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Total Syntheses of Amphidinolides B1, B4, G1, H1 and Structure Revision of Amphidinolide H2

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Abstract: Dinoflagellates of the genus *Amphidinium* produce a "library" of closely related secondary metabolites of mixed polyketide origin, which are extremely scarce but highly promising owing to the exceptional cytotoxicity against various cancer cell lines. Because of the dense array of sensitive functionalities on their largely conserved macrocyclic frame, however, these amphidinolides of the B, D, G and H types elapsed many previous attempts at their synthesis. Described herein is a robust, convergent and hence general blueprint which allowed not only to conquest five prototype members of these series, but also holds the promise of making "non-natural" analogues available by diverted total synthesis. This notion transpires for a synthesis-driven structure revision of amphidinolide H2. The successful route hinges upon a highly productive Stille–Migita cross-coupling reaction at the congested and chemically labile 1,3-diene site present in all such targets, which required the development of a modified chloride- and fluoride-free protocol. The macrocyclic ring could be formed with high efficiency and selectivity by ring-closing metathesis (RCM) engaging a vinyl epoxide unit as one of the reaction partners. Because of the sensitivity of the targets to oxidizing and reducing conditions as well as to pH changes, the proper adjustment of the protecting group pattern for the peripheral -OH functions also constitutes a critical aspect, which has to converge to silyl groups only once the diene is in place. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) turned out to be a sufficiently mild fluoride source to allow for the final deprotection without damaging the precious macrolides.

Keywords: anticancer agents · macrocyclization · metathesis · natural products · Stille coupling

Introduction

Much excitement surrounds the amphidinolides, a family of more than 30 macrolides produced by dinoflagellate strains of the genus *Amphidinium*.[1] Even though many of these taxonomically rather distinctive unicellular organisms live in symbiosis with Okinawan *Amphiscolops* flatworms in the natural habitat, they can be cultivated in the laboratory in appropriate seawater media. Their prolific mixed polyketide biosynthetic machinery[2] is capable of producing a large variety of molecular frameworks adorned with rather unusual structural elements. Particularly distinguishing features are vicinal one-carbon branches, *exo*-methylene groups, s-*cis*-1,3-diene functions, alkenyl epoxides and, in many cases, odd-numbered ring sizes.[1] Low isolation yields, however, limit the supply of material available from the natural sources and hence severely hamper the structure elucidation as well as the in depth biological profiling of these compounds. Since the preliminary data suggest that all known amphidinolides are highly cytotoxic and some of them even reach exceptional levels of potency, these marine natural products constitute rewarding targets for total synthesis.[3–9]

This is particularly true for the individual members of the amphidinolide B, D, G and H series, some of which exhibit IC_{50} values in the picomolar range.[10–16] This impressive level of activity allowed meaningful SAR studies to be performed even with the very limited supply of the naturally occurring "library" of compounds of this sort (Figure 1). From these investigations it was concluded that the sensitive s-*cis*-diene, the ketone at C-20, as well as the alkenyl epoxide are mandatory structural elements for high biological ac-

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tivity.[12] Moreover, amphidinolide H1 (**9**) is known to interfere with the actin cytoskeleton, forming a covalent adduct with Tyr200 in the critical subdomain 4 of the protein by opening of its alkenyl epoxide unit.[17,18] This ligation results in stabilization of filamentous actin (F-actin) in a phalloidin-like manner, thus rendering **9** a potentially valuable probe for chemical biology if the supply of this marine natural product could be improved. Whether the interaction of **9** with actin is the cause for its truly impressive cytotoxicity ($IC_{50} = 0.52\ ng\,mL^{-1}$ for KB human epidermoid carcinoma cells),[10] however, remains to be elucidated.

Despite considerable interest in the amphidinolides of the B, H and G groups ever since their isolation,[19,20] these enticing targets withstood total synthesis for more than a decade. With the preparation of amphidinolide H1 (**9**), our group reported in 2007 the first conquest of any such target;[8] more recently, a total synthesis of the regioisomeric compound amphidinolide B1 (**1**) by Carter and co-workers has followed.[9] Outlined below is a full account of our work in this area. By virtue of improved access routes to the required building blocks and optimized procedures for their assembly, the flexibility inherent to the chosen route could be garnered, bringing amphidinolide B1 (**1**), B4 (**4**), G1 (**14**), H1 (**9**) and the putative H2 (**10**) into reach. In the latter case, however, the recorded data were inconsistent with those of the natural product. Based on the acquired knowledge about the structural subtleties of these compounds we were able to propose a revised structure for this congener, which matches the reported spectra of amphidinolide H2 very well.

Results and Discussion

Strategic considerations: The delicacy of the targets transpires, to some extend, from the structures of amphidinolide B1 (**1**)[13] and H1 (**9**)[11] in the solid state (Figure 2). Their rectangular shape allows a strong transannular hydrogen bond to be formed between the epoxide O-atom and the -OH at C-21; this interaction also persists in solution.[11,21]

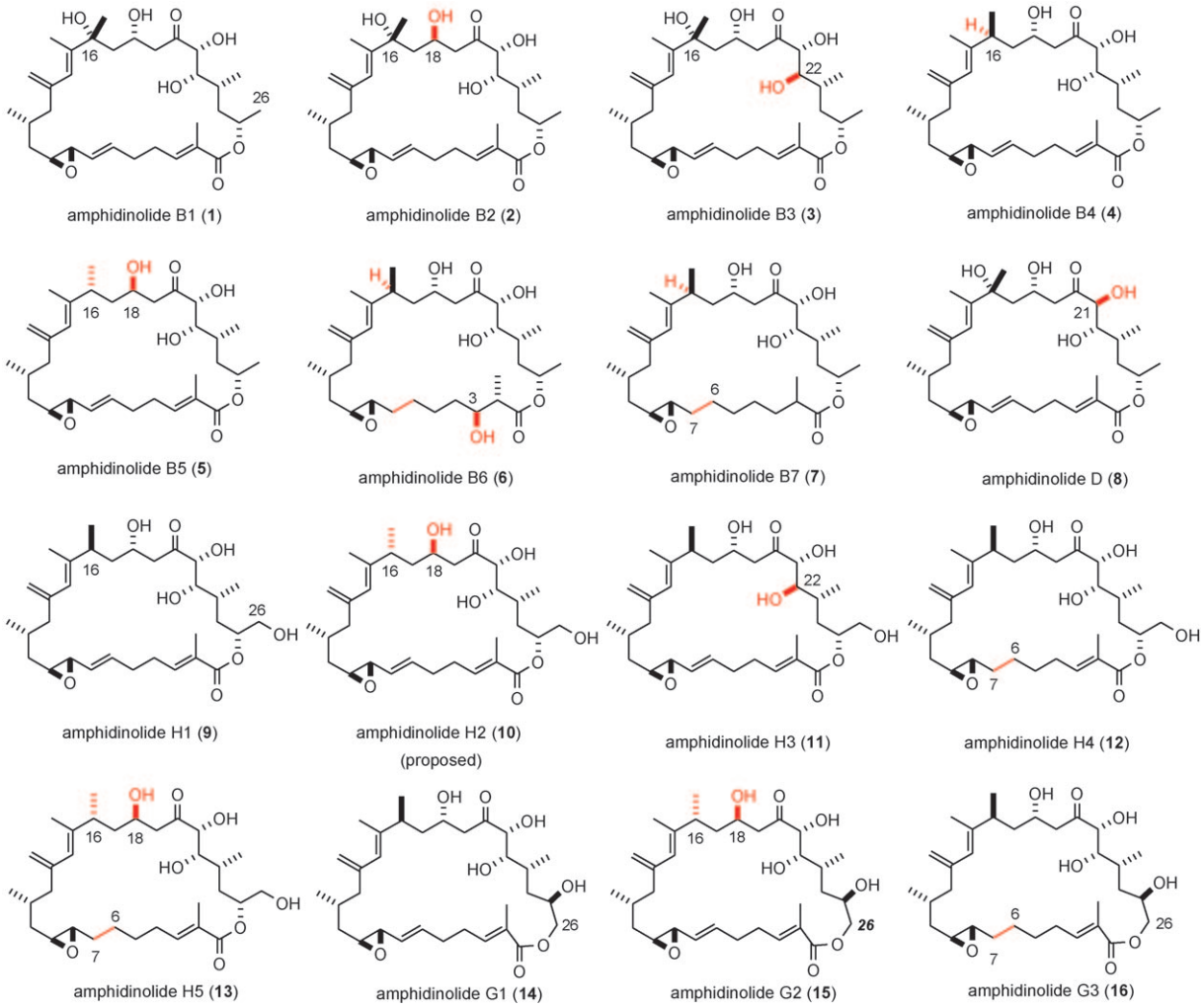


Figure 1. Naturally occuring "library" of amphidinolides of the B, D, G and H types. Highlighted in red are the structural changes relative to the parent compound of each particular series.

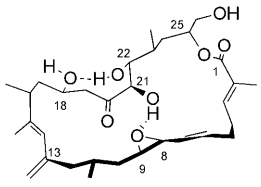
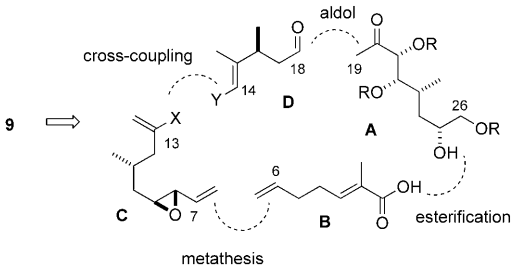


Figure 2. Hydrogen-bonding interactions determining the shape of amphidinolide H1 (**9**) in the solid state, as evident from the published X-ray structure.[11]

One might speculate that the significant distortion of the oxirane ring observed in the crystal structure of **9** is a result of this intramolecular activation.[11] In any case, the C-8–O bond (1.470(3) Å) is much longer than its C-9–O counterpart (1.448(3) Å), hence facilitating attack by a (biological) nucleophile[17,18] or even formation of an allylic cation at this site.

Another remarkable structural attribute is a second intramolecular hydrogen bond between the -OH group at C-22 and the oxygen atom at C-18 serving as the acceptor.[11] This tight contact constrains the Northeastern sector of **9** in an envelope-boat shaped eight-membered ring and forces the neighboring s-*cis*-1,3-diene out of planarity (−35.6(5)°). This twist might actually help stabilizing this unusual structural element, which is expected to be sensitive to isomerization to the thermodynamically more favorable internal 1,3-diene if coplanarity were reached.

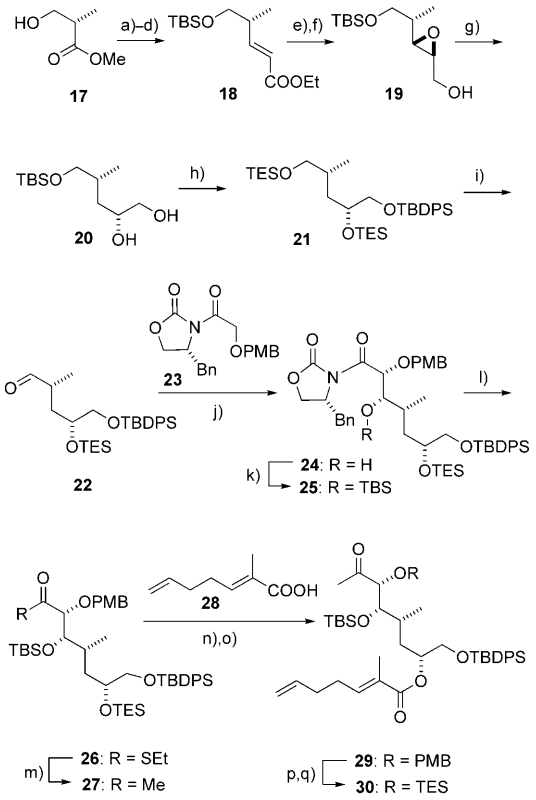
The individual amphidinolides of the B, D, G, and H series are largely isomeric to each other (Figure 1), showing up to three structural "point mutations" in the various sectors of a conserved backbone; the *seco*-acid then forms either a 26-membered (B, D, and H series) or a 27-membered lactone ring (G series).[1,10–16] To cope with this structural diversity, any general synthetic approach must be highly convergent. As exemplified in Scheme 1 for amphidinolide H1 (**9**),[10] we envisaged to assemble the basic skeleton from four building blocks **A**–**D** by esterification, an aldol reaction, metal-catalyzed cross-coupling, and olefin metathesis; proper modifications of these fragments should allow for the preparation of any of the targets shown in Figure 1 by following this basic blueprint. At the outset of the project, however, it was by no means obvious in which order these crucial operations should be executed. While related aldol reactions had already served in different published model studies,[19,20] we were somewhat concerned about the cross-coupling step in view of a literature report, wherein a highly advanced synthesis of **1** had to be abandoned because a late-stage Stille–Migita reaction[22] meant to install the 1,3-diene met with complete failure.[20a] Likewise, inter- as well as intramolecular metathesis reactions of alkenyl epoxides are surprisingly rare.[23,24] As the oxirane in **9** is highly distorted and its reactivity is key—at least in part—for the biological activity of this particular natural product, the likelihood of productive macrocyclization at the C6–C7 double bond adjacent to this reactive functionality was difficult to forecast. Therefore, the orchestration of the final assembly process had to evolve on the basis of the knowledge gathered en route to the targets.



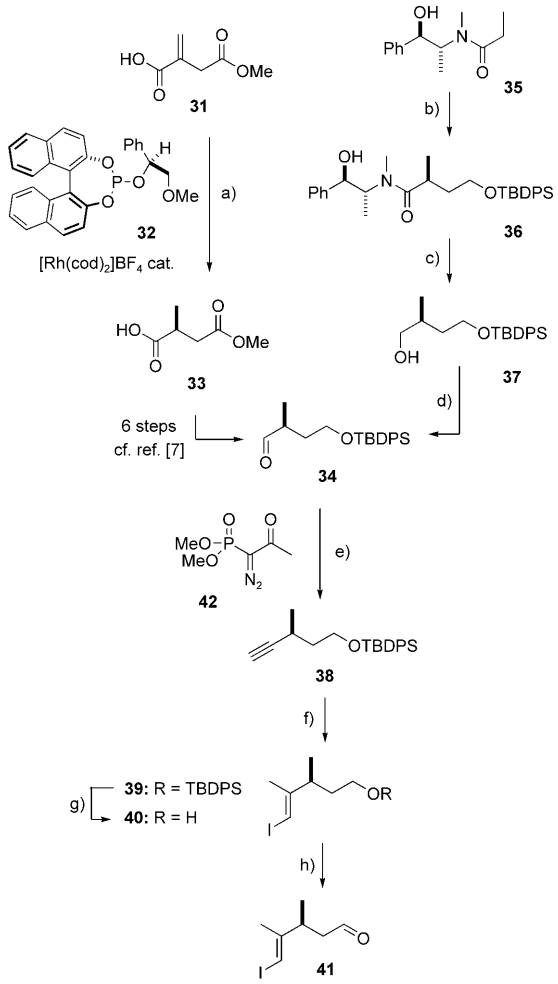
Scheme 1. Retrosynthetic analysis of amphidinolide H1 (**9**), representative for the chosen convergent approach towards all targets of this type of natural product.

Preparation of the building blocks: Our venture began with Roche ester **17**, which was converted into enoate **18** by following a literature route (Scheme 2).[25] Subsequent reduction set the stage for a Sharpless epoxidation[26] to give epoxide **19** which could be regioselectively opened distal to the -OH group on treatment with Dibal-H in toluene (d.r. >20:1).[27] However, it was imperative to quench the reaction with *t*BuOH at −60 °C to avoid cleavage of the primary TBS ether and hence secure good yields, in particular when working on a larger scale. Elaboration of **20** into the trisilylated product **21** followed by Swern oxidation[28] of the primary -OTES ether afforded aldehyde **22**, which was subjected to a *syn*-selective boron glycolate aldol reaction with **23** to give **24** in good yield (d.r. >20:1).[29,30] Following an O-silylation with premixed TBSOTf and 2,6-lutidine, the resulting product **25** was transformed into the corresponding thioester **26**, which readily afforded the required methyl ketone **27** on exposure to Me_2CuLi.[31] Selective removal of the secondary TES group allowed the unsaturated ester motif to be installed and hence completed the preparation of **29** as a fully functional surrogate of the "Southeastern" **AB** sector common to all amphidinolides of the H group. As we had to learn during the course of this investigation that the removal of the -OPMB group from any advanced intermediates is difficult once the 1,3-diene function has been installed, an analogous building block **30** carrying only silyl groups has also been prepared by straightforward protecting group interchange.

