv) and acyl chloride **32** (25 μL, 0.122 mmol, 1.1 equiv). The reaction was stirred for 15 h at RT and volatiles were removed under vacuum. Purification of the resulting crude on preparative TLC (PE/Et_2O 3:2) gave a 95:5 enriched mixture of the diastereoisomer **31** as a colourless oil (37 mg, 82%). R_f=0.65 (PE/Et_2O 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J*=11.8 Hz, 1H, H20), 7.54–7.47 (m, 2H, H_{ar}), 7.45–7.33 (m, 3H, H_{ar}), 6.36 (d, *J*=11.8 Hz, 1H, H19), 6.19 (t, *J*=7.0 Hz, 1H, H17), 3.78 (s, 3H, OCH_3 ester), 3.52 (s, 3H, OCH_3 ether), 2.72 (ddd, *J*=16.8, 7.0, 2.6 Hz, 1H, H16a), 2.57 (ddd, *J*=16.8, 7.0, 2.6 Hz, 1H, H16b), 1.96 (s, 3H, H5′), 1.95 (t, *J*=2.6 Hz, 1H, H14), 1.90 ppm (s, 3H, H4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 165.6 (C22 and C=O Mosher ester), 139.4 (C21), 131.9, 129.7, 128.4, 127.6 (6C, C_{ar}), 131.4 (C20), 128.5 (C18), 125.8 (C19), 123.2 (q, *J*=286.8 Hz, 1C, CF_3), 84.7 (q, *J*=27.8 Hz, 1C, C-CF_3), 78.2 (C15), 72.4 (C17), 71.4 (C14), 55.4 (OCH_3 ether), 52.0 (OCH_3 ester), 23.1 (C16), 19.3 (C4′), 12.6 ppm); ^{19}F NMR (500 MHz, $CDCl_3$): δ = 71.72 ppm; HRMS (ESI+): *m*/*z*: calcd for $C_{22}H_{23}O_5F_3Na$: 447.1395; found: 447.1390 $[M+Na]^+$.

Acetylene fragment 5: To a solution of alkyne **29** (260 mg, 1.25 mmol, 1 equiv) and 2,6-*tert*-butylpyridine (840 μL, 3.75 mmol, 3 equiv) in CH_2Cl_2 (9 mL) under argon at 0 °C was added dropwise MeOTf (420 μL, 3.75 mmol, 3 equiv). The reaction was stirred for 15 h at 60 °C and volatiles were removed under vacuum. Purification of the resulting crude orange oil by flash chromatography (PE/Et_2O 9:1) gave the pure acetylene fragment **5** as a yellow oil (244 mg, 88%). R_f=0.7 (PE/Et_2O 1:1);

$[\alpha]_D = +26.8$ ($c = 2.0$, $CHCl_3$, 25 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, $J = 12.0$ Hz, 1H, H20), 6.42 (d, $J = 12.0$ Hz, 1H, H19), 4.50 (t, $J = 7.0$ Hz, 1H, H17), 3.77 (s, 3H, OCH_3 ester), 3.26 (s, 3H, OCH_3 ether), 2.60 (ddd, $J = 16.7$, 7.0, 2.6 Hz, 1H, H16a), 2.41 (ddd, $J = 16.7$, 7.0, 2.6 Hz, 1H, H16b), 1.98 (t, $J = 2.6$ Hz, 1H, H14), 1.95 (s, 3H, H5′), 1.86 ppm (s, 3H, H4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2 (C22), 143.9 (C21), 132.1 (C20), 126.9 (C18), 125.7 (C19), 80.2 (C15), 76.9 (C17), 70.2 (C14), 56.7 (OCH_3 ether), 51.9 (OCH_3 ester), 23.9 (C16), 18.5 (C4′), 12.4 ppm (C5′); IR (film): ν_{max} = 3306, 2928, 2824, 1705, 1636, 1601, 1436, 1378, 1316, 1257, 1218, 1096, 1019, 913, 751, 731 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{13}H_{18}O_3Na$: 245.1148; found: 245.1149 $[M+Na]^+$.

Alcohol 40: To a solution of the chiral diol **39** (2.5 g, 24 mmol, 1 equiv) and TBDPSCl (6.5 mL, 25 mmol, 1.05 equiv) in DMF (96 mL) under argon at −50 °C was added DBU (5.1 mL, 34 mmol, 1.5 equiv). The reaction was stirred for 30 min at −50 °C before addition of EtOAc (150 mL). The organic layer was successively washed by a saturated aqueous solution of NH_4Cl and a saturated aqueous solution of $NaHCO_3$. Then, the organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude colourless oil by flash chromatography (PE/Et_2O 5:1) gave the pure alcohol **40** as a colourless oil (5.75 g, 70%). $R_f = 0.25$ (PE/Et_2O 4:1); $[\alpha]_D = -5.4$ ($c = 1.0$, $CHCl_3$, 25 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.71 (m, 4H, H_{ar}), 7.51–7.36 (m, 6H, H_{ar}), 3.82–3.66 (m, 2H, H8), 3.56–3.44 (m, 2H, H5), 2.38 (brs, 1H, OH), 1.93–1.81 (m, 1H, H6), 1.75–1.59 (m, 1H, H7a), 1.57–1.44 (m, 1H, H7b), 0.91 ppm (d, $J = 6.8$ Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 133.5, 129.7, 127.7 (12C; C_{ar}), 68.3 (C5), 62.5 (C8), 36.8 (C7), 33.9 (C6), 26.9 (3C, CH_3 (*t*Bu)), 19.2 (Cq (*t*Bu)), 17.1 ppm (C3′); IR (film): ν_{max} = 3344, 3071, 2957, 2930, 2858, 1472, 1428, 1389, 1361, 1106, 1086, 1041, 997, 822, 736, 699, 688 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{21}H_{31}O_2Si$: 343.2093; found: 343.2101 $[M+H]^+$.

Vinyl iodide 37: To a solution of alcohol **40** (2 g, 5.84 mmol, 1 equiv), NMO (718 mg, 6.13 mmol, 1.05 equiv) and MS 4 Å (1.2 g) in CH_2Cl_2 (12 mL) under argon at RT was added freshly prepared TPAP (205 mg, 0.58 mmol, 10 mol%). The reaction was stirred for 15 min at RT and volatiles were removed under vacuum. THF (20 mL) and chloroform (5.75 g, 14.6 mmol, 2.5 equiv) were added to the resulting black slurry. Then, this solution was slowly added via cannula under argon to a solution of $CrCl_2$ (5.39 g, 43.8 mmol, 7.5 equiv) in THF (20 mL). The reaction was stirred for 1.5 h at RT and quenched with H_2O (100 mL). Subsequently, the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude black oil by flash chromatography (PE/Et_2O 99:1) gave the pure vinyl iodide **37** as an orange oil (1.76 g, 65%). $R_f = 0.8$ (PE/Et_2O 98:2); $[\alpha]_D = +9.1$ ($c = 1.0$, $CHCl_3$, 25 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.63 (m, 4H, H_{ar}), 7.47–7.33 (m, 6H, H_{ar}), 6.38 (dd, $J = 14.4$, 8.2 Hz, 1H, H5), 5.93 (d, $J = 14.4$ Hz, 1H, H4), 3.67 (t, $J = 5.8$ Hz, 2H, H8), 2.49–2.41 (m, 1H, H6), 1.61–1.51 (m, 2H, H7), 1.06 (s, 9H, CH_3 (*t*Bu)), 0.97 ppm (d, $J = 7.7$ Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7 (C5), 135.5, 133.9, 129.6, 127.7 (12C, C_{ar}), 73.7 (C4), 61.4 (C8), 38.7 (C7), 37.2 (C6), 26.9 (3C, CH_3 (*t*Bu)), 19.6 (C3′), 19.2 ppm (Cq (*t*Bu)); IR (film): ν_{max} = 3070, 3049, 2958, 2930, 2857, 1731, 1603, 1590, 1472, 1462, 1427, 1389, 1361, 1259, 1172, 1105, 1007, 998, 986, 948, 897, 822, 736, 699, 688 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{22}H_{29}O_1Si_1I_1Na$: 487.0924; found: 487.0920 $[M+Na]^+$.

Alkyne 43: To a solution of but-3-yn-1-ol **42** (2.5 mL, 33 mmol, 1 equiv) and imidazole (4.5 g, 66 mmol, 2 equiv) in CH_2Cl_2 (15 mL) under argon at 0 °C was added via cannula a solution of TBSCl (6.5 g, 43 mmol, 1.3 equiv) in CH_2Cl_2 (20 mL). After stirring for 3 h at RT, the reaction was hydrolysed with a saturated aqueous solution of NH_4Cl and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum to give a crude yellow oil of the corresponding silyl ether (7.5 g) directly engaged in the following step. $R_f = 0.8$ (PE/Et_2O 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (t, $J = 7.1$ Hz, 2H, H2′), 3.99 (dt, $J = 7.1$, 2.6 Hz, 2H, H1′), 1.95 (t, $J = 2.6$ Hz, 1H, H2), 0.90 (s, 9H, CH_3 (*t*Bu)), 0.07 ppm (s, 6H, Si-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.5 (C3), 69.3 (C2), 61.8 (C2′), 25.9 (3C, CH_3 (*t*Bu)), 22.9 (C1′), 18.3 (1C, Cq (*t*Bu)), −5.3 ppm (2C, Si-CH_3); IR (film): ν_{max} = 3316, 2956, 2930, 2886, 2858, 1763, 1722, 1464, 1472, 1253, 1102, 1060, 1006, 915, 834, 775, 663 cm^{-1}.

To a solution of this silyl ether (7.5 g, ca. 33 mmol, 1 equiv) in THF (54 mL) under argon at −40 °C was added a 1.6 M solution of *n*BuLi in hexanes (22.7 mL, 36.3 mmol, 1.1 equiv). After stirring for 30 min at −5 °C, methylchloroformate was added and the reaction was stirred 1.5 h at RT. Then, the reaction was hydrolysed with an aqueous solution saturated in NH_4Cl and the aqueous layer was extracted with Et_2O (3× 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting dark brown oil by flash chromatography (PE/Et_2O 95:5) gave the pure alkyne **43** as a yellow oil (6.39 g, 80% over 2 steps). $R_f = 0.55$ (PE/Et_2O 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (t, $J = 6.9$ Hz, 2H, H2′), 3.76 (s, 3H, OCH_3 ester), 2.55 (t, $J = 6.9$ Hz, 1H, H1′), 0.90 (s, 9H, CH_3 (*t*Bu)), 0.08 ppm (s, 6H, Si-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (C1), 86.8 (C3), 73.7 (C2), 60.7 (C2′), 52.6 (OCH_3 ester), 25.8 (3C, CH_3 (*t*Bu)), 23.1 (C1′), 18.3 (1C, Cq (*t*Bu)), −5.4 ppm (2C, Si-CH_3); IR (film): ν_{max} = 2955, 2930, 2885, 2858, 2246, 1718, 1463, 1472, 1435, 1389, 1249, 1106, 1075, 1006, 909, 835, 812, 776, 752, 664 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{12}H_{23}O_3Si$: 243.1416; found: 243.1368 $[M+H]^+$.