Itaconic acid monoester **31** served as the substrate for the preparation of the second key fragment (Scheme 3). Its asymmetric hydrogenation using the excellent phosphite-based methodology pioneered by Reetz and co-workers allowed multigram amounts of optically pure **33** (97% *ee*) to be prepared with low-catalyst loadings (0.15 mol%).[32] The necessary adjustment of the oxidation states of the termini upon elaboration into aldehyde **34**, however, required a number of protecting group manipulations. Even though these operations are high yielding and can be performed on large scale,[8] we decided to develop an alternative route to this key intermediate. Albeit an auxiliary[33,34] rather than a chiral catalyst forms its basis, the sequence is distinctly shorter (**35** → **37** → **34**). Aldehyde **34** was then homologated with the aid of the Bestmann–Ohira reagent **42**[35] to give alkyne **38**, which underwent a smooth carboalumination/io-



Scheme 2. a) TBSCl, imidazole, DMF; b) Dibal-H, CH_2Cl_2, −78 °C; c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C → RT; d) $(iPr)_2NEt$, LiCl, $(EtO)_2P(O)CH_2COOEt$, MeCN, 69% (over four steps); e) Dibal-H, CH_2Cl_2, −78 °C, 78%; f) (+)-DET, $Ti(OiPr)_4$ cat., *t*BuOOH, MS 4 Å, CH_2Cl_2, −20 °C, 74% (93% de); g) i) Dibal-H, toluene, −40 °C; ii) *t*BuOH/THF, −60 °C → RT, 78%; h) i) TBDPSCl, imidazole, CH_2Cl_2, 91%; ii) PPTS, EtOH, 55 °C; iii) TESCl, imidazole, CH_2Cl_2, 87% (over both steps); i) DMSO, $(COCl)_2$, $(iPr)_2NEt$, CH_2Cl_2, −78 °C → RT, 68%; j) **23**, Bu_2BOTf, toluene, −50 → −30 °C, 82%; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 81%; l) EtSH, *n*BuLi, THF, 0 °C, 87%; m) CuI, MeLi (2 equiv), Et_2O, −60 → −10 °C, 89%; n) PPTS, EtOH, 56%; o) **28**, DCC, DMAP, CH_2Cl_2, 75%; p) DDQ, CH_2Cl_2, 52%; q) TESCl, imidazole, DMAP, DMF, 45 °C, 79%. DET = diethyl tartrate, DMAP = 4-dimethylaminopyridine, TBDPS = *tert*-butyldiphenylsilyl, PPTS = pyridinium *p*-toluenesulfonate, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, MS = molecular sieves.

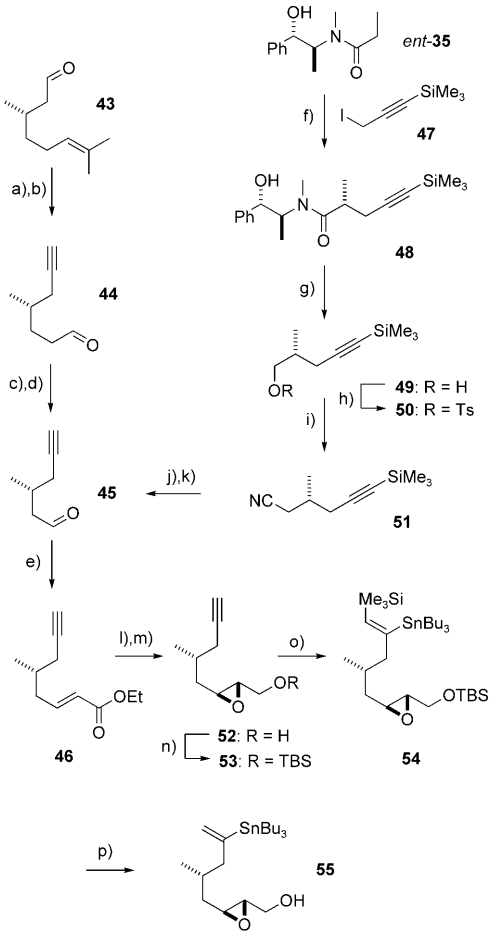


Scheme 3. a) $[Rh(cod)_2]BF_4$ (0.15 mol%), **32** (0.3 mol%), H_2 (1 atm), 1,2-dichloroethane, 99% (97% *ee*); b) i) LDA, LiCl, THF, −78 °C; ii) *tert*-butyl-(2-iodoethoxy)diphenylsilane, −78 → 0 °C, 98%; c) $BH_3{\cdot}NH_3$, LDA, THF, 0 °C → RT, 96%; d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C → RT, 94%; e) **42**, NaOMe, THF, 67%; f) i) Me_3Al, $[Cp_2ZrCl_2]$, 1,2-dichloroethane; ii) I_2, THF, −20 °C, 71–97%; g) TBAF, THF, 98%; h) DMP, $NaHCO_3$, aq. CH_2Cl_2, 0 °C → RT, 98%. TBAF = tetra *n*-butylammonium fluoride, DMP = Dess Martin periodinane.

dination with formation of **39**.[36] This product as well as aldehyde **41** derived thereof were then used as appropriate surrogates of fragment **D** in the assembly process.

The original approach to the third key fragment **C** borrowed the chiral methyl branch from (*S*)-citronellal (**43**, *ee* > 99%) (Scheme 4). After conversion of the aldehyde to an alkyne, two consecutive chemoselective ozonolysis reactions were necessary to adjust the carbon backbone of the "chiral pool" derived material to the current needs.[8] Even though this sequence can be performed on larger scale, the high volatility of the intermediates makes their purification tedious and adversely affects the reproducibility of the route. As a consequence, an alternative approach based on Myers auxiliary *ent*-**35**[33] was developed which avoids such inconveniences. Once the methyl branch was set by asymmetric alkylation, product **48** could be elaborated into ester **46** by an operationally simple and high yielding route. Subsequent Dibal-H reduction followed by Sharpless epoxidation of the resulting allylic alcohol installed the oxirane in **52** with high diastereocontrol (98% *de*). A regioselective and nicely scaleable palladium catalyzed silylstannation of the alkyne unit in **53** with commercial $Bu_3SnSiMe_3$,[37] followed by concomitant cleavage of the C–Si and O–Si bonds in **54** with TBAF in DMSO constitutes the key element of the chosen route to stannane **55** as the envisaged surrogate of fragment **C**.

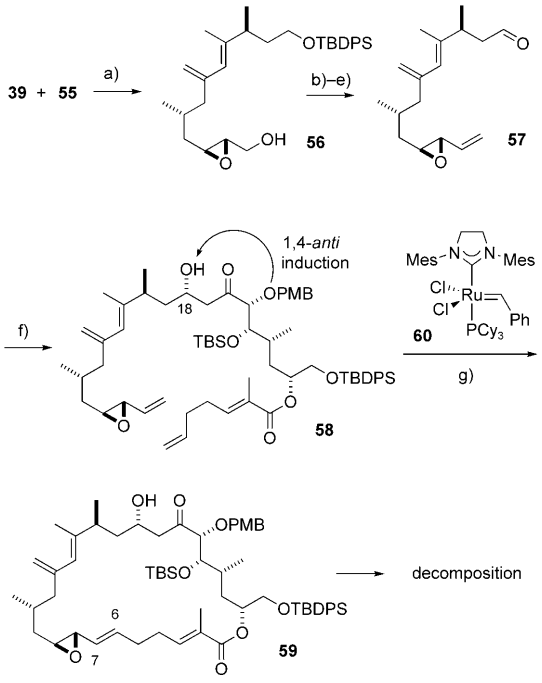
Intelligence gathering: With a good supply of the required building blocks secured, the development of a reliable assembly process became the immediate next goal. In the light of an important literature precedent, which reports the failure of an attempted late-stage Stille–Migita reaction for the formation of the sensitive s-*cis*-1,3-diene motif of the targets



Scheme 4. a) **42**, NaOMe, THF; b) O_3, CH_2Cl_2, −78 °C, then Me_2S; c) i) TBSOTf, Et_3N, CH_2Cl_2, −20 °C; ii) O_3, CH_2Cl_2, −78 °C, then Me_2S; e) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 69%; or: 25% (over five steps a) → e), see main text); f) LDA, LiCl, THF, then **47**, −78 → 0 °C, 97%; g) $BH_3{\cdot}NH_3$, LDA, THF, 0 °C → RT, 80%; h) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → RT, 72%; i) KCN, DMSO, 80 °C, 67%; j) Dibal-H, CH_2Cl_2, −78 °C; k) TBAF, THF, 0 °C → RT, 66% (over both steps); l) Dibal-H, THF, −78 °C, 82%; m) (+)-DET, $Ti(OiPr)_4$ cat., *t*BuOOH, MS 4 Å, CH_2Cl_2, −20 °C, 58% (98% de); n) TBSCl, imidazole, DMAP, CH_2Cl_2, 98%; o) $Bu_3SnSiMe_3$, $[Pd(Ph_3P)_4]$ (2 mol%), 1,2-dimethoxyethane (DME), sealed tube, 100 °C, 79–85%; p) TBAF, DMSO, 80 °C, 79%.

in question,[20a] it was planned to address this critical step early on. Our initial attempts to effect this transformation, however, reiterated the difficulties inherent to this particular transformation. Specifically, all our efforts to join the sensitive and sterically hindered coupling partners **39** and **55** by following the well established protocols were in vain.[38] Whereas the use of different palladium catalysts without further additives led to poor conversions, all attempts to boost the reactivity with the aid of copper co-catalysts and/or various fluoride sources resulted in hardly tractable mixtures. Even though not fully analyzed, inspection of the resulting crude material showed that oxidative dimerization of the stannane, isomerization of the coupling product to the more stable internal 1,3-diene, partial cleavage of the silyl protecting groups, and destruction of the fragile epoxy alcohol had interfered.

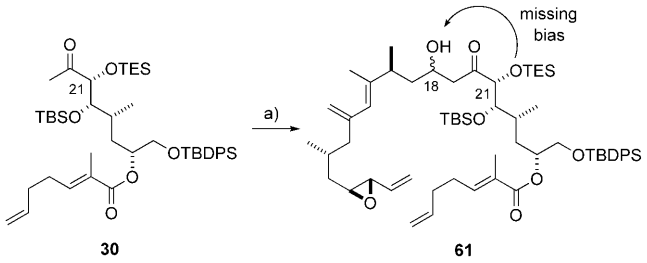
It was only after extensive investigation that a modified procedure could be found that allowed this critical transformation to be performed without any of these deleterious side reactions occurring (Scheme 5). Specifically, a combination of $[Pd(PPh_3)_4]$, copper thiophene-2-carboxylate (CuTC),[39] and $[Ph_2PO_2]^-[NBu_4]^+$[40] was found highly effective. Although the use of each individual ingredient has precedence in the extensive literature on Stille–Migita reactions, their combination is unique and allows to cope with fragile functionalities as well as with different C- and O-silyl protecting groups.[41] Only this particular chloride- and fluoride-free recipe afforded the desired cross-coupling product **56** in excellent yield, uncontaminated with isomerized diene. As the reaction can be performed at ambient temperature, the risk of thermal decomposition of the sensitive material is also minimized. It is worth mentioning that this new procedure has already served very well in other highly demanding cases in our laboratory.[41–43]



Scheme 5. a) $[Pd(Ph_3P)_4]$ (10 mol%), CuTC, $Ph_2PO_2^-$ NBu_4^+, DMF, 82%; b) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → RT; c) $[Ph_3PCH_3]Br$, $Na[N(SiMe_3)_2]$, THF, 0 °C, 65%; d) TBAF, THF, 87%; e) DMP, $NaHCO_3$, aq. CH_2Cl_2, 0 °C → RT; 75%; f) **29**, LDA, THF, −78 °C, 52%; g) **60**, (10 mol%); C_6H_6, 73%. CuTC = copper thiophene-2-carboxylate

Compound **56** was then transformed to the intact "Western" sector of amphidinolide H1 by oxidation of the epoxy alcohol with Dess–Martin periodinane,[44] Wittig olefination, cleavage of the silyl ether on the other terminus, and oxidation. Fragment coupling of the resulting aldehyde **57** was accomplished on treatment with the kinetic lithium enolate of ketone **29**, affording aldol (*S*)-**58** as a single isomer in 52% unoptimized yield. The excellent level of stereoinduction is ascribed to the 1,4-*anti* directing effect exerted by the

-OPMB substituent flanking the enolate.[45,46] This hypothesis was corroborated by the fact that the corresponding ketone **30** bearing an -OTES ether at C-21 instead of the -OPMB group, upon enolization and reaction with aldehyde **57**, gave a poor 2:1 ratio of the two possible aldol diastereomers **61** (Scheme 6). Not only was this mixture difficult to separate, but the Mosher analysis[47] showed that the major isomer had the undesirable *R* configuration, opposite to the one produced in the -OPMB case.



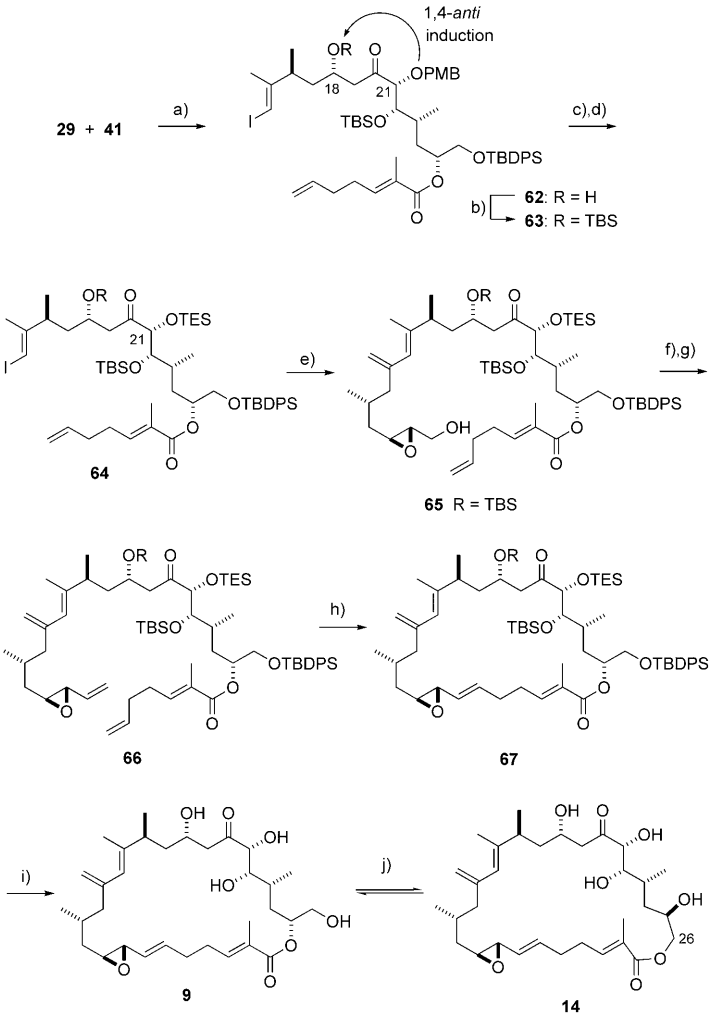
Scheme 6. a) LDA, THF, −78 °C, then **57**, 50–60 % (d.r. ≈2:1).

Although only a few metathesis reactions of vinyl epoxides had previously been reported,[23] exposure of **58** to catalytic amounts of the second generation Grubbs carbene complex **60**[48,49] at ambient temperature afforded the desired 26-membered cycloalkene **59** in 73 % yield as a single *E* isomer ($^3J_{H6,H7}$ = 18 Hz) (Scheme 5). Interestingly, the reaction proceeded only in benzene as the solvent, whereas the use of CH_2Cl_2 resulted in marginal conversion under otherwise identical conditions. This provides a striking illustration of our previous observation that second generation ruthenium carbene catalysts may exhibit (much) higher reactivity in aromatic media as compared to the widely used chlorinated solvents.[50]

With the macrocycle closed, the completion of the total synthesis of amphidinolide H required only the cleavage of the oxygen protecting groups. Whereas the silyl ethers could be deprotected with the aid of TASF as a particularly mild fluoride source,[51–53] all attempts to remove the PMB ether were met with failure. The destruction of the valuable material is ascribed to an uncontrolled oxidation of the diene that occurs at a competitive rate on treatment with either DDQ or CAN.[54,55] This notion is corroborated by the fact the acyclic diene **58** was equally destroyed, whereas deprotection of methyl ketone **29** devoid of the diene afforded the corresponding alcohol without incident (Scheme 2). Unfortunately, acidic or reductive conditions previously used in the literature for the cleavage of PMB ethers equally met with failure when applied to **59**.[54]

Total syntheses of amphidinolide H1 and G1: Although the synthetic venture summarized above had ultimately failed, important lessons could be drawn from it. Whereas the cross-coupling and the metathesis events, which seemed problematic at the outset, could be cleanly effected under optimized conditions, it became obvious that the choice and correct adjustment of the protecting groups is critical. Because of the sensitivity of the material, the final deprotection steps require notably mild conditions, whereas the aldol reaction needs bias from an adjacent donor site able to ligate the metal enolate intermediate.