Stannane 44: To a solution of iPr_2NH (10.9 mL, 77.8 mmol, 2.3 equiv) in THF (110 mL) under argon at 0 °C were sequentially added a 1.6 M solution of *n*BuLi in hexanes (44.4 mL, 66.6 mmol, 2 equiv) and Bu_3SnH (20 g, 66.6 mmol, 2 equiv). After cooling at −20 °C, CuSPh (11.5 g, 66.6 mmol, 2 equiv) was added in four portions and reaction was stirred for 20 min. To the reaction cooled at −100 °C WERE added via a cannula a cold (−40 °C) solution of alkyne **43** (8.06 g, 33.3 mmol, 1 equiv) in THF (54 mL) and MeOH (2.3 mL). Then, the reaction was stirred for 3 h at −78 °C before addition of MeOH (8 mL) and warming to RT. Subsequently, the reaction was poured in H_2O (300 mL). The aqueous layer was extracted with Et_2O (2×250 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude dark brown oil by flash chromatography (PE/Et_2O 100:0 → 97:3) gave the pure stannane **44** as an orange oil (15.1 g, 85%). $R_f = 0.75$ (PE/Et_2O 98:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (s, 1H, H2), 3.70 (s, 3H, OCH_3 ester), 3.67 (t, $J = 7.1$ Hz, 2H, H2′), 3.11 (t, $J = 7.1$ Hz, 2H, H1′), 1.54–1.44 (m, 6H, CH_2 (*n*Bu)), 1.32 (sex, $J = 7.3$ Hz, 6H, CH_2 (*n*Bu)), 0.97 (t, $J = 8.2$ Hz, 6H, Sn-CH_2), 0.90 (t, $J = 7.3$ Hz, 9H, CH_3 (*n*Bu)), 0.89 (s, 9H, CH_3 (*t*Bu)), 0.06 ppm (s, 6H, Si-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8 (C1), 164.4 (C3), 129.3 (C2), 62.6 (C2′), 50.8 (OCH_3 ester), 38.8 (C1′), 29.0 (3C, CH_2 (*n*Bu)), 27.4 (3C, CH_2 (*n*Bu)), 26.0 (3C, CH_3 (*t*Bu)), 18.4 (1C, Cq (*t*Bu)), 13.6 (3C, CH_3 (*n*Bu)), 10.1 (3C, Sn-CH_2), −5.2 ppm (2C, Si-CH_3); IR (film): ν_{max} = 2954, 2927, 2856, 1709, 1598, 1463, 1435, 1330, 1252, 1213, 1194, 1182, 1090, 1049, 1005, 835, 774, 665 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{24}H_{51}O_3SiSn$: 535.2629; found: 535.2672 $[M+H]^+$.

Stannane 36b: To a solution of stannane **44** (2.7 g, 5.07 mmol, 1 equiv) in acetone (14.3 mL) at 0 °C was slowly added a freshly made and precooled at 0 °C solution of Jones reagent (1.52 g of CrO_3 in 3.4 mL of H_2O and 1.4 mL of concentrated H_2SO_4, 15.21 mmol, 3 equiv). The reaction was stirred for 10 min at 0 °C before addition of H_2O (15 mL) and Et_2O (30 mL). Subsequently, the aqueous layer was extracted with Et_2O (2× 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting brown oil by flash chromatography (PE/Et_2O 5:1) gave the pure corresponding carboxylic acid as a yellow oil (1.27 g, 68%). $R_f = 0.35$ (PE/Et_2O 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 1H, H2), 3.95 (s, 2H, H1′), 3.75 (s, 3H, OCH_3 ester), 1.56–1.42 (m, 6H, CH_2 (Bu)), 1.31 (sex, $J = 7.3$ Hz, 6H, CH_2 (Bu)), 1.00 (t, $J = 8.2$ Hz, 6H, Sn-CH_2), 0.89 ppm (t, $J = 7.3$ Hz, 9H, CH_3 (Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8 (C2′), 165.5 (C3), 164.9 (C1), 130.3 (C2), 51.5 (OCH_3 ester), 40.2 (C1′), 28.9 (3C, CH_2 (Bu)), 27.3 (3C, CH_2 (Bu)), 13.6 (3C, CH_3 (Bu)), 10.6 ppm (3C, Sn-CH_2); HRMS (ESI+): m/z: calcd for $C_{18}H_{35}O_4Sn$ $[M+H]^+$: 435.1557; found: 435.1621. To a solution of this carboxylic acid (880 mg, 2.03 mmol, 1 equiv) in MeOH (0.8 mL) and CH_2Cl_2 (3.3 mL) at 0 °C was added a 2 M solution of $TMSCHN_2$ in Et_2O (1.22 mL, 2.44 mmol, 1.2 equiv). The reaction was stirred at 0 °C for 40 min before removal of volatile under

vacuum. Purification of the resulting crude yellow oil by flash chromatography (PE/Et_2O 95:5) gave the pure stannane **36b** as a pale yellow oil (910 mg, quant). R_f=0.55 (PE/Et_2O 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (s, 1H, H2), 4.01 (s, 2H, H1′), 3.70 (s, 3H, OCH_3 ester), 3.61 (s, 3H, OCH_3 ester), 1.56–1.39 (m, 6H, CH_2 (Bu)), 1.31 (sex, J=7.3 Hz, 6H, CH_2 (Bu)), 0.97 (t, J=8.2 Hz, 6H, Sn-CH_2), 0.89 ppm (t, J=7.3 Hz, 9H, CH_3 (Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C2′), 164.8 (C3), 164.5 (C1), 129.8 (C2), 51.9, 51.0 (2C, OCH_3 ester), 39.1 (C1′), 28.9 (3C, CH_2 (Bu)), 27.3 (3C, CH_2 (Bu)), 13.7 (3C, CH_3 (Bu)), 10.7 ppm (3C, Sn-CH_2); IR (film): ν_{max} = 2955, 2924, 2872, 2853, 1733, 1715, 1599, 1457, 1435, 1377, 1325, 1250, 1195, 1163, 1072, 1002, 865, 690, 672 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{19}H_{36}O_4SnNa$: 471.1533; found: 471.1559 $[M+Na]^+$.

Dienes 41a and 41b: To a solution of vinyl iodide **37** (592 mg, 1.27 mmol, 1 equiv) and stannane **36b** (737 mg, 1.78 mmol, 1.4 equiv) in DMF under argon at RT were added $Ph_2PO_2NBu_4$ (812 mg, 1.78 mmol, 1.4 equiv), [$Pd(PPh_3)_4$] (73 mg, 0.06 mmol, 5 mol%) and CuTC (190 mg, 1.00 mmol, 0.8 equiv). The reaction was stirred for 1 h at RT and then Et_3N (7 mL) was added. After stirring for 30 min at RT, H_2O (15 mL) and Et_2O (15 mL) were added and the resulting orange suspension was filtered through a pad of Celite (eluent: Et_2O (100 mL)). The aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude orange oil by flash chromatography (PE/Et_2O 9:1) gave the pure diene **41a** as a yellow oil (375 mg, 60%) and the pure diene **41b** as a yellow oil (125 mg, 20%). Data for **41a**: R_f=0.1 (PE/Et_2O 9:1); $[\alpha]_D$=+4.0 (c=1.0, $CHCl_3$, 25°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.60 (m, 4H, H_{ar}), 7.47–7.33 (m, 6H, H_{ar}), 6.09 (d, J=16.0 Hz, 1H, H4), 5.92 (dd, J=16.0, 7.5 Hz, 1H, H5), 5.86 (s, 1H, H2), 3.92 (s, 2H, H1′), 3.72 (s, 3H, OCH_3 ester), 3.65 (t, J=7.5 Hz, 2H, H8), 3.64 (s, 3H, OCH_3 ester), 2.60–2.42 (m, 1H, H6), 1.66–1.52 (m, 2H, H7), 1.05 (s, 9H, CH_3 (tBu)), 1.01 ppm (d, J=7.5 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (C2′), 167.5 (C1), 148.6 (C3), 143.7 (C5), 135.9, 131.0, 130.0, 128.0 (13C, 12 C_{ar} and C4), 119.9 (C2), 62.0 (C8), 52.4, 51.6 (2C, OCH_3 ester), 39.6 (C7), 34.1 (C6), 33.5 (C1′), 27.3 (3C, CH_3 (tBu)), 20.4 (Cq (tBu)), 19.6 ppm (C3′); IR (film): ν_{max} = 2952, 2931, 2858, 1741, 1713, 1636, 1615, 1429, 1324, 1261, 1192, 1154, 1106, 1008, 823, 738, 701, 688 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{29}H_{38}O_5SiNa$: 517.2386; found: 517.2385 $[M+Na]^+$. Data for **41b**: R_f=0.15 (PE/Et_2O 9:1); $[\alpha]_D$=−2.4 (c=1.27, $CHCl_3$, 25°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.62 (m, 4H, H_{ar}), 7.53 (d, J=16.1 Hz, 1H, H4), 7.45–7.31 (m, 6H, H_{ar}), 6.01 (dd, J=16.1, 7.8 Hz, 1H, H5), 5.70 (s, 1H, H2), 3.71 (s, 3H, OCH_3 ester), 3.66 (t, J=6.6 Hz, 2H, H8), 3.62 (s, 3H, OCH_3 ester), 3.29 (br s, 2H, H1′), 2.63–2.53 (m, 1H, H6), 1.67 (q, J=6.6 Hz, 2H, H7), 1.05 (s, 9H, CH_3 (tBu)), 1.04 ppm (d, J=7.0 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C2′), 166.3 (C1), 147.1 (C3), 145.0 (C5), 135.6, 134.0, 129.6, 127.6 (12C, C_{ar}), 124.9 (C4), 118.4 (C2), 61.8 (C8), 52.1, 51.2 (2C, OCH_3 ester), 40.4 (C1′), 39.3 (C7), 34.0 (C6), 26.9 (3C, CH_3 (tBu)), 20.0 (Cq (tBu)), 19.2 ppm (C3′); HRMS (ESI+): m/z: calcd for $C_{29}H_{38}O_5SiNa$: 517.2386; found: 517.2388 $[M+Na]^+$.

Alcohol 47: To the diene **41a** (100 mg, 0.20 mmol, 1 equiv) under argon at 0°C was added a 1.25 M solution of HCl in MeOH (2.42 mL, 3.03 mmol, 15 equiv). The reaction was stirred for 4 h during warming to RT. Then, the reaction was neutralised with solid $NaHCO_3$ (255 mg, 3.03 mmol, 15 equiv) and the volatiles were removed under vacuum. Purification of the resulting crude white solid by flash chromatography (PE/Et_2O 1:2) gave the pure alcohol **47** as a yellow oil (52 mg, quant.). R_f=0.2 (PE/Et_2O 1:2); $[\alpha]_D$=+29.7 (c=1.0, $CHCl_3$, 25°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (d, J=15.7 Hz, 1H, H4), 5.92 (dd, J=15.7, 8.1 Hz, 1H, H5), 5.85 (s, 1H, H2), 3.98 (d, J=16.2 Hz, 1H, H1a′), 3.85 (d, J=16.2 Hz, 1H, H1b′), 3.66 (s, 3H, OCH_3 ester), 3.64 (s, 3H, OCH_3 ester), 3.65–3.52 (m, 2H, H8), 2.47–2.36 (m, 1H, H6), 2.05–1.93 (br s, 1H, OH), 1.64–1.50 (m, 2H, H7), 1.01 ppm (d, J=6.7 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (C2′), 167.4 (C1), 148.3 (C3), 143.5 (C5), 131.0 (C4), 120.1 (C2), 61.0 (C8), 52.4, 51.6 (2C, OCH_3 ester), 39.7 (C7), 34.7 (C6), 33.4 (C1′), 20.6 ppm (C3′); IR (film): ν_{max} = 3425, 2953, 1736, 1710, 1636, 1614, 1435, 1378, 1327, 1261, 1238, 1193, 1152, 1049, 1028, 1003, 971, 917, 878, 834, 731 cm^{-1}; HRMS (ESI+): m/z: calcd for $C_{13}H_{20}O_5Na$: 279.1208; found: 279.1216 $[M+Na]^+$.

Mosher ester 48: To a solution of alcohol **47** (5 mg, 0.020 mmol, 1 equiv) in THF (0.2 mL) under argon at RT were added DMAP (3 mg, 0.024 mmol, 1.1 equiv) and acyl chloride **32** (5 μL, 0.024 mmol, 1.1 equiv). The reaction was stirred for 15 h at RT and volatiles were removed under vacuum. Purification of the resulting crude on preparative TLC (PE/Et_2O 3:2) gave a 95:5 enriched mixture of the diastereoisomer **48** as a white solid (8 mg, 86%). R_f=0.55 (PE/Et_2O 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.45 (m, 2H, H_{ar}), 7.45–7.36 (m, 3H), 6.03 (d, J=15.7 Hz, 1H, H4), 5.87 (s, 1H, H2), 5.86 (dd, J=15.7, 8.2 Hz, 1H, H5), 4.36–4.16 (m, 2H, H8), 3.97 (d, J=16.2 Hz, 1H, H1a′), 3.91 (d, J=16.2 Hz, 1H, H1b′), 3.72 (s, 3H, OCH_3 ester), 3.68 (s, 3H, OCH_3 ester), 3.54 (s, 3H, OCH_3 ether), 2.40–2.29 (m, 1H, H6), 1.84–1.63 (m, 2H, H7), 1.04 ppm (d, J=6.7 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$ δ = 170.7, 169.9, 165.7, 166.4 (3C, C1, C2′ and C=O Mosher ester), 147.6 (C3), 141.3 (C5), 132.3, 129.7, 128.5, 127.9, 127.3 (6C, C_{ar}), 131.6 (C4), 120.2 (C2), 123.3 (q, J=286.9 Hz, 1C, CF_3), 84.5 (q, J=27.6 Hz, 1C, C-CF_3), 64.4 (C8), 55.4 (OCH_3 ether), 52.1, 51.3 (2C, OCH_3 ester), 34.9 (C7), 34.1 (C6), 33.2 (C1′), 20.1 ppm (C3′); ^{19}F NMR (500 MHz, $CDCl_3$): δ = −71.71 ppm; HRMS (ESI+): m/z: calcd for $C_{23}H_{27}O_7F_3Na$: 495.1607; found: 495.1606 $[M+Na]^+$.