The necessary compromise between these opposing needs was reached by changing the order of the fragment coupling events. Specifically, the Stille–Migita reaction was postponed until after the aldol step and elaboration of the proper protecting group regimen. To this end, the lithium enolate of **29** was reacted with the iodine-containing aldehyde **41** to give aldol **62** in good yield and appreciable selectivity (d.r. >10:1) (Scheme 7). Once the newly formed alcohol had been masked as a TBS ether, the protecting group at O-21 in **63** was swapped from PMB to TES. Gratifyingly, the cross-coupling of the elaborate vinyl iodide **64** thus formed

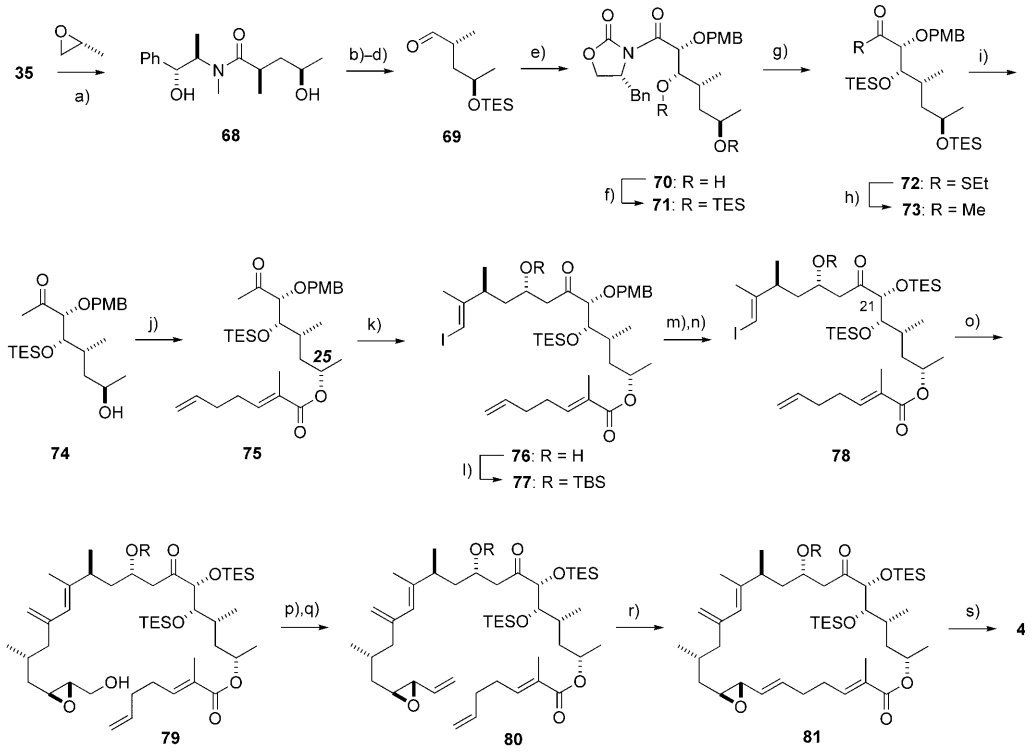


Scheme 7. a) LDA, THF, −78 °C, 70 %; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 79–94 %; c) DDQ, CH_2Cl_2/H_2O, 55–62 %; d) TESCl, imidazole, DMAP, DMF, 45 °C, 79 %; e) **55**, $[Pd(Ph_3P)_4]$ (0.7 equiv), CuTC, $Ph_2PO_2^-$ NBu_4^+, DMF, 89 %; f) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C; g) $[Ph_3PCH_3]Br$, $Na[N(SiMe_3)_2]$, THF, 0 °C, 65 % (over both steps); h) **60** (10 mol %), C_6H_6, 68–72 %; i) TASF, aq. THF/DMF (10:1), 0 °C → RT, 55 %; j) HCl cat., $CHCl_3$, **9**/**14** ≈3:1. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

with stannane **55** worked remarkably well under the previously optimized conditions. However, it was necessary to increase the catalyst loading to ensure complete conversion of these encumbered partners at ambient temperature. The resulting product **65** was then converted into vinyl oxirane **66**, which underwent a clean RCM reaction to give **67** as the required *E* isomer only. Because of the sensitivity of the compound, it was again imperative to perform the macrocyclization at $< 30\,^{\circ}C$. Finally, treatment of **67** with excess TASF allowed us to discard all silyl ethers, thus affording amphidinolide H1 in analytically pure form. Its spectroscopic properties were in good accord with the published data (cf. Tables 1–3 in the Experimental Section).[10,56] Moreover, synthetic **9** could be equilibrated with the ring expanded 27-membered congener amphidinolide G1 (**14**) under slighly acidic conditions.[10] Since these two isomers are separable by HPLC, a total synthesis of the latter has also been achieved.[56]

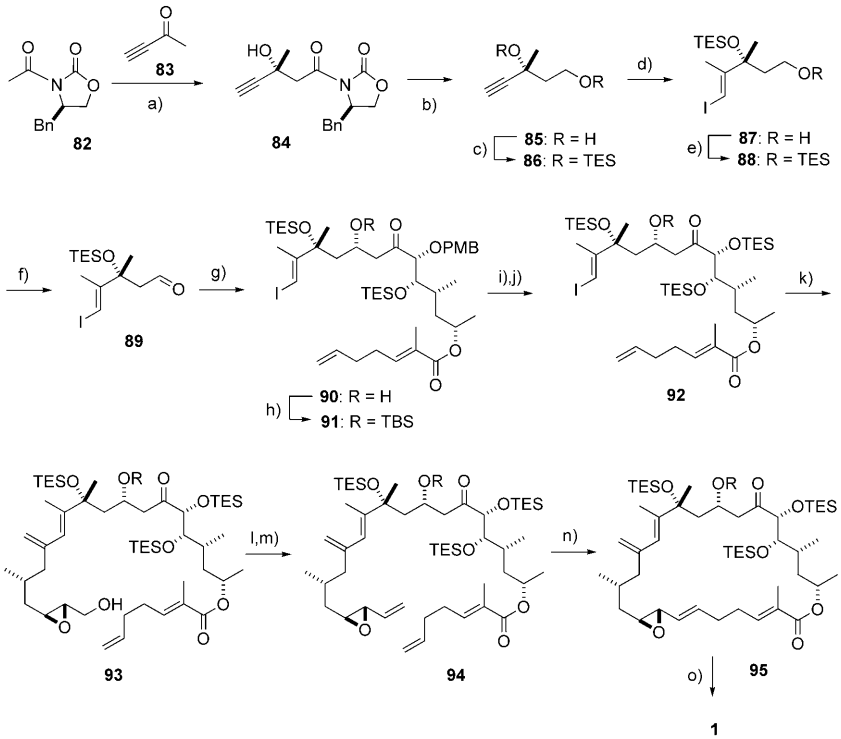
Amphidinolide B4: Next, we set out to probe the generality of the synthesis blueprint underlying the successful conquest of amphidinolide H1. Amphidinolide B4 (**4**)[15] was chosen as target for the initial foray, because it constitutes a fairly close relative; it only lacks the hydroxy group at C-26 and hence requires adjustment of a single building block. This extremely scarce metabolite of a recently collected *Amphidinium* strain (Y-100) exhibits exceptional potency, although only two cancer cell lines have been screened so far.[15]

The modified polyhydroxylated Eastern sector to be incorporated into its frame was again obtained by a *syn*-selective glycolate aldol reaction[29] between **23** and aldehyde **69**, which was prepared by alkylation of **35** with (*R*)-propenoxide[57] as the matched electrophile,[58] followed by appropriate oxidation state management (Scheme 8). The subsequent elaboration of product **70** followed the established route, except that the attachment of the ester moiety to C-25 had to occur with inversion of configuration (**74** → **75**).[59] A high yielding Mitsunobu reaction[60] served this purpose well. Upon deprotonation with LDA in Et_2O at low temperature, the resulting methyl ketone **75** added to aldehyde **41** to give both diastereomeric aldol products **76** in a 3.2:1 ratio.[61] The reason why this particular transformation shows significantly lower selectivity than the corresponding aldol reaction en route to amphidinolide H1 is not entirely clear. Since the two isomers were separable by routine chromatography, however, no attempt was made to further optimize this transformation. Rather, (*S*)-**76** was advanced to the cyclization precursor **80** by applying the successful sequence of protecting group swap at O-21 and Stille–Migita cross-coupling to install the 1,3-diene; in line with our ex-



Scheme 8. a) LDA, LiCl, THF −78 °C → RT, then (*R*)-propenoxide, −5 °C, 98% (85% de); b) TESCl, Et_3N, DMAP, CH_2Cl_2; c) $BH_3{\cdot}NH_3$, LDA, THF, 0 °C → RT, 80% (over both steps); d) TPAP, NMO, CH_2Cl_2; e) **23**, Bu_2BOTf, Et_3N, toluene, −40 °C, 62% (over both steps); f) TESCl, imidazole, CH_2Cl_2, 80%; g) EtSH, *n*BuLi, THF, 0 °C, 90%; h) CuI, MeLi (2 equiv), Et_2O, −60 °C, quant.; i) PPTS, EtOH, −15 °C, 89%; j) acid **28**, DIAD, PPh_3, toluene, 91%; k) LDA, Et_2O, −78 °C, then **41**, 58% (d.r. 3.2:1); l) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 81%; m) DDQ, CH_2Cl_2/H_2O, 73%; n) TESCl, imidazole, DMAP, DMF, 81% (over both steps); o) **55**, [$Pd(Ph_3P)_4$] (0.7 equiv), CuTC, $Ph_2PO_2^-$ NBu_4^+, DMF, 85%; p) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → RT; q) $Ph_3P{=}CH_2$, THF, 0 °C, 44% (over both steps); r) **60** (10 mol%), C_6H_6, 84%; s) TASF, aq. THF/DMF 10:1, 0 °C, 58%. DIAD = diisopropylazodicarboxylate, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

pectations, this crucial fragment coupling event again proceeded in excellent yield using the newly developed protocol.[41] After transformation of the hydroxy epoxide in **79** to the corresponding vinyl oxirane **80**, the material was subjected to RCM, which produced the required macrocycle **81** in 84% yield as a single stereoisomer. Finally, the total synthesis of amphidinolide B4 (**4**) was completed by removal of the peripheral silyl ethers with the aid of TASF.[51–53] The analytical and spectroscopic data of the synthetic samples were in excellent agreement with the reported spectra of this precious marine natural product (cf. Experimental Section).[15]



Scheme 9. a) LDA, THF/Et_2O, −78°C, 54%; b) $LiBH_4$, THF, MeOH, 90%; c) TESCl, imidazole, DMAP, DMF, 88%; d) i) *n*BuLi, Bu_3Sn–S*n*Bu_3, CuCN, MeI; ii) I_2, CH_2Cl_2, 90% (over both steps); e) TESCl, Et_3N, imidazole, DMAP, 84%; f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C → RT, quant.; g) **75**, LDA, Et_2O, 45%; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 86%; i) DDQ, CH_2Cl_2/H_2O, 0°C → RT, 92%; j) TESCl, imidazole, DMAP, DMF, 75%; k) **55**, [$Pd(Ph_3P)_4$] (0.7 equiv), CuTC, $Ph_2PO_2^-$ NBu_4^+, DMF, 87%; l) DMP, $NaHCO_3$, CH_2Cl_2, 0°C → RT; m) PPh_3=CH_2, THF, 0°C, 52% (over two steps); n) **60** (10 mol%), C_6H_6, 91%; o) TASF, aq. DMF, 0°C, 93%.

Amphidinolide B1: Amphidinolide B1 (**1**)[9,13,14,20] is a more stringent test for the generality of the chosen approach than the previous example, because it features a tertiary alcohol rather than a simple methyl branch at C-16. This site flanks the sensitive 1,3-diene moiety and hence provides additional steric impediment for the Stille–Migita coupling, notably when the -OH carries a bulky silyl protecting group. From the biological point of view, **1** retains one of the top positions amongst the amphidinolides known to date (IC_{50}= 0.00014 μg mL^{-1} (L1210 murine lymphoma); IC_{50}= 0.0042 μg mL^{-1} (KB human epidermoid carcinoma); IC_{50}= 0.122 μg mL^{-1} (HCT116 human colon cancer)).[13,14]

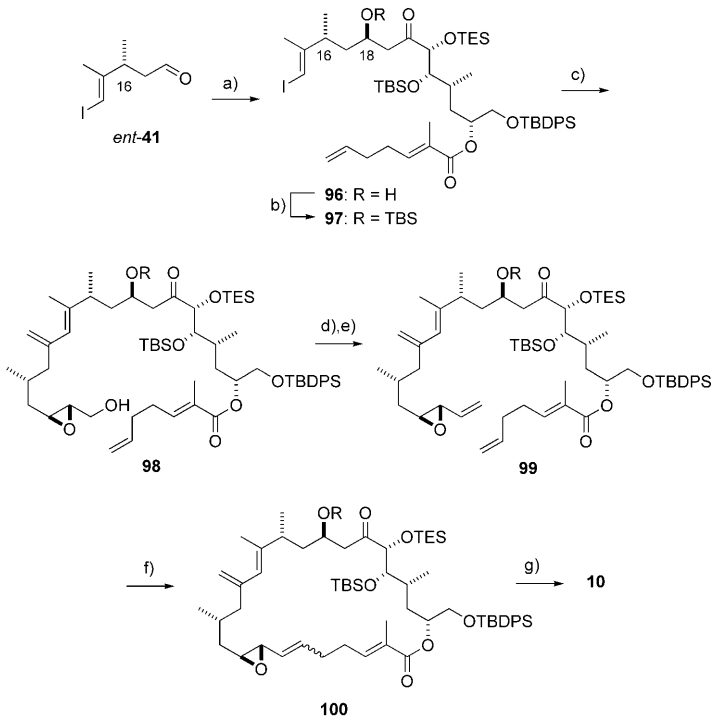
The modified Northern segment to be incorporated into the framework of this target was prepared as shown in Scheme 9. An Evans aldol reaction of **82** with alkynyl ketone **83** furnished **84** as the major isomer (d.r. 7.2:1).[30] Reduction with $LiBH_4$ followed by bis-silylation set the stage for a carbostannation/iodination of the terminal alkyne in **86**. In contrast to the literature, however, this transformation was best performed with a Gilman-type stannyl cuprate rather than the "higher order" stannyl cuprates previously recommended,[62] which led to significant decomposition in our case.[63] Under the optimized conditions, the reaction was exceptionally clean and afforded 90% yield over two steps. Since the primary TES-ether of the substrate was cleaved during the iodination, the resulting alcohol **87** could be directly converted into the corresponding aldehyde **89** with the aid of Dess–Martin periodinane (57%)[44] or by Swern oxidation (55%).[28] Interestingly, however, the Swern reaction was much improved and occurred in essentially quantitative yield when the corresponding di-TES ether **88** was employed. Even though this requires reprotection of **87** and hence renders the sequence one step longer, this variant is prefered for its higher efficiency.

With aldehyde **89** in hand, the assembly of amphidinolide B1 was accomplished by following the route outlined above. Thereby, it was the aldol reaction with methyl ketone **75** which was the least productive step of the entire sequence. In contrast, the challenging Stille–Migita cross-coupling, when performed under the newly developed conditions,[41] was insensitive to the increased steric bulk in the electrophilic component **92**, delivering the desired 1,3-diene product **93** in remarkably high yield. Likewise, the cyclization of the macrolactone ring by RCM (**94** → **95**) occurred uneventfully and stereoselectively. Synthetic amphidinolide B1 (**1**) matched the data of the natural sample in every regard (see the Experimental Section).[9,13,14]

Amphidinolide H2—Preparation and structure revision: A subset of the amphidinolides of the B/H/G types, that is compounds **5**, **10**, **13**, **15**, is reported to show a stereochemical relationship between the methyl branch at C-16 and the hydroxyl group at C-18 opposite to that of amphidinolide H1.[1] To demonstrate that our approach can also cope with

products of this type, we undertook the total synthesis of amphidinolide H2 (**10**).[12]

The required fragment *ent*-**41** was prepared by following the sequence depicted in Scheme 3 using the enantiomeric auxiliary *ent*-**35**. Not unexpectedly, addition of alkali enolates of **30** to this aldehyde afforded the—in this case undesired—aldol (*S*)-**96** as the major product.[64] Gratifyingly, however, the corresponding boron enolate, derived from **30** on treatment with Cy_2BCl and Et_3N, furnished the required compound (*R*)-**96** in a workable 4:1 ratio (Scheme 10).[45] After removal of the minor isomer by flash chromatography, the product was elaborated into compound **99** by following the established route; the configurational changes did not diminish the efficiency of the Stille–Migita fragment coupling at all (**97** → **98**). In contrast, the macrocyclization of **99** was somewhat less efficient and also gave small amounts of the isomeric (*Z*)-alkene **100** (*E*/*Z* 5.2:1). This outcome illustrates how subtle changes at remote sites of a given cyclization precursor can substantially alter the stereochemical course of ring-closing metathesis reactions catalyzed by Grubbs-type ruthenium carbene complexes.[65] Removal of the protecting groups with TASF then furnished **10** proposed to represent amphidinolide H2. However, the recorded spectra of this compound unmistakably deviated from the reported ^1H and ^{13}C NMR data of the natural product (see Table 8 in the Experimental Section for the full data set).[12,66,67]



Scheme 10. a) **30**, Cy_2BCl, Et_3N, −78 → −20 °C, then H_2O_2, pH 7 buffer, 58% (d.r. 4:1); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 89%; c) **55**, [Pd(Ph_3P)$_4$] (0.7 equiv), CuTC, $Ph_2PO_2^-$ NBu_4^+, DMF, 87%; d) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → RT; e) PPh_3=CH_2, THF, 0 °C, 57% (over both steps); f) **60** (10 mol%), C_6H_6, 56% (*E*/*Z* 5.2:1); g) TASF, aq. DMF, 0 °C, 46%.

As evident from Figure 3, substantial deviations were recorded for the "south-western" C-6–C-13/C-28 sector. This result was unexpected because this region is strictly conserved within all amphidinolides of the B/D/G/H series known to date (cf. Figure 1).[1] As evident from the X-ray structures of **1**[13] and **9**,[11] however, the C-6–C-13 segment entertains a close transannular relationship with the polyhydroxylated sector of the molecule through a strong meridial hydrogen bond engaging the epoxide O atom (Figure 2). Therefore we contemplated that the observed mismatch at C-6–C-13 may actually report a stereochemical misassignment in the transannular region of this particular macrolide, residing somewhere between C-16 and C-23. Under this premise, it seemed likely that the hydroxyl group at C-21 might be a "hot-spot" since the epoxide directly connects to this site. Moreover, the shift difference of no less than $\Delta\delta = -1$ ppm of the aldol at C-18, which is known to engage in a hydrogen bond with the -OH group at C-22,[11] also raises doubts about the assignment of this latter chiral center.[68] In view of these data and in consideration of the other known amphidinolides (Figure 1),[1] we presumed that structures **101** or **102**, which solely differ from each other by the configuration of C-16, might possibly represent amphidinolide H2. Among them, **102** seemed more likely, because the methyl branches C-30 and C-31 in **10** also show appreciable deviations from the reported values (Figure 3).

Compound **102** was hence prepared in a stereochemically unambiguous manner for comparison with the natural product (Scheme 11). This goal was attained by using the antipodal auxiliary *ent*-**23** for a *syn*-glycolate aldol reaction with aldehyde **22**.[29] With the resulting product **103** in hand, it sufficed to follow the customary route to the required cyclization precursor **109**. The only modification lies in the aldol

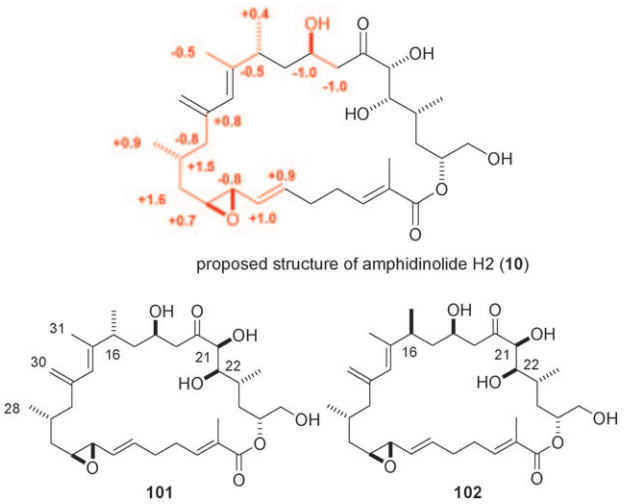
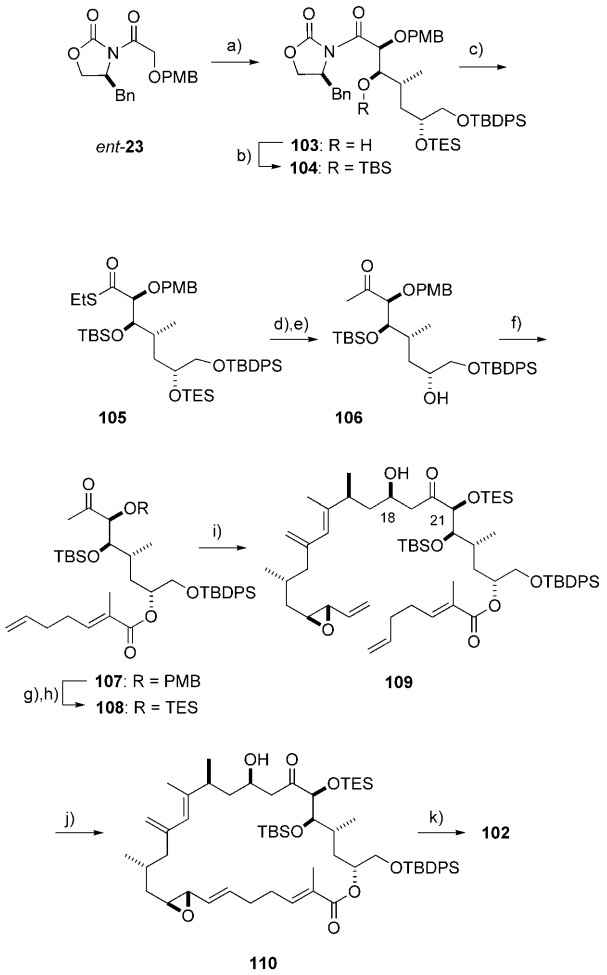


Figure 3. Characteristic shift differences ($\Delta\delta_C$) between the ^{13}C NMR data of amphidinolide H2 and synthetic **10**, which corresponds to the originally proposed structure. The regions showing the biggest mismatch are highlighted in red (for the full data set, see Table 8 in the Experimental Section). Two possible revised structures that might represent the natural product, cf. main text.



Scheme 11. a) Bu_2BOTf, Et_3N, toluene, −50 °C, then aldehyde **22**, 82 %; b) TBSOTf, 2,6-lutidine, 0 °C; c) EtSH, *n*BuLi, THF, 0 °C, 61 % (over both steps); d) CuI, MeLi (2 equiv), Et_2O, −60 → −20 °C; e) PPTS, EtOH, 69 % (over both steps); f) acid **28**, DCC, DMAP, CH_2Cl_2, 73 %; g) DDQ, CH_2Cl_2/H_2O, 0 °C → RT; h) TESCl, imidazole, DMAP, DMF, 50 °C, 65 % (over both steps); i) LDA, THF, −78 °C, then aldehyde **57**, 49 %; j) **60** (10 mol %), C_6H_6, 54 %; k) TASF, aq. THF/DMF 4:1, 0 °C, 80 %.

reaction, which was best performed with the TES-ether derivative **108** rather than its O-PMB congener **107**. As this avoids a subsequent protecting group interchange at O-21, the fragment coupling can be performed with excellent selectivity (d.r. >20:1) using the more advanced aldehyde **57**, which already contains the sensitive 1,3-diene entity. The ring-closing metathesis and ultimate silyl cleavage performed well. It was gratifying to see that the NMR spectra of the resulting product **102** recorded at 600 MHz were in excellent agreement with the published data of amphidinolide H2 (see Table 8 in the Experimental Section).[12] Even though we are aware that the ultimate proof would require preparation of all possible stereoisomers and their direct comparison with an authentic sample, the striking match provides compelling evidence that the stereostructure of amphidinolide H2 needs to be revised from **10** to **102**.[67]

Conclusion

The delicacy and dense array of functional groups decorating the conserved carbon framework of the amphidinolides of the B/D/G/H types impeded their synthesis for many years. Gratifyingly, however, we were able to devise a robust entry into this class of extremely scarce but expetionally potent anticancer agents of marine origin. The convergency of the chosen route holds the promise that each member of this family should be available upon suitable modification of the required four basic building blocks. This notion is supported by the fact that a set of five representative members has been prepared by such simple adaptations without need to change the underlying synthesis blueprint to any significant extent. The appreciable overall yields illustrate the reliability of the approach, even though not all steps were fully optimized for each individual analogue prepared during this campaign. Moreover, the fact that the synthesis can be readily diverted from a given to a conceived target was instrumental for the structure revision of amphidinolide H2. The inherent flexibility expressed in these examples should enable a more profound and systematic editing of the molecular architecture and hence could power a detailed evaluation of the cytotoxicity profile and actin-binding capacity of these valuable lead compounds.[69] Although dealing with a different type of amphidinolides, our first attempts along such lines are outlined in the accompanying papers.[70,71]

Key to success of this synthetic endeavour was a careful adjustment of the protecting groups as well as the development of a highly productive protocol for Stille–Migita cross-coupling of alkenyl iodides,[41–43] which allowed the conspicuous but very sensitive s-*cis*-1,3-diene unit of the targets to be installed with high efficiency, despite the bulk of the reaction partners. It is anticipated that this method should pay dividends in other demanding settings too. Moreover, the remarkable ease of formation of the macrocyclic frame by RCM at the activated alkenyl oxirane site constitutes yet another triumph for Grubbs-type second-generation catalysts,[48–50] and augurs well for further metathesis reactions of vinyl epoxides,[23] which remained a relatively unexplored class of alkenes despite the vast literature on metathesis in general that has accumulated during the last decade.[24]

Experimental Section

General: All reactions were carried out under Ar in flame-dried glassware. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, Et_3N, CH_3CN, DMSO, (CaH_2), hexane, toluene (Na/K), DMF (Desmodur 15, dibutyl tin dilaurate), MeOH, EtOH (Mg). Flash chromatography (FC): Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on Bruker DPX 300, AMX 300, AV 400, AV 400, DPX 600 and AVIII 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C = 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H = 7.26$ ppm; CD_2Cl_2: $\delta_C = 53.8$ ppm; residual ^1H: $\delta_H =$

5.32 ppm; CD_3OD $\delta_C = 49.0$ ppm; residual ^1H: $\delta_H = 3.30$ ppm; [D_8]acetone: $\delta_C = 29.8$ ppm; residual ^1H: $\delta_H = 2.05$ ppm). Where indicated, the signal assignments are unambiguous; the numbering scheme is arbitrary as shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs, cosydqtp, and cosygpqf); HSQC (invietgssi, and hsqcedetgpsisp^2.2) optimized for ^1J(C,H) = 145 Hz; HMBC (inv4gslplrnd, and hmbcetgpl3nd); for correlations via ^nJ(C,H); HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms; NOESY (noesygpph). IR: Magna IR750 (Nicolet) or Spectrum One (Perkin-Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

Preparation of the building blocks of type C

Compound 48: iPr$_2$NH (22 mL, 15.12 mmol) and nBuLi (1.6 M solution in hexane, 9 mL, 14.5 mmol) were successively added to a suspension of flame-dried LiCl (1.34 g, 31.5 mmol) in THF (15 mL) at 0 °C. The yellow slurry was stirred for 15 min at this temperature and for 20 min at ambient temperature before it was cooled to −78 °C. A solution of *ent*-**35** (900 mg, 4.2 mmol) in THF (9 mL) was added via cannula and stirring continued for 45 min at −78 °C. To complete the enolization, the mixture was stirred at 0 °C for 15 min and another 15 min at room temperature. The mixture was then cooled to −78 °C before iodide **47** (1.5 g, 6.3 mmol) was added neat. The reaction was allowed to reach 0 °C and stirred at this temperature for 18 h. For work up, sat. aq. NH_4Cl (60 mL) was added and the mixture extracted with EtOAc (2×50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 7:3) to give product **48** as a colorless syrup (1.26 g, 97 %). $[\alpha]_D^{20} = +13.8$ ($c = 0.5$, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6, rotamers; signals of the minor rotamer are marked *): $\delta = 7.13$ (d, $J = 7.1$ Hz, 2H), 7.05–6.87 (m, 3H), 4.41 (brs, 1H, OH), 4.35 (d, $J = 6.8$ Hz, 1H), 4.16 (d, $J = 7.8$ Hz, 1H)*, 3.71 (m, 1H), 2.69 (s, 3H)*, 2.41–2.38 (m, 1H), 2.31 (dd, $J = 16.6$, 6.3 Hz, 1H), 2.22 (s, 3H), 2.11 (dd, $J = 16.9$, 7.8 Hz, 1H), 1.04 (d, $J = 6.6$ Hz, 3H)*, 0.84 (d, $J = 6.6$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H), 0.51 (d, $J = 6.6$ Hz, 3H)*, 0.03 (s, 9H)*, −0.01 ppm (s, 9H); ^{13}C NMR (100 MHz, C_6D_6): $\delta =$ 175.9, 175.5*, 143.1, 142.4*, 128.3, 128.1*, 127.8, 127.5, 126.6*, 125.2, 106.8*, 105.9, 85.4*, 85.2, 75.8, 75.2*, 59.8, 58.1*, 36.1, 35.6*, 27.2, 21.0, 20.3*, 17.2, 15.2*, 1.1*, 0.28 ppm; HRMS (ESI): m/z: calcd for $C_{19}H_{30}NO_2Si$ [M^+]: 332.2042, found: 322.2045.

Compound 50: nBuLi (1.6 M solution in hexanes, 78.8 mL, 126 mmol) was added dropwise to a solution of iPr$_2$NH (18.3 mL, 132 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at room temperature for 10 min and then cooled again to 0 °C before $BH_3{\cdot}NH_3$ (4.75 g, 153.8 mmol, 90 %) was added in portions. After stirring of the slurry at room temperature for 1 h, a solution of compound **48** (10.2 g, 30.7 mmol) in THF (60 mL) was added at 0 °C and the mixture stirred at ambient temperature for 2 h. For work up, the reaction was quenched at 0 °C with aq. HCl (1 M, 18 mL). Extraction with Et_2O (3×120 mL), drying of the organic layers over Na_2SO_4, evaporation of the solvents and purification of the residue by flash chromatography (pentanes/diethyl ether 1:1) afforded alcohol **49** (4.2 g, 80 %) which was immediately used in the next step.

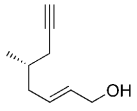
To a solution of **49** thus obtained in CH_2Cl_2 (30 mL) at 0 °C were successively added Et_3N (5.1 mL, 36.1 mmol), DMAP (0.1 g) and tosyl chloride (5.5 g, 28.9 mmol). The resulting mixture was stirred overnight before the reaction was quenched with sat. aq. NH_4Cl (40 mL). A standard extractive work up followed by flash chromatography (hexanes/*tert*-butyl methyl ether 4:1) afforded tosylate **50** as a pale yellow oil (5.75 g, 72 %). $[\alpha]_D^{20} = +9.0$ ($c = 0.3$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 3.85 (m, 2H), 2.32 (s, 3H), 2.16 (m, 2H), 1.94 (app. oct., $J = 6.3$ Hz, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.01 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.7$, 132.9, 129.8, 127.9, 103.6, 86.7, 73.3, 32.3, 23.4, 21.6, 15.8, −0.01 ppm; IR (film): $\tilde{\nu} =$ 2962, 2174, 1598, 1495, 1457, 1362, 1291, 1249, 1188, 1175, 1097, 1036, 1020, 999, 971, 945, 837, 790, 665 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{24}SSi$ [M^++H]: 325.1291, found: 325.1293.

Compound 51: KCN (400 mg, 6.1 mmol) was added to a solution of tosylate **50** (1.0 g, 3.08 mmol) in DMSO (15 mL) and the resulting mixture was stirred for 12 h at 80 °C. For work up, the mixture was diluted with sat. aq. $NaHCO_3$ (200 mL) and Et_2O (200 mL), the aqueous layer was extracted with Et_2O (2×150 mL), the combined organic phases were washed with brine (2×150 mL), dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) provided product **51** as a yellow oil (369 mg, 67 %). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.41$ (dd, $J = 16.7$, 5.8 Hz, 1H), 2.32–2.24 (m, 2H), 2.18 (dd, $J = 16.9$, 6.8 Hz, 1H), 2.02 (app. oct., $J = 6.1$ Hz, 1H), 1.07 (d, $J = 6.6$ Hz, 3H), 0.07 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 118.4$, 103.1, 87.6, 34.1, 30.2, 26.3, 23.3, 19.0, 14.1, 0.01 ppm; IR (film): $\tilde{\nu} = 2963$, 2247, 2176, 1458, 1426, 1345, 1250, 1035, 996, 842, 760, 699 cm^{-1}; HRMS (EI): m/z: calcd for $C_{10}H_{17}NSi$ [M^++H]: 180.1207, found: 180.1208.

Aldehyde 45: Dibal-H (1 M in CH_2Cl_2, 4 mL, 4 mmol) was added to a solution of nitrile **51** (369 mg, 2.06 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After stirring for 1 h at this temperature, the reaction was quenched with a cold (0 °C) sat. aq. solution of Rochelle salt (80 mL) and the mixture slowly warmed to room temperature over a period of 4 h. The separated aqueous layer was extracted with Et_2O (2×100 mL), the combined organic phases were washed with brine (2×100 mL), dried over Na_2SO_4 and evaporated. The resulting crude aldehyde was dissolved in THF (5 mL) and treated with a solution of TBAF (1 M in THF, 3 mL, 3 mmol). After stirring for 2 h, all volatile materials were evaporated and the residue purified by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) to give aldehyde **45** as a colorless oil (149 mg, 66 %). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.79$ (t, J 1.8 Hz, 1H), 2.68–2.58 (m, 1H), 2.40–2.15 (m, 4H), 2.00 (t, $J = 2.7$ Hz, 1H), 1.06 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.9$, 82.0, 70.4, 49.7, 27.5, 25.7, 19.8 ppm.