Aldehyde 49: To a solution of alcohol **47** (180 mg, 0.70 mmol, 1 equiv) in CH_2Cl_2 (5 mL) under argon at 0°C was added Dess–Martin periodinane (358 mg, 0.84 mmol, 1.2 equiv). The reaction was stirred 1 h at RT and cooled at 0°C before addition of PE (5 mL). The white suspension is then filtered through a pad of silica (PE/Et_2O 1:1 (200 mL)). The volatiles were removed under vacuum to give the expected aldehyde **49** as a yellow oil (180 mg, quant.) clean enough to proceed the next step. R_f=0.2 (PE/Et_2O 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (t, J=1.8 Hz, 1H, H8), 6.14 (d, J=15.9 Hz, 1H, H4), 5.99 (dd, J=15.9, 7.2 Hz, 1H, H5), 5.90 (s, 1H, H2), 3.93 (br s, 2H, H1′), 3.69 (s, 3H, OCH_3 ester), 3.67 (s, 3H, OCH_3 ester), 2.95–2.82 (m, 1H, H6), 2.50 (ddd, J=16.8, 6.7, 1.8 Hz, 1H, H7a), 2.43 (ddd, J=16.8, 7.0, 1.8 Hz, 1H, H7b), 1.11 ppm (d, J=6.8 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0 (C8), 170.6 (C2′), 166.8 (C1), 147.5 (C3), 140.7 (C5), 131.1 (C4), 120.5 (C2), 52.0, 51.3 (2C, OCH_3 ester), 50.0 (C7), 33.1 (C1′), 31.7 (C6), 19.8 ppm (C3′); HRMS (ESI+): m/z: calcd for $C_{13}H_{18}O_5Na$: 277.1052; found: 277.1057 $[M+Na]^+$.

Aldehyde 66: To a 1 M solution of DiBAL-H (100 mL, 100 mmol, 3.5 equiv) in hexanes under argon at −20°C was added slowly pentynol **65** (3.7 mL, 40 mmol, 1 equiv). The reaction was stirred for 15 h at RT before removal of volatiles under vacuum. The resultant colourless oil was dissolved in THF (40 mL) and a solution of iodine (12.18 g, 48 mmol, 1.2 equiv) in THF (67 mL) was slowly added at −78°C under argon. Then the reaction was stirred for 20 min at −78°C and warmed to RT. Next, the brown solution was cautiously poured at 0°C in a 2 N solution of HCl (17 mL) and more 2 N HCl (13 mL) was carefully added. After complete solubilisation of the aluminium salts, the aqueous layer was extracted with PE/Et_2O 1:1 (2×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude yellow oil by flash chromatography (PE/Et_2O 1:1) gave the pure corresponding vinyl iodide as a yellow oil (4.72 g, 56%). R_f=0.45 (PE/Et_2O 2:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (dt, J=14.4, 7.2 Hz, 1H, H12), 6.05 (d, J=14.4 Hz, 1H, H13), 3.72–3.62 (m, 2H, H9), 2.17 (q, J=7.2 Hz, 2H, H11), 1.72–1.62 ppm (m, 2H, H10); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8 (C12), 75.0 (C13), 61.9 (C9), 32.3 (C11), 31.2 ppm (C10); IR (film): ν_{max} = 3305, 3078, 2936, 2882, 1641, 1435, 1221, 1056, 994, 946, 911, 851 cm^{-1}. To a solution of this vinyl iodide (2.9 g, 13.6 mmol, 1 equiv) and Celite (5.86 g) in CH_2Cl_2 under argon at 0°C was added PCC (5.86 g, 27.2 mmol, 2 equiv). The reaction was stirred at RT for 6 h and then was filtered through a pad of silica using as eluent PE/Et_2O 3:1 (400 mL). Volatiles were removed under vacuum to give the aldehyde **66** as a yellow oil (2.72 g, 95%) clean enough to proceed the next step. R_f=0.75 (PE/Et_2O 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1H, H9), 6.52 (dt, J=14.4, 7.1 Hz, 1H, H12), 6.12 (d, J=14.4 Hz, 1H, H13), 2.57 (t, J=7.1 Hz, 2H, H10), 2.39 ppm (q, J=7.1 Hz, 2H, H11); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6 (C9), 143.9 (C12), 76.3 (C13), 42.2 (C10), 28.4 ppm (C11); IR (film): ν_{max} = 3052, 2927, 2826, 2723, 1723, 1607, 1409, 1389, 1211, 1176,

945, 856, 659 cm^{-1}; HRMS (ESI+): *m/z*: calcd for C_5H_7OINa: 232.9439; found: 232.1700 $[M+Na]^+$.