Compound 46: $(EtO)_2P(O)CH_2COOEt$ (3.0 mL, 15 mmol) was added to a suspension of NaH (360 mg, 15 mmol) in THF (15 mL) at 0 °C and the resulting mixture stirred for 1.5 h at ambient temperature. A solution of aldehyde **45** (1.5 g, 13.6 mmol) in THF (15 mL) was introduced and stirring continued for 1 h. The reaction was then carefully quenched with an aqueous solution of citric acid (10 % *w*/*w*, 10 mL), the mixture was extracted with CH_2Cl_2 (2×20 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 10:1) to give ester **46** as a colorless oil (1.69 g, 69 %). $[\alpha]_D^{20} = +25$ ($c = 0.4$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 6.91 (dt, $J = 15.6$, 7.4 Hz, 1H), 5.85 (dt, $J = 15.6$, 1.5 Hz, 1H), 4.18 (q, $J =$ 7.1 Hz, 2H), 2.39–2.30 (m, 1H), 2.22–2.09 (m, 3H), 1.99 (t, $J = 2.7$ Hz, 1H), 1.87 (ttd, $J = 6.7$, 6.7, 6.7 Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.02 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.6$, 147.1, 123.2, 82.4, 69.9, 60.3, 38.4, 32.0, 25.4, 19.5, 14.5 ppm; IR (film): $\tilde{\nu} = 3307$, 2960, 2929, 2205, 1716, 1654, 1458, 1368, 1319, 1265, 1200, 1160, 1043, 983, 837 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{16}O_2Na$ [M^++Na]: 203.1048, found 203.10469.

(5*S*,*E*)-5-Methyloct-2-en-7-yn-1-ol: Dibal-H (1 M in hexanes, 106 mL, 106 mmol) was added over 30 min to a solution of ester **46** (7.62 g, 42.3 mmol) in THF (100 mL) at −78 °C and the resulting mixture was stirred for 1 h at this temperature. The reaction was quenched by the careful addition of MeOH (50 mL) and the mixture was allowed to warm to ambient temperature. A sat. aq. solution of Rochelle's salt was added (200 mL) and the mixture was vigorously stirred for 2 h to reach a clean phase separation. The aqueous phase was extracted with *tert*-butyl methyl ether (3×50 mL), the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and evaporated. Flash chromatography of the residue (pentanes/Et_2O 2:1) afforded the title compound as colorless oil (4.80 g, 82 %). $[\alpha]_D^{20} = +18$ ($c = 0.25$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.71$–5.60 (m, 2H), 4.10–4.08 (m, 2H), 2.20–2.12 (m, 3H), 2.10 (dd, $J = 6.0$, 3.3 Hz, 1H), 1.96 (t, $J = 2.6$ Hz, 1H), 1.75 (oct, $J = 6.7$ Hz 1H), 1.3 (brs, 1H), 0.99 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 131.1, 130.8, 83.1, 69.5, 63.8, 38.6, 32.6, 25.7, 19.3 ppm; IR (film): $\tilde{\nu} =$



3310, 2956, 2928, 2857, 1461, 1252, 1000, 971 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_9H_{14}ONa$ [M^++Na]: 161.09423, found: 161.09422.

Compound 52: A suspension of powdered, flame-dried molecular sieves (4 Å, 2.0 g) in CH_2Cl_2 (70 mL) was stirred for 3 h. The resulting mixture was cooled to −20 °C before L-(+)-DET (236 μL, 12 mol %) and Ti(O*i*Pr)$_4$ (340 μL, 10 mol %) were introduced, followed by the dropwise addition of *t*BuOOH (4.20 mL, 45.1 mmol, dried over activated molecular sieves for 3 h prior to use). After stirring for 30 min, a solution of (5*S*,2*E*)-5-methyloct-2-en-7-yn-1-ol (2.84 g, 20.5 mmol) in CH_2Cl_2 (20 mL), which had also been stirred over activated MS 4 Å for 3 h prior to use, was added and the mixture was stirred at −20 °C for 14 h. After reaching 0 °C, the mixture was slowly poured into a cold (0 °C) solution of $FeSO_4 \cdot 7H_2O$ (7.0 g) and citric acid (2.5 g) in H_2O (23 mL). After stirring for 30 min, the aqueous phase was extracted with CH_2Cl_2 (2× 50 mL), the combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and evaporated, and the residue purified by flash chromatography (pentanes/Et_2O 2:1) to give **52** as a colorless oil (1.84 g, 58 %). $[\alpha]_D^{20}$ = −27.1 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (br d, *J* = 12.6 Hz, 1H), 3.68–3.60 (m, 1H), 3.00 (ddd, *J* = 7.2, 5.2, 2.3 Hz, 1H), 2.93–2.91 (m, 1H), 2.22 (ddd, *J* = 16.7, 6.4, 2.6 Hz, 1H), 2.21 (ddd, *J* = 16.7, 6.4, 2.6 Hz, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.96–1.90 (m, 1H), 1.72–1.65 (m, 2H), 1.52 (ddd, *J* = 13.6, 8.2, 6.4 Hz, 1H), 1.08 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.6, 69.9, 61.6, 58.7, 54.5, 37.8, 30.7, 26.1, 19.5 ppm; IR (film): $\tilde{\nu}$ = 3422, 3296, 1460, 1428, 1075, 1025, 703 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_9H_{14}O_2Na$ [M^++Na]: 177.0891, found 177.0891.

Compound 53: Imidazole (1.36 g, 20.0 mmol), DMAP (170 mg, 1.34 mmol) and TBSCl (2.40 g, 16.0 mmol) were added to a solution of the compound **52** (2.06 g, 13.36 mmol) in CH_2Cl_2 (40 mL) and the resulting mixture was stirred overnight. A standard extractive work up followed by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) afforded product **53** as a colorless oil (3.54 g, 98 %). $[\alpha]_D^{20}$ = −8.1 (*c* = 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.69 (dd, *J* = 11.9, 4.4 Hz, 1H), 2.86–2.82 (m, 2H), 2.24 (ddd, *J* = 16.7, 6.2, 2.6 Hz, 1H), 2.16 (ddd, *J* = 16.7, 6.7, 2.6 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.95–1.88 (m, 1H), 1.72–1.65 (m, 1H), 1.46 (ddd, *J* = 13.8, 8.4, 5.2 Hz, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.8, 69.7, 63.6, 58.9, 55.0, 38.0, 30.8, 26.1, 26.0, 19.4, 14.1, −5.1, −5.2 ppm; IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1472, 1463, 1252, 1109, 1088, 833, 776 cm^{-1}; MS (EI): *m/z* (%): 181 (3), 129 (4), 101 (10), 117 (100), 75 (58); HRMS (ESI): *m/z*: calcd for $C_{15}H_{28}O_2SiNa$ [M^++Na]: 291.1752, found: 291.1751.

Compound 54: Bu_3Sn-$SiMe_3$ (1.50 mL, 4.46 mmol) was added to a solution of alkyne **53** (1.0 g, 3.73 mol) in degassed 1,2-dimethoxyethane (DME, 10 mL). [Pd(PPh_3)$_4$] (86 mg, 2 mol %) was then added, the Schlenck tube was sealed and heated to 100 °C overnight. Celite was added to the black mixture and all volatile materials were evaporated. The loaded Celite was added to the top of a silica gel column and the product was eluded with pentanes/Et_2O (1:0 → 75:1) to afford a yellow oil contaminated with PPh_3. To remove this impurity, the residue was dissolved in CH_3CN (5 mL) before MeI (1.2 mL, 18.6 mmol, 5.0 equiv) was added. The mixture was stirred for 0.5 h before it was filtered though a pad of silica gel (washed with pentanes) to afford pure **54** as a colorless oil (1.42 g, 85 %). $[\alpha]_D^{20}$ = −1.3 (*c* = 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (br s, 1H), 3.77 (dd, *J* = 15.7, 4.6 Hz, 1H), 3.68 (dd, *J* = 15.7, 6.0 Hz, 1H), 2.82–2.77 (m, 2H), 2.30 (dd, *J* = 17.0, 8.9 Hz, 1H), 2.17 (dd, *J* = 17.0, 9.6 Hz, 1H), 1.76–1.64 (m, 2H), 1.52–1.42 (m, 6H), 1.37–1.26 (m, 6H), 1.20–1.10 (m, 1H), 0.94–0.86 (m, 27H), 0.09 (s, 9H), 0.08 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 146.0, 64.0, 59.5, 56.1, 55.3, 38.4, 30.4, 29.4, 27.7, 26.0, 19.4, 18.5, 13.9, 11.4, 0.4, −5.1, −5.2 ppm; IR (film): $\tilde{\nu}$ = 2955, 2928, 2856, 1463, 1247, 832, 776 cm^{-1}; MS (EI): *m/z* (%): 575 (54), 417 (67), 291 (45), 235 (35), 193 (43), 177 (36), 117 (20), 73 (100); HRMS (ESI): *m/z*: calcd for $C_{30}H_{64}O_2Si_2SnNa$ [M^++Na]: 655.3353, found: 655.3358.

Compound 55: A solution of TBAF (1 M in THF, 720 μL, 0.72 mmol) was added to a solution of **54** (100 mg, 0.16 mmol) in DMSO (2 mL). The mixture was stirred at 80 °C for 45 min, cooled to ambient temperature and adsorbed on silica, which was loaded on top of a silica gel column (pentanes/Et_2O 2:1) to furnish stannane **55** as a yellow oil (55 mg, 79 %). $[\alpha]_D^{20}$ = −6.1 (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (td, *J* = 2.8, 1.3, 1H), 5.16 (br d, *J* = 2.8 Hz, 1H), 3.92 (br d, *J* = 12.1 Hz, 1H), 3.64 (br d, *J* = 12.1 Hz, 1H), 2.97 (ddd, *J* = 8.4, 6.1, 2.3 Hz, 1H), 2.89 (ddd, *J* = 4.3, 2.3, 1.8 Hz, 1H), 2.45–2.41 (m, 2H), 2.29 (dd, *J* = 13.4, 6.4, 1H), 2.13 (dd, *J* = 13.4, 7.4, 1H), 1.75–1.63 (m, 2H), 1.53–1.41 (m, 5H), 1.36–1.26 (m, 7H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87–0.84 ppm (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 126.7, 61.7, 59.0, 54.7, 49.7, 38.6, 30.8, 29.3, 27.6, 20.9, 19.7, 13.8, 9.8 ppm; IR (film): $\tilde{\nu}$ = 3417, 2955, 2926, 2871, 1458, 1376, 1247, 1073, 913 cm^{-1}; MS (EI): *m/z* (%): 393 (16), 389 (100), 329 (40), 251 (19), 217 (23), 175 (59), 137 (31); HRMS (ESI): *m/z*: calcd for $C_{21}H_{42}O_2SnNa$ [M^++Na]: 469.2100, found: 469.2098.

Preparation of type D building blocks

Compound 33: A solution of phosphite **32** (271 mg, 0.52 mmol) and [Rh(cod)$_2$]BF_4 (106 mg, 0.26 mmol) in 1,2-dichloroethane (5 mL) was transferred via cannula to a degassed solution of itaconic acid monomethyl ester **31** (25.0 g, 173.4 mmol) in 1,2-dichloroethane (300 mL). Hydrogen gas was bubbled through the mixture over a period of 4 h. For work-up, the mixture was purged with Ar for 5 min to remove any remaining H_2, the flask was fitted with a distillation head and the product isolated by distillation under reduced pressure (10^{-3} mbar, b.p. 76–78 °C). Yellow oil (18.7 g, 99 %, 97 % *ee*); $[\alpha]_D^{20}$ = −10.3 (*c* = 1.0, $CHCl_3$);^{1}H NMR (400 MHz, C_6D_6): δ = 10.21 (br. s, 1H), 3.36 (s, 3H), 2.84–2.92 (m, 1H), 2.67 (dd, *J* = 16.7, 8.0 Hz, 1H), 2.36 (dd, *J* = 16.7, 6.0 Hz, 1H), 1.19 ppm (d, *J* = 7.2 Hz, 3H). The analytical and spectroscopic data are consistent with those previously reported.[72]

***tert*-Butyl(2-iodoethoxy)diphenylsilane**: A solution of 2-iodoethanol (10.0 g, 58 mmol), TBDPSCl (17.9 mL, 69.8 mmol) and imidazole (4.7 g, 69.8 mmol) in CH_2Cl_2 (70 mL) was stirred for 18 h. Water (30 mL) was added and the mixture extracted with CH_2Cl_2 (2×30 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the crude material purified by flash chromatography (hexanes) to yield the title compound as a white solid (23.0 g, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 8.3, 2.4 Hz, 4H), 7.40–7.47 (m, 6H), 3.90 (t, *J* = 6.7 Hz, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 1.11 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 129.4, 127.4, 64.2, 26.4, 6.41 ppm; MS (EI): *m/z* (%): 309 (100); HRMS (ESI): *m/z*: calcd for $C_{18}H_{23}IOSiNa$ [M^++Na]: 433.0455, found: 433.0450.

Compound 36: *n*BuLi (1.6 M solution in hexane, 5.6 mL, 8.9 mmol) was added to a suspension of flame-dried LiCl (806 mg, 19.2 mmol) and *i*Pr_2NH (1.3 mL, 0.96 mmol) in THF at 0 °C. The resulting yellow slurry was stirred for 15 min at 0 °C and 20 min at ambient temperature before it was cooled to −78 °C. A solution of compound **35** (1.0 g, 4.52 mmol) in THF (25 mL) was added via cannula, the reaction was stirred for 45 min at −78 °C, warmed to 0 °C for 15 min and then stirred at ambient temperature for another 15 min before it was again cooled to −78 °C. *tert*-Butyl(2-iodoethoxy)diphenylsilane (1.31 g, 3.2 mmol) was added neat and the mixture was warmed to 0 °C and stirred at this temperature for 18 h. The reaction was quenched with sat. aq. NH_4Cl (40 mL) and the aqueous phase extracted with EtOAc (2×40 mL). The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 3:2) to give amide **36** as a colorless syrup (2.23 g, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$, 7:1 mixture of rotamers; peaks of the minor rotamer are marked *): δ = 7.67 (t, *J* = 7 Hz, 4H)*, 7.61–7.65 (m, 4H), 7.23–7.44 (m, includes the minor rotamer peak, 11H), 4.52 (d, *J* = 7.6 Hz, 1H), 4.48 (d, *J* = 7.6 Hz, 1H)*, 4.38–4.36 (m, 1H, OH), 3.65 (m, 1H)*, 3.56 (m, 1H), 3.50 (m, 1H), 2.91 (m, 1H), 2.82 (s, 3H)*, 2.80 (s, 3H), 1.74 (m, 1H), 1.46 (m, 1H), 1.19 (m, 2H), 0.98 (d, *J* = 6.1 Hz, 3H), 0.97 (d, *J* = 6.1 Hz, 3H)*, 0.96 (s, 9H)*, 0.95 (s, 9H), 0.79 (d, *J* = 6.1 Hz, 3H), 0.77 ppm (d, *J* = 6.1 Hz, 3H)*; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 147.4*, 142.17, 135.14, 133.35*, 129.33, 129.29*, 128.3*, 127.9, 127.3, 126.6*, 125.9, 75.4, 61.01, 40.98, 36.35, 32.25, 28.7, 26.60*, 26.50, 22.26, 18.12, 16.5, 13.9, 11.07 ppm; IR (film): $\tilde{\nu}$ = 3371, 2931, 2858, 1618, 1472, 1427, 1106, 1084, 907, 729, 699 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{31}H_{41}NO_3SiNa$ [M^++Na]: 526.2736, found: 526.2747. *ent*-**36** was prepared analogously using *ent*-**35** as the substrate.

Compound 37: *n*BuLi (1.6 M solution in hexanes, 76.9 mL, 124.8 mmol) was added dropwise to a solution of *i*Pr_2NH (17.7 mL, 131 mmol) in THF

(150 mL) at 0 °C. The mixture was stirred at room temperature for 10 min before it was cooled to 0 °C. $BH_3{\cdot}NH_3$ (4.3 g, 124.8 mmol, 90 %) was added in portions and the resulting slurry was warmed to room temperature over 1 h. A solution of amide **36** (15.8 g, 31.3 mmol) in THF (20 mL) was added via cannula at 0 °C and the mixture allowed to warm to room temperature over a period of 2 h once the addition was complete. The reaction was quenched at 0 °C with aq. HCl (1 M, 21 mL), the aqueous layer was extracted with Et_2O (3×150 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 4:1) to give alcohol **37** as a colorless oil (10.3 g, 96 %). $[\alpha]_D^{20} = -3.0$ ($c=0.95$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.69$–7.66 (m, 4H), 7.44–7.39 (m, 6H), 3.79–3.67 (m, 2H), 3.53–3.45 (m, 2H), 2.33 (br s, 1H), 1.85 (qd, $J=13.2$, 6.7 Hz, 1H), 1.64 (ddd, $J=7.6$, 6.6, 5.2 Hz, 1H), 1.53–1.40 (m, 1H), 1.06 (s, 9H), 0.90 ppm (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.7$, 133.7, 129.9, 127.8, 68.4, 62.7, 36.9, 34.0, 27.0, 19.3, 17.3 ppm; IR (film): $\tilde{\nu}=3346$, 2930, 2857, 1427, 1106, 1086, 699 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{30}O_2SiNa$ [M^++Na]: 365.1902, found: 365.1907. The recorded analytical and spectroscopic data were consistent with those previously reported in the literature.[73]

Compound 34: A solution of DMSO (1.5 mL, 21.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of $(COCl)_2$ (930 μL, 10.5 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After stirring for 10 min, a solution of alcohol **37** (2.8 g, 8.06 mmol) in CH_2Cl_2 (15 mL) was introduced and stirring continued for 1 h at −78 °C before Et_3N (8.0 mL, 56.4 mmol) was added and the mixture allowed to warm to ambient temperature. After 1 h, the reaction was quenched with brine (40 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (2×30 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated to afford aldehyde **34** (2.6 g, 94 % crude) as a pale yellow oil which was used in the next step without further purification. $[\alpha]_D^{20} = +3.5$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.68$ (d, $J=1.6$ Hz, 1H), 7.67–7.64 (m, 4H), 7.46–7.37 (m, 6H), 3.77–3.66 (m, 2H), 2.58 (qdd, $J=8.4$, 7.0, 1.6 Hz, 1H), 2.01 (ddd, $J=12.7$, 6.8, 5.6 Hz, 1H), 1.62 (m, 1H), 1.09 (d, $J=7.0$ Hz, 3H), 1.05 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=205.0$, 135.7, 133.7, 129.8, 127.8, 61.3, 43.6, 33.6, 26.9, 19.3, 13.2 ppm; IR (film): $\tilde{\nu}=2931$, 2857, 1726, 1427, 1105, 1087, 699 cm^{-1}; MS (EI): *m/z* (%): 283 (87), 253 (25), 205 (62), 199 (100), 175 (57), 139 (30); HRMS (ESI): *m/z*: calcd for $C_{21}H_{28}O_2SiNa$ [M^++Na]: 363.1750, found: 363.1751.

Alkyne 38: A solution of NaOMe (6.55 g, 80 mmol) in MeOH (15 mL) was added to a solution of **42** (15.4 g, 80 mmol) in THF (80 mL) at −78 °C. The resulting mixture was stirred at this temperature for 0.5 h before a solution of the crude aldehyde **34** (7.0 g, 20 mmol) in THF (50 mL) was slowly introduced. The mixture was stirred for 0.5 h at −78 °C before it was stirred overnight at ambient temperature. Water (50 mL) was added and the mixture extracted with *tert*-butyl methyl ether (2×50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 15:1) to give alkyne **38** as a pale yellow oil (4.5 g, 67 %). $[\alpha]_D^{20} = +25.0$ ($c=1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.70$–7.66 (m, 4H), 7.45–7.36 (m, 6H), 3.86–3.74 (m, 2H), 2.74 (qdd, $J=9.3$, 6.9, 2.4 Hz, 1H), 1.99 (d, $J=2.4$ Hz, 1H), 1.69 (ddd, $J=9.3$, 6.8, 1.1 Hz, 2H), 1.19 (d, $J=6.9$ Hz, 3H), 1.05 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.7$, 134.2, 129.7, 127.7, 88.9, 68.4, 61.7, 39.6, 27.0, 22.3, 21.0, 19.4 ppm; IR (film): $\tilde{\nu}=3307$, 2932, 2858, 1427, 1107, 1088, 699 cm^{-1}; MS (EI): *m/z* (%): 279 (100), 201 (93), 183 (23), 171 (10), 137 (10); HRMS (ESI): *m/z*: calcd for $C_{22}H_{28}OSiNa$ [M^++Na]: 359.1804, found: 359.1802.

Vinyl iodide 39: A solution of $AlMe_3$ (2.0 M in heptane, 21.2 mL, 42.4 mmol) was added to a suspension of [Cp_2ZrCl_2] (4.64 g, 15.9 mmol) in 1,2-dichloroethane (70 mL). After stirring for 0.5 h, a solution of alkyne **38** (3.56 g, 10.57 mmol) in 1,2-dichloroethane (15 mL) was added dropwise. The resulting yellow solution was stirred for 24 h at ambient temperature before the mixture was cooled to −20 °C and a solution of iodine (16.10 g, 63.5 mmol) in THF (60 mL) was slowly introduced. After stirring for 20 min at −20 °C and 30 min at 0 °C, the reaction was carefully quenched with water (10 mL). A sat. aq. Na_2SO_3 solution was then added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×40 mL), the combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 30:1) afforded vinyl iodide **39** as a colorless oil (5.06 g, 94 %). $[\alpha]_D^{20} = +12.8$ ($c=0.71$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.67$–7.63 (m, 4H), 7.43–7.36 (m, 6H), 5.91 (br s, 1H), 3.59–3.55 (m, 2H), 2.67 (q, $J=9.2$ Hz, 1H), 1.69 (d, $J=1.2$ Hz, 3H), 1.64–1.52 (m, 2H), 1.04 (s, 9H), 0.99 ppm (d, $J=9.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.7$, 135.7, 134.0, 129.7, 127.8, 75.4, 61.8, 39.9, 37.7, 27.0, 20.5, 19.6, 19.3 ppm; IR (film): $\tilde{\nu}=3070$, 2959, 2930, 1427, 1104, 699 cm^{-1}; MS (EI): *m/z* (%): 421 (100), 309 (68), 249 (16), 215 (15), 211 (15), 199 (32), 183 (21); HRMS (ESI): *m/z*: calcd for $C_{23}H_{31}IOSiNa$ [M^++Na]: 501.1083, found: 501.1081.

Compound 40: A solution of TBAF in THF (1 M, 2.5 mL, 2.5 mmol) was added to a solution of **39** (1.0 g, 2.09 mmol) in THF (6 mL). After stirring for 1.5 h, the mixture was carefully evaporated (30 °C, 400 mbar) and the residue purified by flash chromatography (pentanes/Et_2O 1:0 → 30:1 → 10:1) to afford alcohol **40** as a colorless oil (502 mg, 98 %). $[\alpha]_D^{20} = +24.0$ ($c=0.3$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.99$–5.98 (m, 1H), 3.59 (ddd, $J=16.8$, 10.6, 6.4 Hz, 2H), 2.62 (qd, $J=13.6$, 6.8 Hz, 1H), 1.76 (d, $J=1.0$ Hz, 3H), 1.71–1.49 (m, 3H), 1.05 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.7$, 75.4, 61.0, 40.3, 37.6, 37.6, 20.4, 19.6 ppm; IR (film): $\tilde{\nu}=3330$, 2960, 2929, 2873, 1377, 1267, 1046, 774, 660 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_7H_{13}IO$ [M^+]: 240.0014, found: 240.0011.

Aldehyde 41: A mixture containing alcohol **40** (502 mg, 2.10 mmol) and solid $NaHCO_3$ (1.76 g, 21.0 mmol) in CH_2Cl_2 (8.0 mL) was stirred for 30 min at ambient temperature before Dess–Martin periodinane (980 mg, 2.30 mmol) was introduced and stirring continued for 1.5 h. The solvent was evaporated and the residue suspended in pentanes (10 mL). The resulting mixture was then filtered through a pad of Celite and the filtrate was evaporated. This operation was repeated twice to afford the crude aldehyde which was then purified by flash chromatography (hexanes/*tert*-butyl methyl ether 30:1) to give analytically pure **41** as a pale yellow oil (492 mg, 98 %). $[\alpha]_D^{20} = +25.0$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.69$ (d, $J=2.0$ Hz, 1H), 6.08–6.07 (m, 1H), 3.02 (qd, $J=13.8$, 6.8 Hz, 1H), 2.56 (ddd, $J=16.6$, 6.8, 2.0 Hz, 1H), 2.52 (ddd, $J=16.6$, 7.6, 2.0 Hz, 1H), 1.81 (d, $J=1.0$ Hz, 3H), 1.10 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.2$, 150.3, 76.5, 48.8, 37.7, 21.5, 19.6 ppm; IR (film): $\tilde{\nu}=2964$, 2928, 1721, 1377, 1277, 777 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_7H_{11}IO$+Na [M^++Na]: 260.9752, found: 260.9755.

Compound 84: A solution of LDA (0.8 M in THF, 5.8 mL, 4.6 mmol) was added to a solution of (*R*)-3-acetyl-4-benzyloxazolidin-2-one (**82**; 1.0 g, 4.6 mmol) in Et_2O (42 mL) at −78 °C and the resulting mixture was stirred at this temperature for 1 h. Ketone **83** (185 mg, 2.71 mmol) was added and stirring continued for 30 min. The reaction was then quenched with aq. sat. NH_4Cl (20 mL) and warmed to ambient temperature. The aqueous layer was extracted with *tert*-butyl methyl ether (3×50 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (EtOAc in pentanes, 10 → 15 → 20 % *v/v*) to afford product **84** as a white solid (394 mg, 54 %). M.p. 114–116 °C; $[\alpha]_D^{20} = -95.0$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.27$–7.22 (m, 5H), 4.77–4.71 (m, 1H), 4.43 (s, 1H), 4.27–4.19 (m, 2H), 3.78 (d, $J=17.4$ Hz, 1H), 3.31 (dd, $J=13.4$, 3.2 Hz, 1H), 2.96 (d, $J=17.4$ Hz, 1H), 2.86 (dd, $J=13.5$, 9.3 Hz, 1H), 2.46 (s, 1H), 1.61 ppm (d, $J=0.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.9$, 153.2, 134.8, 129.5, 129.0, 127.5, 86.6, 70.9, 66.3, 65.3, 55.0, 46.8, 37.8, 29.6 ppm; IR (film): $\tilde{\nu}=3502$, 3293, 2991, 1771, 1679, 1379 cm^{-1}; MS (EI): *m/z* (%): 287 (5) [M^+], 269 (13), 241 (8), 219 (7), 178 (11), 86 (100); HRMS (ESI): *m/z*: calcd for $C_{16}H_{17}NO_4$+Na [M^++Na]: 310.10498, found: 310.10476.

Compound 85: MeOH (0.22 mL, 5.5 mmol) and $LiBH_4$ (119 mg, 5.5 mmol) were successively added to a solution of compound **84** (391 mg, 1.37 mmol) in THF (14 mL) at 0 °C. The mixture was stirred at ambient temperature for 2 h before the reaction was quenched with aq. sat. NH_4Cl (10 mL) and diluted with *tert*-butyl methyl ether (20 mL) and HCl (2 M, 0.05 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3×20 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chroma-

tography (Et_2O/pentanes 1:1) to afford diol **85** as a colorless oil (141 mg, 90%). $[\alpha]_D^{20} = +11.2$ ($c=1.2$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 4.15 (td, $J=10.4$, 3.2 Hz, 1H), 3.89 (dt, $J=11.0$, 4.3 Hz, 1H), 3.14 (br s, 2H), 2.48 (s, 1H), 1.98 (ddd, $J=14.3$, 9.8, 4.3 Hz, 1H), 1.52 (s, 3H), 1.08 ppm (ddd, $J=14.6$, 4.6, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=87.0$, 71.9, 68.6, 60.5, 43.3, 30.5 ppm; IR (film): $\tilde{\nu}=3362$, 3299, 2934, 1424, 1372, 1090 cm^{-1}; HRMS (EI): m/z: calcd for $C_6H_{10}O_2$: 114.06808, found: 114.06805.

Compound 86: Imidazole (204 mg, 3.0 mmol), DMAP (489 mg, 4.0 mmol) and TESCl (0.368 mL, 2.2 mmol) were successively added to a solution of diol **85** (115 mg, 1.0 mmol) in DMF (1 mL). After stirring for 15 h, the reaction was quenched with aq. sat. NH_4Cl (1 mL), the aqueous layer was extracted with Et_2O (3×10 mL), the combined extracts were dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (5% *v*/*v* Et_2O in pentanes) to afford compound **86** as a colorless oil (302 mg, 88%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.82$ (t, $J=$ 7.6 Hz, 2H), 2.39 (s, 1H), 1.91 (s, 2H), 1.46 (s, 3H), 0.94 (td, $J=8.0$ Hz, 18H), 0.62 ppm (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=87.8$, 71.9, 67.4, 59.5, 47.6, 47.6, 31.4, 6.9, 6.8, 6.1, 4.4 ppm; IR (film): $\tilde{\nu}=3311$, 2954, 2877, 1118, 1089, 1003 cm^{-1}; MS (EI): m/z (%): 313 (100) [M^+-Et], 285 (57), 217 (74), 189 (47), 115 (55), 87 (59); HRMS (ESI): m/z: calcd for $C_{18}H_{38}O_2Si_2$+Na [M^++Na]: 365.23026, found: 365.23030.

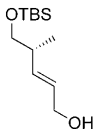
Compound 88: *n*BuLi (1.6 M in hexanes, 0.75 mL, 1.2 mmol) was added to a solution of hexabutylditin (0.61 mL, 1.22 mmol) in THF (3 mL) at −78 °C. Once the addition was complete, the mixture was stirred at −40 °C for 30 min before CuCN (104 mg, 1.16 mmol) was introduced and stirring continued at −20 °C for 2 min. The resulting red solution was cooled to −78 °C and a solution of compound **86** (100 mg, 0.29 mmol) in THF (1 mL) was added. The reaction was quenched after 3 h with aq. sat. NH_4Cl (5 mL), the aqueous layer was extracted with Et_2O (3× 10 mL), the combined organic phases were dried (Na_2SO_4), filtered and evaporated. The remaining oil was dissolved in CH_2Cl_2 (5 mL) and a saturated solution of I_2 in CH_2Cl_2 was added dropwise until the pink color persisted. The solvent was evaporated and the residue was purified by flash chromatography (1 → 30% *v*/*v* Et_2O in hexanes) to afford product **87** (106 mg, 90%, two steps) as a colorless oil.

Imidazole (5 mg, 0.076 mmol), DMAP (0.5 mg, 0.0038 mmol) and TESCl (0.007 mL, 0.041 mmol) were added to a solution of compound **87** (14 mg, 0.038 mmol) in CH_2Cl_2 (0.1 mL) and the resulting mixture stirred for 2 h. The reaction was quenched with aq. sat. NH_4Cl (3 mL), the aqueous phase extracted with Et_2O (3×5 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (5% *v*/*v* Et_2O in hexanes) to afford product **88** (11 mg, 84%) as a colorless oil. $[\alpha]_D^{20} = +6.8$ ($c=1.23$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.29$ (s, 1H), 3.64–3.58 (m, 1H), 3.49–3.42 (m, 1H), 1.95–1.88 (m, 1H), 1.84 (s, 3H), 1.81–1.74 (m, 1H), 1.39 (s, 3H), 0.95 (t, $J=7.9$ Hz, 9H), 0.94 (t, $J=7.9$ Hz, 9H), 0.63–0.54 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.6$, 78.6, 77.9, 59.0, 44.4, 27.8, 21.7, 7.1, 6.8, 6.7, 4.0 ppm; IR (film): $\tilde{\nu}=2954$, 2876, 1091, 1002 cm^{-1}; MS (EI): m/z (%): 484 (1) [M^+], 455 (18), 427 (11), 325 (100), 217 (24), 115 (38); HRMS (ESI): m/z: calcd for $C_{19}H_{41}IO_2Si_2Na$ [M^++Na]: 507.15821, found: 507.15824.

Compound 89: A solution of DMSO (0.13 mL, 1.9 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of oxalyl chloride (0.11 mL, 0.9 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After stirring for 30 min, a solution of **88** (150 mg, 0.31 mmol) in CH_2Cl_2 (0.5 mL) was slowly introduced and stirring continued for 3 h at −78 °C. (iPr)$_2$NEt (0.6 mL, 3.72 mmol) was added and the mixture allowed to warm to 0 °C. After 1 h, the reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with Et_2O (3×10 mL), the combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by flash chromatography (10% *v*/*v* Et_2O in hexanes) to afford product **89** (123 mg, quant.) as a colorless oil. $[\alpha]_D^{20} = +25.7$ ($c=0.9$, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta=9.63$ (t, $J=2.9$ Hz, 1H), 6.51 (s, 1H), 2.63 (dd, $J=15.2$, 2.7 Hz, 1H), 2.42 (dd, $J=15.2$, 3.1 Hz, 1H), 1.90 (d, $J=$ 0.8 Hz, 3H), 1.49 (s, 3H), 0.95 (t, $J=7.7$ Hz, 9H), 0.62 ppm (q, $J=7.9$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=201.9$, 150.5, 79.5, 77.9, 53.8, 27.7, 21.6, 7.0, 6.6 ppm; IR (film): $\tilde{\nu}=2955$, 2876, 1723, 1003 cm^{-1}; MS (EI): m/z (%): 368 (1) [M^+], 339 (97), 325 (18), 295 (11), 211 (32), 129 (100); HRMS: m/z: calcd for $C_{13}H_{25}IO_2SiNa$ [M^++Na]: 391.05607, found: 391.05628.

Preparation of the building blocks of type AB

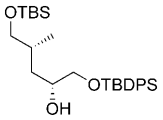
(*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylpent-2-en-1-ol: Dibal-H (1.0 M solution in hexane, 91.8 mL, 91.8 mmol) was slowly added to a solution of compound **18** (10.8 g, 39.9 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 30 min at −78 °C, the reaction was quenched with MeOH (until effervescence ceased) at −78 °C and then poured into a sat. aq. solution of cold (0 °C) Rochelle's salt. The mixture was stirred overnight at room temperature, leading to a clean phase separation. The aqueous phase was extracted with EtOAc (3× 100 mL), the combined organic portions were dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 4:1) to give the title compound as a colorless oil (7.13 g, 78%). The material must be stored at low temperature (≤ −20 °C). $[\alpha]_D^{20} = +10.7$ ($c=0.65$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=5.68$–5.63 (m, 2H), 4.11–4.08 (m, 2H), 3.50 (dd, $J=9.7$, 6.2 Hz, 1H), 3.41 (dd, $J=9.7$, 7.0 Hz, 1H), 2.34 (app. sept., $J=6.6$ Hz, 1H), 1.9 (br s, 1H), 1.00 (d, $J=6.7$ Hz, 3H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.7$, 128.9, 68.1, 64.0, 39.1, 26.1, 18.5, 16.5, −5.2 ppm; IR (film): $\tilde{\nu}=3342$, 2956, 2929, 2857, 1471, 1463, 1252, 1085, 833, 773 cm^{-1}; MS (EI): m/z (%): 230 (<1), 173 (7), 115 (3), 105 (81), 89 (14), 75 (100); HRMS (ESI): m/z: calcd for $C_{12}H_{26}O_2SiNa$ [M^++Na]: 253.1595, found: 253.1594.