Triiodide 64: To aldehyde **66** (2 g, 9.53 mmol, 1 equiv) at 0 °C was added hydrazine monohydrate (925 μL, 19.06 mmol, 2 equiv) and reaction was stirred for 1 h at RT. Then, H_2O (10 mL) and CH_2Cl_2 (10 mL) were added and the aqueous layer was extracted 2 times with CH_2Cl_2 (2× 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. To this crude pale yellow oil at RT and under argon were added Et_3N (2.39 mL, 17.15 mmol, 1.8 equiv) and iodine in 3 portions (2.66 g, 10.48 mmol, 1.1 equiv) and the reaction was stirred for 10 min. After hydrolysis with a 25 %/w aqueous solution of Na_2SO_3 (60 mL), the aqueous layer was extracted with CH_2Cl_2 (2× 60 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude brown oil by flash chromatography (pure PE) gave the triiodide **64** as a yellow oil (1.7 g, 40 %). R_f=0.8 (PE/Et_2O 99.5:0.5); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.45 (dt, *J*=14.2, 7.2 Hz, 1H, H12), 6.16 (d, *J*=14.2 Hz, 1H, H13), 5.04 (t, *J*=6.6 Hz, 1H, H9), 2.45 (dt, *J*=7.2, 6.6 Hz, 2H, H10), 2.18 ppm (q, *J*=7.2 Hz, 2H, H11); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3 (C12), 77.2 (C13), 46.1 (C10), 38.0 (C11), −28.4 ppm (C9); IR (film): ν_{max} = 3044, 2934, 2837, 1604, 1425, 1220, 1191, 1085, 939, 784, 732, 663 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_5H_7I_3$: 447.7676; found: 447.7670 $[M]^+$.

Vinyl iodide 4: To a solution of $CrCl_2$ (645 mg, 5.25 mmol, 7.5 equiv) in THF (8 mL) under argon at RT was added a solution of aldehyde **49** (180 mg, 0.7 mmol, 1 equiv) and *gem*-diiodide **7** (950 mg, 2.1 mmol, 3 equiv) in THF (4 mL). The reaction was stirred at RT for 4.5 h. Then, H_2O (15 mL) and Et_2O (15 mL) were added and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude yellow oil by flash chromatography (PE/Et_2O 9:1) gave the pure vinyl iodide **4** as a yellow oil (238 mg, 79 %). R_f=0.2 (PE/Et_2O 9:1); $[\alpha]_D$=+11.1 (*c*=1.2, $CHCl_3$, 25 °C); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.49 (dt, *J*=14.8, 6.6 Hz, 1H, H12), 6.10 (d, *J*=15.8 Hz, 1H, H4), 5.99 (d, *J*=14.8 Hz, 1H, H13), 5.98 (dd, *J*=15.8, 6.9 Hz, 1H, H5), 5.90 (s, 1H, H2), 5.42–5.31 (m, 2H, H8 and H9), 3.98 (d, *J*= 16.3 Hz, 1H, H1′a), 3.93 (d, *J*=16.3 Hz, 1H, H1′b), 3.71 (s, 3H, OCH_3 ester), 3.69 (s, 3H, OCH_3 ester), 2.35–2.25 (m, 1H, H6), 2.22–1.97 (m, 6H, H7, H10 and H11), 1.02 ppm (d, *J*=6.7 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C2′), 167.1 (C1), 148.2 (C3), 145.9 (C12), 143.2 (C5), 130.7 (C4), 130.4 (C9), 128.9 (C8), 119.6 (C2), 74.8 (C13), 52.0, 51.2 (2C, OCH_3 ester), 39.7 (C7), 37.4 (C6), 35.9 (C11 or C10), 33.2 (C1′), 31.3 (C10 or C11), 19.4 ppm (C3′); IR (film): ν_{max} = 2926, 1741, 1714, 1637, 1615, 1435, 1378, 1325, 1262, 1193, 1157, 1026, 968 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{18}H_{26}O_4I$: 433.0876; found: 433.0881 $[M+H]^+$.