((2*S*,3*S*)-3-((*S*)-1-(*tert*-Butyldimethylsilyloxy)propan-2-yl)oxiran-yl)methanol (19): A suspension of powdered MS 4 Å (≈1.0 g) in CH_2Cl_2 (20 mL) was stirred under Ar for 3 h before it was cooled to −20 °C and L-(+)-DET (0.36 mL, 2.1 mmol) and Ti(OiPr)$_4$ (0.51 mL 1.71 mmol) were introduced. After stirring for 20 min, a solution of *t*BuOOH (6.32 mL, 34.8 mmol), which had been pretreated with powdered MS 4 Å for 3 h prior to use, was added and the resulting mixture stirred for 20 min before a solution of (*R*,*E*)-5-(*tert*-butyldimethylsilyloxy)-4-methylpent-2-en-1-ol (4.0 g, 17.5 mmol) in CH_2Cl_2 (30 mL, pre-dried with activated MS 4 Å for 3 h) was added via cannula. The mixture was stirred for 15 h at −20 °C, then warmed to 0 °C, and poured into a cold (0 °C) solution of $FeSO_4 \cdot 7H_2O$ (9.15 g) and citric acid (3.0 g) in water (40 mL). This mixture was stirred for 0.5 h before it was extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 2:1) to yield product **19** as a colorless oil (3.2 g, 74%). $[\alpha]_D^{20} = -15.8$ ($c=0.57$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.91$ (d, $J=12.6$ Hz, 1H), 3.63 (d, $J=5.1$ Hz, 2H), 3.61–3.57 (m, 1H), 2.99 (ddd, $J=4.8$, 2.6, 2.6 Hz, 1H), 2.92 (dd, $J=7.0$, 2.6 Hz, 1H), 1.78 (br s, 1H), 1.68–1.58 (m, 1H), 0.95 (d, $J=7.0$ Hz, 3H), 0.89 (s, 9H), 0.052 (s, 3H), 0.048 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=65.3$, 62.1, 57.7, 57.2, 38.00, 26.0, 18.5, 13.0, −5.3 ppm; IR (film): $\tilde{\nu}=3439$, 2955, 2929, 2857, 1472, 1252, 1095, 832, 773 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{26}O_3SiNa$ [M^++Na]: 269.1545, found: 269.1543.

Compound 20: A solution of Dibal-H (1.0 M in hexanes, 123 mL, 123 mmol) was added dropwise to a solution of epoxide **19** (7.6 g, 30.84 mmol) in toluene (25 mL) at −78 °C over the course of 1 h. The temperature was then raised to −40 °C and stirring continued for 4 h before the reaction was carefully quenched at −60 °C with a solution of *t*BuOH in THF (1:1, 25 mL). The resulting mixture was poured into an ice-cold solution of Rochelle's salt (85 g in 250 mL water) and vigorously stirred for 2 h until a clear separation of the phases was reached. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 1:1) to give product **19** as a colorless oil (5.98 g, 78%). $[\alpha]_D^{20} = +3.1$ ($c=0.43$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.79$–3.70 (m, 1H), 3.59–3.51 (m, 2H), 3.44–3.35 (m, 2H), 1.86–1.74 (m, 1H), 1.48–1.32 (m, 2H), 0.89 (s, 9H), 0.88 (d, $J=6.7$ Hz, 3H), 0.06 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 71.1, 69.5, 67.5, 39.4, 34.2, 26.0, 18.4, 18.0, −5.3, −5.4 ppm; IR (film): $\tilde{\nu}=$ 3350, 2929, 2857, 1471, 1251, 1077, 832, 773 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{28}O_3SiNa$ [M^++Na]: 271.1699, found: 271.1698.

(6*R*,8*R*)-2,2,8,11,11,12,12-Heptamethyl-3,3-diphenyl-4,10-dioxa-3,11-disilatridecan-6-ol: Imidazole (4.95 g, 72.56 mmol) and TBDPSCl (18.79 mL, 72.56 mmol) were added to a solution of diol **19** (18.0 g, 72.56 mmol) in CH_2Cl_2 (500 mL) and the reaction was stirred at ambient temperature overnight. The reaction was quenched with water, the mixture was washed with aq. sat. $NaHCO_3$ (200 mL), extracted with CH_2Cl_2 (2×200 mL), and the organic phases were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 10:1) furnished the title compound as a colorless syrup (32.0 g, 91%). $[\alpha]_D^{20} = +3.6$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.70$–7.66 (m, 4H), 7.45–7.36 (m, 6H), 3.83–3.76 (m, 1H), 3.62 (dd, $J=10.0$, 4.4 Hz, 1H), 3.56 (dd, $J=10.0$, 6.6 Hz, 1H), 3.47–3.42 (m, 2H), 1.89–1.79 (m, 1H), 1.51–1.44 (m, 1H), 1.33–1.26 (m, 1H), 1.08 (s, 9H), 0.92–0.88 (m, 12H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.7$, 133.6, 133.5, 129.9, 127.8, 70.5, 69.1, 68.7, 37.8, 33.2, 27.1, 26.1, 19.4, 17.2, −5.3, −5.3 ppm; IR (film): $\tilde{\nu}=3452$, 2955, 2929, 2857, 1471, 1428, 1105, 834, 699 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{28}H_{46}O_3Si_2Na$ [M^++Na]: 509.2874, found: 509.2878.



Compound 21: Pyridinium *p*-toluenesulfonate (11.6 g, 46 mmol) was added to a solution of (6*R*,8*R*)-2,2,8,11,11,12,12-heptamethyl-3,3-diphenyl-4,10-dioxa-3,11-disilatridecan-6-ol (32 g, 66 mmol) in EtOH (160 mL) and the resulting mixture was stirred overnight before the solvent was evaporated. The residue was taken up in *tert*-butyl methyl ether (300 mL), the organic phase was washed with aq. sat. $NaHCO_3$ (300 mL), dried over Na_2SO_4 and evaporated to give crude (2*R*,4*R*)-5-(*tert*-butyldiphenylsilyloxy)-2-methylpentane-1,4-diol, which was used in the next step without further purification. For analytical purposes, a small fraction was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 30:1) to give the diol as a colorless oil which analyzed as follows: $[\alpha]_D^{20} = +1.2$ ($c=0.43$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.68$–7.63 (m, 4H), 7.45–7.34 (m, 6H), 3.83 (dd, $J=4.1$, 1.3 Hz, 2H), 3.57 (dd, $J=10.9$, 5.2 Hz, 1H), 3.47 (dd, $J=10.9$, 5.3 Hz, 1H), 2.17 (s, 1H), 1.91 (app. quint., $J=6.8$ Hz, 1H), 1.72–1.61 (m, 1H), 1.56 (app. quint., $J=6.4$ Hz, 1H), 1.06 (s, 9H), 0.97 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 188.0, 135.8, 135.7, 133.5, 129.9, 127.8, 80.1, 67.7, 65.1, 42.8, 37.8, 34.4, 32.4, 26.9, 19.4, 17.6 ppm; IR (film): $\tilde{\nu}=3334$, 2930, 2858, 1472, 1427, 1110, 699 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{32}O_3SiNa$ [M^++Na]: 395.2011, found: 395.2013.

Imidazole (13.5 g, 198 mmol) and TESCl (49.7 g, 330 mmol) was added to a solution of the crude diol (24.6 g, 66 mmol) in CH_2Cl_2 (160 mL) and the resulting mixture was stirred overnight. A standard extractive work up followed by flash chromatography of the crude material (hexanes/EtOAc 30:1) gave product **21** as a colorless oil (34.5 g, 87%). $[\alpha]_D^{20} = +19.1$ ($c=1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.71$–7.66 (m, 4H), 7.44–7.36 (m, 6H), 3.84–3.77 (m, 1H), 3.61 (dd, $J=10.0$, 4.8 Hz, 1H), 3.49 (dd, $J=10.0$, 5.6 Hz, 1H), 3.46 (dd, $J=10.0$, 6.9 Hz, 1H), 3.39 (dd, $J=10.0$, 6.7 Hz, 1H), 1.86–1.76 (m, 1H), 1.51–1.46 (m, 2H), 1.06 (s, 9H), 0.97 (t, $J=8.0$ Hz, 9H), 0.92 (d, $J=6.7$ Hz, 3H), 0.89 (t, $J=8.0$ Hz, 9H), 0.60 (q, $J=8.0$ Hz, 6H), 0.52 ppm (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 135.8, 134.0, 133.9, 129.7, 129.7, 127.8, 71.1, 69.0, 68.6, 38.7, 32.2, 27.0, 19.4, 17.0, 7.0, 6.9, 5.2, 4.7 ppm; IR (film): $\tilde{\nu}=2954$, 2876, 1105, 1005, 735, 699 cm^{-1}; MS (EI): *m*/*z* (%): 571 (21), 543 (29), 411 (20), 367 (21), 313 (83), 285 (39), 257 (18), 253 (19), 213 (95), 199 (100).

Compound 22: $(COCl)_2$ (0.73 mL, 8.93 mmol) was added to a solution of DMSO (0.71 mL, 10.49 mmol) in CH_2Cl_2 (25 mL) at −78 °C. After stirring for 10 min, a solution of **21** (1.3 g, 2.10 mmol) in CH_2Cl_2 (15 mL) was added dropwise and the resulting mixture stirred at −78 °C overnight. $(i\text{Pr})_2$NEt (≈5 mL, 21 mmol) was slowly introduced and the mixture was warmed to ambient temperature over the course of 2 h. The reaction was quenched with water (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3×20 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 10:1) to yield aldehyde **22** as a colorless oil (670 mg, 68%). $[\alpha]_D^{20} = +24.4$ ($c=0.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$,): $\delta=9.62$ (d, $J=1.9$ Hz, 1H), 7.67–7.63 (m, 4H), 7.46–7.36 (m, 6H), 3.79–3.72 (m, 1H), 3.62 (dd, $J=10.0$, 4.7 Hz, 1H), 3.45 (dd, $J=10.0$, 7.5 Hz, 1H), 2.58–2.47 (m, 1H), 1.90 (ddd, $J=14.1$, 8.7, 5.8 Hz, 1H), 1.68 (ddd, $J=14.1$, 7.9, 3.5 Hz, 1H), 1.10 (d, $J=7.0$ Hz, 3H), 1.05 (s, 9H), 0.86 (t, $J=8.0$ Hz, 9H), 0.47 ppm (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 205.3, 135.7, 133.6, 133.5, 129.9, 129.8, 127.9, 70.8, 68.0, 43.3, 35.9, 27.0, 19.4, 13.9, 6.9, 5.0 ppm; IR (film): $\tilde{\nu}=2956$, 2933, 2876, 1727, 1428, 1106, 1006, 823, 736 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{28}H_{44}O_3Si_2$+Na [M^++Na]: 507.2727, found: 507.2725.

Aldol product 24: Et_3N (211 mg, 0.29 mL, 2.09 mmol) and Bu_2BOTf (479 mg, 0.4 mL, 1.79 mmol) were sequentially added to a solution of **23** (529 mg, 1.5 mmol) in toluene (3 mL) at −50 °C. The resulting mixture was stirred for 1.5 h before a solution of aldehyde **22** (600 mg, 1.24 mmol) in toluene (1.25 mL) was slowly introduced and stirring continued at −50 °C for 40 min. The mixture was then warmed to −30 °C and stirred at that temperature for 1 h. For work up, the reaction was quenched with phosphate buffer (pH 7, 5 mL) and diluted with MeOH (5 mL) and THF (5 mL). The mixture was warmed to 0 °C before a solution of aq. H_2O_2 (30% *w*/*w*, 1.2 mL) in MeOH (2 mL) was added. After stirring for 1 h, the mixture was extracted with EtOAc (3×15 mL), the combined extracts were washed with phosphate buffer solution (20 mL, pH 7), the aqueous phase was extracted with Et_2O (3×10 mL), the combined organic layers were dried over $MgSO_4$ and evaporated, and the residue purified by chromatography (hexanes/EtOAc 7:3) to give aldol adduct **24** as a colorless oil (853 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.59$ (m, 4H), 7.35–7.20 (m, 11H), 7.12 (d, $J=8.4$ Hz, 2H), 6.76 (d, $J=8.8$ Hz, 2H), 5.24 (d, $J=1.3$ Hz, 1H), 4.58 (m, 1H), 4.54 (d, $J=11.1$ Hz, 1H), 4.46 (d, $J=11.1$ Hz, 1H), 4.09 (m, 4H), 3.70 (m, 2H), 3.65 (s, 3H), 3.52 (m, 2H), 3.35 (dd, $J=9.8$, 6.8 Hz, 1H), 3.18 (dd, $J=13.4$, 3.3 Hz, 1H), 2.63 (dd, $J=13.4$, 9.6 Hz, 1H), 1.94 (m, 1H), 1.49 (m, 1H), 0.97 (s, 9H), 0.94 (d, $J=6.6$ Hz, 3H), 0.80 (t, $J=8.1$ Hz, 9H), 0.43 ppm (q, $J=7.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.8$, 159.0, 135.3, 135.2, 130.0, 129.9, 129.3, 129.2, 129.1, 128.6, 127.4, 127.3, 127.0, 113.4, 77.1, 76.4, 72.1, 70.3, 68.3, 66.5, 60.0, 55.3, 54.8, 37.3, 32.3, 26.7, 26.5, 20.7, 15.0, 13.8, 6.6, 4.7 ppm; IR (film): $\tilde{\nu}=2955$, 2875, 1779, 1708, 1612, 1587, 1463, 1427, 1389, 1360, 1301, 1247, 1210, 1175, 1108, 1032, 1008, 906, 823, 740 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{48}H_{65}NO_8Si_2Na$ [M^++Na]: 862.4137, found: 862.4140.

Aldol product 103: Prepared analogously from aldehyde **22** (600 mg, 1.24 mmol) and amide *ent*-**23** (529 mg, 1.5 mmol) as a colorless oil (853 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.59$ (m, 4H), 7.32–7.22 (m, 11H), 7.18 (d, $J=8.4$ Hz, 2H), 6.81 (d, $J=8.8$ Hz, 2H), 5.22 (d, $J=0.9$ Hz, 1H), 4.64 (m, 1H), 4.63 (d, $J=12.0$ Hz, 1H), 4.32 (d, $J=12.0$ Hz, 1H), 4.13 (m, 2H), 3.70 (m, 2H), 3.74 (s, 3H), 3.74 (m, 2H), 3.49 (dd, $J=12.8$, 3.2 Hz, 1H), 3.48 (dd, $J=9.6$, 1.2 Hz, 1H), 2.77 (dd, $J=14.2$, 6.5 Hz, 1H), 1.97 (m, 1H, -OH), 178 (m, 1H), 1.18 (m, 1H), 0.97 (d, $J=6.6$ Hz, 3H), 0.96 (s, 9H), 0.79 (t, $J=8.1$ Hz, 9H), 0.40 ppm (q, $J=7.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.3$, 158.6, 152.3, 134.6, 134.2, 132.6, 132.5, 129.3, 129.2, 128.8, 128.6, 128.5, 128.0, 126.7, 126.6, 112.8, 112.8, 75.9, 71.4, 69.9, 67.6, 66.0, 54.8, 36.8, 31.8, 25.8, 18.2, 14.7, 5.8, 5.7, 5.6, 4.5, 3.9 ppm.