Trimethyl iso- and bongkrekate triesters IBAMe$_3$ 3 and BAMe$_3$ 70: To a solution of vinyl iodide **4** (24 mg, 56 μmol, 1 equiv) in Et_3N (1.7 mL) were added successively CuI (2 mg, 11 μmol, 0.2 equiv) and $[Pd(PPh_3)_4]$ (4 mg, 6 μmol, 0.1 equiv) under argon at RT. Then a solution of alkyne **5** (16 mg, 72 μmol, 1.3 equiv) in Et_3N was slowly added and the resulting orange suspension was stirred for 4 h. Solvent was removed under vacuum and the resulting oil was purified by a flash chromatography on silica gel (toluene/acetone 95:5). 32 mg mixture of the two expected isomers **67**/**68** and the Glaser dimer **69** were isolated. To a microwave sealed tube containing this mixture, methanol (0.9 mL), water (0.9 mL) and Zn-(CuAg) (550 mg, 8.4 mmol, 150 equiv) were added. The resulting black slurry was vigorously stirred for 20 h at 65 °C before adding more Zn-(CuAg) (275 mg, 4.2 mmol, 75 equiv) and stirred for 15 h more at 65 °C. The slurry was filter through a pad of Celite and rinsed with Et_2O. Volatiles were removed under vacuum and the crude was purified on a preparative TLC (toluene/acetone 96:4) to give pure IBAMe$_3$ **3** (17.5 mg, 59 %) and pure BAMe$_3$ **70** (4 mg, 14 %) for a total yield of 73 % over two steps. Data for IBAMe$_3$ **3**: Pale yellow oil; R_f=0.45 (PE/Et_2O 2:1); $[\alpha]_D$=+110.0 (*c*=0.15, $CHCl_3$, 25 °C); ^1H NMR (700 MHz): δ = 7.51 (d, *J*=12.0 Hz, 1H, H20), 6.36 (d, *J*=12.0 Hz, 1H, H19), 6.26 (dd, *J*=14.3, 11.3 Hz, 1H, H13), 6.09 (d, *J*=15.9 Hz, 1H, H4), 6.01–5.96 (m, 1H, H14), 5.99 (dd, *J*=15.9, 7.7 Hz, 1H, H5), 5.89 (s, 1H, H2), 5.67 (dt, *J*= 14.3, 7.2 Hz, 1H, H12), 5.40 (dt, *J*=15.2, 7.2 Hz, 1H, H9), 5.33 (dt, *J*= 15.2, 7.2 Hz, 1H, H8), 5.21 (ddd, *J*=10.7, 7.4, 7.2 Hz, 1H, H15), 4.34 (t, *J*=7.2 Hz, 1H, H17), 3.97 (d, *J*=16.2 Hz, 1H, H1′a), 3.93 (d, *J*=16.2 Hz, 1H, H1′b), 3.75 (s, 3H, OCH_3 ester), 3.70 (s, 3H, OCH_3 ester), 3.69 (s, 3H, OCH_3 ester), 3.21 (s, 3H, OCH_3 ether), 2.58 (dt, *J*=14.7, 7.2 Hz, 1H, H16a), 2.37 (ddd, *J*=14.7, 7.4, 7.2 Hz, 1H, H16b), 2.32–2.26 (m, 1H, H6), 2.15 (q, *J*=7.2 Hz, 2H, H11), 2.08 (q, *J*=7.2 Hz, 2H, H10), 2.06 (dt, *J*=13.9, 7.2 Hz, 1H, H7a), 1.99 (dt, *J*=13.9, 7.2 Hz, 1H, H7b), 1.94 (s, 3H, H5′), 1.83 (s, 3H, H4′), 1.01 ppm (d, *J*=6.7 Hz, 3H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C2′), 169.1 (C22), 167.1 (C1), 148.2 (C3), 145.6 (C21), 143.3 (C5), 134.9 (C12), 132.2 (C20), 131.7 (C9), 130.6 (C4), 130.3 (C14), 128.1 (C8), 126.5 (C18), 125.7 (C13), 125.0 (C19), 124.4 (C15), 119.5 (C2), 78.4 (C17), 56.4 (OCH_3 ether), 52.0, 51.8, 51.2 (3C, OCH_3 ester), 39.7 (C7), 37.4 (C6), 33.2 (C1′), 32.9 (C11), 32.3 (C10), 32.1 (C16), 19.3 (C3′), 18.7 (C4′), 12.3 ppm (C5′); HRMS (ESI+): *m/z*: calcd for $C_{31}H_{44}O_7Na$: 551.2985; found: 551.2997 $[M+Na]^+$. Data for BAMe$_3$ **28**: Colourless oil; R_f=0.50 (PE/Et_2O 2:1); $[\alpha]_D$=+81.2 (*c*=0.25, $CHCl_3$, 25 °C); ^1H NMR (700 MHz): δ = 7.51 (bd, *J*=15.7 Hz, 2H, H4 and H20), 6.36 (d, *J*=11.8 Hz, 1H, H19), 6.26 (dd, *J*=15.1, 11.1 Hz, 1H, H13), 6.05 (dd, *J*=16.1, 7.4 Hz, 1H, H5), 5.99 (t, *J*=11.1 Hz, 1H, H14), 5.69 (s, 1H, H2), 5.67 (dt, *J*=15.1, 7.1 Hz, 1H, H12), 5.41 (dt, *J*=15.2, 6.4 Hz, 1H, H9), 5.35 (dt, *J*=15.2, 7.0 Hz, 1H, H8), 5.21 (dt, *J*=11.1, 7.3 Hz, 1H, H15), 4.34 (t, *J*=7.3 Hz, 1H, H17), 3.75 (s, 3H, OCH_3 ester), 3.71 (s, 3H, OCH_3 ester), 3.68 (s, 3H, OCH_3 ester), 3.33 (d, *J*=15.9 Hz, 1H, H1′a), 3.30 (d, *J*=15.9 Hz, 1H, H1′b), 3.21 (s, 3H, OCH_3 ether), 2.58 (dt, *J*=14.8, 7.3 Hz, 1H, H16a), 2.38 (dt, *J*=14.8, 7.3 Hz, 1H, H16b), 2.38–2.32 (m, 1H, H6), 2.15 (q, *J*=7.1 Hz, 2H, H11), 2.08 (dt, *J*=7.1, 6.4 Hz, 2H, H10), 2.08–2.03 (m, 1H, H7a), 2.02–1.97 (m, 1H, H7b), 1.94 (s, 3H, H5′), 1.84 (s, 3H, H4′), 1.02 ppm (d, *J*=6.7 Hz, 3H, H3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7 (C2′), 169.1 (C22), 166.3 (C1), 147.2 (C3), 145.5 (C21), 145.0 (C5), 135.0 (C12), 132.1 (C20), 131.5 (C9), 130.5 (C14), 128.2 (C8), 126.4 (C18), 125.6 (C13), 125.0 (C19), 124.6 (C4), 124.3 (C15), 118.3 (C2), 78.3 (C17), 56.4 (OCH_3 ether), 52.2, 51.8, 51.1 (3C, OCH_3 ester), 40.4 (C1′), 39.7 (C7), 37.5 (C6), 32.9 (C11), 32.4 (C10), 32.1 (C16), 19.2 (C3′), 18.6 (C4′), 12.3 ppm (C5′); IR (film): ν_{max} = 2952, 2692, 1742, 1711, 1636, 1603, 1435, 1377, 1258, 1232, 1155, 1096, 970, 863, 752 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{31}H_{44}O_7Na$: 551.2985; found: 551.2991 $[M+Na]^+$.

Isobongkrekic acid IBA 1: To a 4:1 mixture of IBAMe$_3$ **3** and BAMe$_3$ **70** (25 mg, 47 μmol, 1 equiv) in DME (19 mL) was added a 1 M solution of KOH (4.7 mL, 4.7 mmol, 100 equiv) in H_2O. The solution was stirred at RT for 8 h and neutralised with 5 mL of aqueous 1 N HCl. The aqueous layer is extracted with Et_2O (3×15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude yellow oil on preparative TLC (CH_2Cl_2/MeOH/AcOH 97:3:0.5) furnished the pure desired IBA **1** (8 mg, 35 %) and the pure desired BA **2** (3.9 mg, 17 %) as two white oily solids. Data for IBA **1**: White oily solid; R_f=0.25 ($CHCl_3$/MeOH/AcOH 94:5:1); $[\alpha]_D$=+55.5 (*c*=0.31, $CHCl_3$, 25 °C); ^1H NMR (700 MHz): δ = 7.65 (d, *J*=12.2 Hz, 1H, H20), 6.32 (d, *J*=12.2 Hz, 1H, H19), 6.26 (dd, *J*=14.8, 10.9 Hz, 1H, H13), 6.10 (d, *J*=15.8 Hz, 1H, H4), 6.05 (t, *J*=10.9 Hz, 1H, H14), 5.97 (dd, *J*=15.8, 8.2 Hz, 1H, H5), 5.91 (s, 1H, H2), 5.72 (dt, *J*= 14.8, 7.4 Hz, 1H, H12), 5.45 (dt, *J*=10.9, 7.4 Hz, 1H, H15), 5.40–5.32 (m, 1H, H9), 5.29 (dt, *J*=15.3, 7.6 Hz, 1H, H8), 4.34 (d, *J*=16.7 Hz, 1H, H1′a), 4.29 (dd, *J*=9.7, 3.8 Hz, 1H, H17), 3.77 (d, *J*=16.7 Hz, 1H, H1′b), 3.19 (s, 3H, OCH_3), 2.36 (ddd, *J*=13.7, 9.7, 7.4 Hz, 1H, H16a), 2.34–2.27 (m, 1H, H6), 2.29 (ddd, *J*=13.7, 7.4, 3.8 Hz, 1H, H16b), 2.22–2.16 (m, 1H, H7a), 2.08 (q, *J*=7.4 Hz, 2H, H11), 2.05–1.98 (m, 2H, H10), 1.94 (s, 3H, H5′), 1.93–1.82 (m, 1H, H7b), 1.87 (s, 3H, H4′), 1.06 ppm (d, *J*= 6.7 Hz, 3H, H3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.4 (C2′), 174.6 (C22), 169.1 (C1), 149.6 (C3), 149.1 (C21), 144.4 (C5), 135.7 (C12), 134.4 (C20), 131.7 (C4), 131.1 (C14), 130.5 (C9), 127.7 (C8), 125.2 (C18), 125.0, 124.7 (2C, C13 and C15), 123.6 (C19), 118.7 (C2), 80.6 (C17), 57.0 (OCH_3), 40.4 (C7), 38.4 (C6), 33.1 (C11), 32.9, 32.8 (2C, C1′ and C10), 32.6 (C16), 20.5 (C3′), 18.7 (C4′), 11.7 ppm (C5′); IR (film): ν_{max} = 2926, 1683, 1631, 1614, 1420, 1268, 1203, 1094, 967, 947, 875, 737 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{28}H_{38}O_7Na$: 509.2516; found: 509.2515 $[M+Na]^+$.

Bongkrekic acid BA 2: To a 4:1 mixture of IBAMe$_3$ **3** and BAMe$_3$ **70** (25 mg, 47 μmol, 1 equiv) in DME (19 mL) was added a 1 M solution of

LiOH (4.7 mL, 4.7 mmol, 100 equiv) in H_2O. The solution was stirred at RT for 15 h and neutralised with 5 mL of an aqueous 1 N HCl. The aqueous layer is extracted with Et_2O (3×15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the resulting crude yellow oil on preparative TLC (CH_2Cl_2/MeOH/AcOH: 97:3:0.5) furnished pure IBA **1** (8 mg, 31%) and the pure desired BA **2** (3.9 mg, 23%) as two white oily solids. Data for BA **2**: White oily solid, R_f=0.35 ($CHCl_3$/MeOH/AcOH 94:5:1); $[\alpha]_D$= −47.2 (c=0.175, $CHCl_3$, 25°C); ^{1}H NMR (700 MHz): δ = 7.63 (d, J= 12.2 Hz, 1H, H20), 7.43 (d, J=16.0 Hz, 1H, H4), 6.34 (d, J=12.2 Hz, 1H, H19), 6.28 (dd, J=14.9, 11.1 Hz, 1H, H13), 6.05 (t, J=11.1 Hz, 1H, H14), 6.00 (dd, J=16.0, 8.2 Hz, 1H, H5), 5.74 (dt, J=14.9, 6.6 Hz, 1H, H12), 5.72 (s, 1H, H2), 5.41 (dt, J=15.3, 6.3 Hz, 1H, H9), 5.41–5.36 (m, 1H, H15), 5.34 (dt, J=15.3, 7.1 Hz, 1H, H8), 4.33 (dd, J=8.8, 5.0 Hz, 1H, H17), 3.46 (d, J=16.0 Hz, 1H, H1′a), 3.32 (d, J=16.0 Hz, 1H, H1′b), 3.21 (s, 3H, OCH_3), 2.45 (ddd, J=13.7, 8.8, 7.9 Hz, 1H, H16a), 2.39–2.32 (m, 1H, H6), 2.27 (ddd, J=13.7, 9.0, 5.0 Hz, 1H, H16b), 2.21–2.15 (m, 1H, H7a), 2.12 (dt, J=9.6, 6.6 Hz, 2H, H11), 2.03 (dt, J=9.6, 6.3 Hz, 2H, H10), 1.94 (s, 3H, H5′), 1.92–1.85 (m, 1H, H7b), 1.87 (s, 3H, H4′), 1.07 ppm (d, J=6.7 Hz, 3H, H3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5 (C2′), 174.7 (C22), 169.7 (C1), 148.8 (C3), 148.6 (C21), 145.4 (C5), 135.9 (C12), 134.5 (C20), 131.5 (C9), 131.3 (C14), 128.1 (C8), 125.3 (C4), 125.1 (C18), 124.6 (C13), 124.3 (C15), 124.1 (C19), 118.0 (C2), 80.0 (C17), 56.8 (OCH_3), 40.7 (C1′), 40.0 (C7), 38.8 (C6), 33.2 (C11), 32.5 (C10), 32.2 (C16), 20.5 (C3′), 18.6 (C4′), 11.7 ppm (C5′); HRMS (ESI+): m/z: calcd for $C_{28}H_{39}O_7$: 487.2696; found: 487.2695 $[M+H]^+$.

Re-esterification procedure: To IBA **1** or BA **2** (5 mg, 10 μmol, 1 equiv) in CH_2Cl_2 (200 μL) and MeOH (50 μmol) was added a 2 M solution of $TMSCHN_2$ (25 μL, 50 μmol, 50 equiv) in Et_2O. The solution was stirred at RT for 40 min and volatiles were removed under vacuum. Purification of the resulting crude yellow oil on preparative TLC (PE/Et_2O 2:1) furnished the pure desired $IBAMe_3$ **27** (5.4 mg, quant) or the pure desired $BAMe_3$ **28** (5.4 mg, quant) as a colourless oil. Both products afforded identical analytical data as the original substrates prior to their saponification.

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