Compound 25: 2,6-Lutidine (281 mg, 0.31 mL, 2.62 mmol) and TBSOTf (629 mg, 550 μL, 2.38 mmol) were added to a solution of alcohol **24** (1.0 g, 1.19 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 1 h, the mixture was warmed to room temperature and the reaction quenched with sat. aq. NH_4Cl (15 mL). A standard extractive work up followed by flash chromatography (hexanes/*tert*-butyl methyl ether 4:1) gave product **25** as a colorless oil (833 mg, 81%). $[\alpha]_D^{20} = -13.0$ ($c=0.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.55$ (m, 4H), 7.32–7.24 (m, 6H), 7.21–7.14 (m, 5H), 7.03 (d, $J=8.4$ Hz, 2H), 6.73 (d, $J=8.4$ Hz, 2H), 5.2 (d, $J=1.3$ Hz, 1H), 4.62 (d, $J=11.6$ Hz, 1H), 4.39 (d, $J=11.6$ Hz, 1H), 4.36 (m, 1H), 3.91 (m, 3H), 3.63 (s, 3H), 3.58 (m, 1H), 3.42 (dd, $J=10$, 4.8 Hz, 1H), 3.29 (dd, $J=10$, 7.6 Hz, 1H), 2.97 (dd, $J=14.4$, 3.2 Hz, 1H), 2.14 (dd, $J=13.2$, 2.8 Hz, 1H), 1.75 (m, 1H), 1.58 (m, 1H), 1.34 (m, 1H), 0.84 (s, 9H), 0.81 (d, $J=6.7$ Hz, 3H), 0.77 (s, 9H), 0.69 (t, $J=8.4$ Hz, 9H), 0.27 (q, $J=8.5$ Hz, 6H), 0.01 (s, 3H), −0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.8$, 159.0, 135.3, 135.0, 133.3, 133.2, 130.0, 129.6, 129.2, 129.1, 128.9, 128.6, 127.3, 127.2, 126.9, 113.2, 77.9, 72.1, 70.3, 68.1, 65.8, 55.5, 54.8, 40.1, 37.0, 31.3, 30.0, 26.5, 25.8, 25.5, 25.3, 25.3, 18.9, 18.8, 12.7, 6.7, 6.5, 5.1, 4.6, −4.0, −4.1, −4.7 ppm; IR (film): $\tilde{\nu}=2955$,

2931, 2857, 1682, 1614, 1514, 1463, 1428, 1389, 1250, 1112, 1079, 1038, 834, 776, 739, 702 cm^{-1}.

Compound 71: Flame dried molecular sieves (4 Å, 4.6 g) were added to a solution of (2*R*,4*R*)-2-methyl-4-(trimethylsilyloxy)pentan-1-ol (2.0 g, 8.6 mmol)[9] in CH_2Cl_2 (86 mL). *N*-Methyl-morpholine-*N*-oxide (NMO, 1.5 g, 12.9 mmol) was added followed by tetrapropylammonium perruthenate (TPAP, 151 mg, 0.43 mmol)[74] and the resulting mixture was stirred for 30 min before the reaction was filtered through a pad of silica which was carefully rinsed with Et_2O/hexanes (3:7, 400 mL). The combined filtrates were evaporated and the crude aldehyde **69** was used without further purification.

Et_3N (1.4 mL, 9.8 mmol) and Bu_2BOTf (2.2 mL, 8.9 mmol) were successively added to a solution of compound **23** (3.48 g, 9.8 mmol) in toluene (41 mL) at −50 °C. After stirring for 30 min at this temperature and for 2 h at −40 °C, a solution of crude **69** in toluene (41 mL) was added dropwise. Stirring was continued for 12 h before the reaction was quenched with phosphate buffer (pH 7, 20 mL) and diluted with MeOH (20 mL) and THF (20 mL). The solution was warmed to 0 °C before aq. H_2O_2 (30 % *w*/*w*, 20 mL) in MeOH (20 mL) was slowly added. After stirring for 60 min, the mixture was extracted with EtOAc (3×100 mL) and the combined organic layers were washed with pH 7 buffer (100 mL). The aqueous phase was extracted with Et_2O (3×100 mL), the combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue purified by flash chromatography (EtOAc in hexanes, 20 % → 30 % *v*/*v*) to afford diol **70** (2.5 g, 62 %) as a colorless oil.

TESCl (2 mL, 12.19 mmol) and imidazole (1.8 g, 26.5 mmol) were added to a solution of diol **70** (2.5 g, 5.3 mmol) in CH_2Cl_2 (53 mL). After stirring for 15 h, the reaction was quenched with aq. sat. $NaHCO_3$ (20 mL), the aqueous layer was extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (EtOAc in hexanes, 5 → 10 %) to afford product **71** as a colorless oil (2.97 g, 80 %). $[\alpha]_D^{20} = -33.2$ (c = 1.25, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 5H), 7.19–7.16 (m, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.25 (d, J = 6.0 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.49–4.44 (m, 1H), 4.11–4.06 (m, 2H), 3.97 (dd, J = 5.8, 2.1 Hz, 1H), 3.80 (q, J = 6.0 Hz, 1H), 3.75 (s, 3H), 3.11 (dd, J = 13.0, 3.0 Hz, 1H), 2.39 (dd, J = 13.5, 13.3 Hz, 1H), 1.61–1.42 (m, 3H), 1.09 (d, J = 6.0 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.93 (t, J = 7.7 Hz, 9H), 0.89 (d, J = 6.2 Hz, 3H), 0.64–0.55 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 159.4, 152.9, 135.3, 130.1, 129.9, 129.3, 129.0, 127.3, 113.6, 77.0, 73.0, 67.2, 66.3, 56.0, 55.2, 44.3, 37.4, 33.5, 23.7, 14.8, 7.0, 6.9, 5.4, 5.0 ppm; IR (film): $\tilde{\nu}$ = 2955, 2876, 1784, 1247 cm^{-1}; MS (EI): m/z (%): 670 (1) [M^+ -Et], 440 (9), 348 (12), 213 (24), 121 (100); HRMS (ESI): m/z: calcd for $C_{38}H_{61}NO_7Si_2Na$ [M^++Na]: 722.38788, found: 722.38714.

Thioester 26: *n*BuLi (1.6 M in hexane, 1.2 mL, 1.92 mmol) was added to a solution of EtSH (144 mg, 0.17 mL, 2.32 mmol) in THF (9.0 mL) at 0 °C. After stirring for 20 min, a solution of **25** (1.22 g, 1.29 mmol) in THF (3.0 mL) was slowly introduced and stirring continued for 20 min. The reaction was quenched with sat. aq. NH_4Cl (25 mL), the aqueous layer extracted with Et_2O (3×20 mL), the combined organic phases were dried over $MgSO_4$ and evaporated, and the residue quickly passed through a plug of silica gel (hexanes/*tert*-butyl methyl ether 85:15) to give thioester **26** as a colorless oil (1.3 g, 87 %). $[\alpha]_D^{20} = -58.0$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (m, 4H), 7.39 (m, 6H), 7.31 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.57 (d, J = 10.8 Hz, 1H), 4.36 (d, J = 10.8 Hz, 1H), 3.91 (d, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.76 (dd, J = 7.2, 1.6 Hz, 1H), 3.64 (m, 1H), 3.54 (dd, J = 10.0, 4.4 Hz, 1H), 3.37 (dd, J = 9.6, 8.0 Hz, 1H), 2.89 (dq, J = 13.2, 7.6 Hz, 1H), 2.78 (dq, J = 13.2, 7.6 Hz, 1H), 1.85 (3d, J = 11.2, 4, 2 Hz, 1H), 1.77 (m, 1H), 1.32 (m, 1H), 1.22 (t, J = 7.6 Hz, 3H), 1.03 (s, 9H), 0.93 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.80 (t, J = 7.8 Hz, 9H), 0.39 (q, J = 8 Hz, 6H), 0.02 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 158.8, 135.3, 135.2, 133.2, 129.3, 129.27, 129.12, 127.2, 113.2, 88.1, 78.1, 72.0, 70.2, 67.9, 54.9, 40.5, 30.7, 29.3, 26.5, 25.8, 22.0, 18.8, 14.1, 12.0, 6.5, 4.5, −4.1, −4.9 ppm; IR (film): $\tilde{\nu}$ = 2931, 1683, 1515, 1464, 1250, 1110, 822, 741, 702 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{46}H_{74}O_6Si_3Na$ [M^++Na]: 861.44024, found: 861.44061.

Compound 72: Prepared analogously from compound **71** (2.34 g, 3.36 mmol) as a colorless oil (1.77 g, 90 %). $[\alpha]_D^{20} = +47.4$ (c = 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.38 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 4.62 (d, J = 10.7 Hz, 1H), 4.43 (d, J = 10.6 Hz, 1H), 3.95 (d, J = 6.9 Hz, 1H), 3.91 (q, J = 6.1 Hz, 1H), 3.85 (dd, J = 6.9, 2.4 Hz, 1H), 3.80 (s, 3H), 2.93–2.85 (m, 2H), 1.68–1.60 (m, 1H), 1.50–1.46 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 5.9 Hz, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.94 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.63–0.54 ppm (m, 12H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 202.1, 160.5, 130.5, 130.4, 114.4, 89.1, 78.1, 73.3, 67.6, 55.5, 45.9, 30.3, 24.2, 22.9, 15.0, 14.4, 7.4, 7.3, 6.0, 5.8 ppm; IR (film): $\tilde{\nu}$ = 2951, 2875, 1682, 1514, 1248, 1004 cm^{-1}; MS (EI): m/z (%): 555 (1) [M^+−Et], 387 (7), 325 (4), 233 (4), 213 (39), 121 (100); HRMS (ESI): m/z: calcd for $C_{30}H_{56}O_5SSi_2Na$ [M^++Na]: 607.32792, found: 607.32729.

Methyl ketone 27: MeLi (1.6 M in Et_2O, 10.9 mL, 17.6 mmol) was added to a suspension of CuI (1.7 g, 8.79 mmol) in Et_2O (7.0 mL) at −20 °C. After stirring for 35 min, the resulting solution was cooled to −60 °C before a solution of thioester **26** (1.2 g, 1.43 mmol) in Et_2O (5 mL) was slowly added. Once the addition was complete, the mixture was allowed to warm to −20 °C over a period of 2 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL) at −10 °C, the resulting mixture was warmed to ambient temperature and stirred for 1 h. The aqueous phase was extracted with *tert*-butyl methyl ether (3×10 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the crude product purified by flash chromatography (hexanes/EtOAc 9:1) to give ketone **27** as a colorless oil (1.0 g, 89 %). $[\alpha]_D^{20} = +35.5$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (m, 4H), 7.37–7.27 (m, 6H), 7.16 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 4.37 (d, J = 11.2 Hz, 1H), 4.26 (d, J = 11.3 Hz, 1H), 3.73 (br.s, 3H), 3.68 (m, 1H), 3.63 (d, J = 7 Hz, 1H), 3.56 (m, 1H), 3.48 (dd, J = 9.8, 4.5 Hz, 1H), 3.30 (dd, J = 9.8, 8.1 Hz, 1H), 2.0 (s, 3H), 1.82 (tdd, J = 11.4, 2.0, 1.8 Hz, 1H), 1.52 (m, 1H), 1.26 (tdd, J = 11.4, 2.5, 1.5 Hz, 1H), 0.97 (s, 9H), 0.81 (s, 9H), 0.79 (d, J = 6.7 Hz, 3H), 0.71 (t, J = 7.8 Hz, 9H), 0.33 (q, J = 7.8 Hz, 6H), −0.01 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 158.9, 135.3, 135.2, 133.2, 129.3, 129.3, 129.2, 127.2, 113.3, 89.9, 77.5, 72.2, 70.0, 67.8, 54.9, 40.7, 31.0, 26.5, 26.0, 25.8, 25.4, 18.8, 18.1, 11.8, 6.4, 4.5, −4.1, −4.9 ppm; IR (film): $\tilde{\nu}$ = 2954, 2858, 1715, 1613, 1515, 1462, 1428, 1388, 1249, 1111, 1037, 1066, 832, 777, 739, 702 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{45}H_{72}O_3Si_5Na$ [M^++Na]: 815.45290, found: 815.45302.

Compound 73: Prepared analogously as a pale yellow oil (1.66 g, quant.). $[\alpha]_D^{20} = +30.6$ (c = 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.32 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.95–3.86 (m, 2H), 3.80 (s, 3H), 3.74 (d, J = 6.8 Hz, 1H), 2.15 (s, 3H), 1.59–1.43 (m, 3H), 1.10 (d, J = 6.1 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.94 (t, J = 7.7 Hz, 9H), 0.90 (d, J = 6.6 Hz, 3H), 0.66–0.56 ppm (m, 12H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 209.8, 160.5, 130.6, 130.5, 114.5, 89.6, 77.3, 73.1, 67.7, 55.5, 45.4, 33.7, 27.0, 24.0, 14.4, 7.4, 7.4, 7.3, 6.0, 5.8 ppm; IR (film): $\tilde{\nu}$ = 2954, 2874, 1715, 1514, 1248, 1004 cm^{-1}; MS (EI): m/z (%): 373 (2), 345 (1), 308 (2), 279 (6), 213 (36), 121 (100); HRMS (ESI): m/z: calcd for $C_{29}H_{54}O_5Si_2Na$ [M^++Na]: 561.340203, found: 561.339699.

Compound 106: MeLi (2.2 M in Et_2O, 1.06 mL, 2.34 mmol) was added to a suspension of CuI (223 mg, 1.17 mmol) in Et_2O (2.0 mL) at −20 °C. After 35 min, the colorless solution was cooled to −60 °C before a solution of thioester derivative **105** (160 mg, 0.19 mmol) in Et_2O (5 mL) was slowly introduced. The mixture was allowed to warm to −20 °C over 2 h before the reaction was quenched with sat. aq. NH_4Cl (10 mL) at −10 °C. After stirring at ambient temperature for 1 h, the aqueous phase was extracted with *tert*-butyl methyl ether (3×10 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc 9:1) to give the corresponding methyl ketone (127 mg, 82 %) as a colorless oil. Pyridinium *p*-toluene sulfonate (36.2 mg, 0.14 mmol) was added to a solution of this product (127 mg, 0.16 mmol) in EtOH (0.3 mL) and the mixture was stirred for 1 h before the reaction was quenched with a sat. aq. $NaHCO_3$ (3 mL). A standard extractive work up followed by flash chromatography (hexanes/*tert*-butyl methyl ether 12:1) gave product **106** as a colorless oil (75 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 4H), 7.40–7.33 (m, 6H), 7.19 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.35 (d, J = 2.8 Hz, 2H),

3.77 (m, 1H), 3.77 (br s, 3H), 3.71 (m, 1H), 3.68 (m, 1H), 3.56 (dd, J= 14.0, 9.9 Hz, 1H), 3.45 (dd, J=14.0, 6.6 Hz, 1H), 2.13 (s, 3H), 1.79 (m, 2H), 1.77 (m, 1H), 1.22 (m, 1H), 1.01 (s, 9H), 0.90 (d, J=6.7 Hz, 3H), 0.98 (s, 9H), 0.02 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=210.1, 135.2, 135.2, 129.5, 129.4, 127.4, 113.4, 95.4, 87.9, 77.0, 76.7, 76.3, 72.2, 69.1, 54.9, 33.9, 32.2, 27.0, 26.5, 25.7, 16.6, −4.5, −5.0 ppm; IR (film): $\tilde{\nu}$=3545, 2958, 2931, 2857, 1713, 1648, 1613, 1514, 1463, 1428, 1362, 1302, 1275, 1258, 1112, 835, 703 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{39}H_{58}O_6Si_2Na$ [M^++Na]: 701.36595, found: 701.36641.

Compound 74: Pyridinium *p*-toluenesulfonate (PPTS, 47 mg, 0.19 mmol) was added to a solution of **73** (1.66 g, 3.08 mmol) in EtOH (93 mL) at −15 °C. After stirring for 3 h, the reaction was quenched with aq. sat. $NaHCO_3$ (20 mL), the aqueous layer was extracted with EtOAc (3× 100 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (15 → 30 % *v*/*v* EtOAc in hexanes) to afford alcohol **74** as a colorless oil (1.15 g, 89 %). $[\alpha]_D^{20}$ = +21.4 (c=0.42, CH_2Cl_2); ^{1}H NMR (300 MHz, [D$_6$]acetone): δ= 7.32 (d, J=8.7 Hz, 2H), 6.91 (d, J=8.7 Hz, 2H), 4.39 (d, J=2.8 Hz, 2H), 4.03 (dd, J=7.4, 2.0 Hz, 1H), 3.86–3.81 (m, 1H), 3.80 (s, 3H), 3.70 (d, J= 7.3 Hz, 1H), 3.41 (d, J=5.3 Hz, 1H), 2.13 (s, 3H), 1.70–1.52 (m, 2H), 1.32–1.22 (m, 1H), 1.11 (d, J=6.2 Hz, 3H), 0.93 (t, J=7.9 Hz, 9H), 0.87 (d, J=6.6 Hz, 3H), 0.65–0.53 ppm (m, 6H); ^{13}C NMR (75 MHz, [D$_6$]acetone): δ=209.6, 160.4, 130.6, 114.4, 90.5, 75.1, 73.0, 65.2, 55.5, 44.2, 32.8, 26.2, 24.7, 14.6, 7.4, 6.0 ppm; IR (film): $\tilde{\nu}$=3467, 2959, 2875, 1713, 1514, 1054 cm^{-1}; MS (EI): m/z (%): 288 (1), 213 (3), 201 (10), 121 (100); HRMS (ESI): m/z: calcd for $C_{23}H_{40}O_5SiNa$ [M^++Na]: 447.25372, found: 447.25359.

Compound 75: PPh_3 (1.5 g, 5.86 mmol) and DIAD (1.15 mL, 5.86 mmol) were successively added to a solution of alcohol **74** (1.15 g, 2.71 mmol) and acid **28** (713 mg, 5.08 mmol) in toluene (40 mL) at −20 °C. Once the addition was complete, the mixture was stirred for 1 h at ambient temperature before the reaction was quenched with aq. sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3×30 mL), the combined organic phases were dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (5 % *v*/*v* EtOAc in hexanes) to afford ester **75** as a colorless oil (1.34 g, 91 %). $[\alpha]_D^{20}$ = +29.4 (c=1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]acetone): δ=7.33 (d, J=8.7 Hz, 2H), 6.92 (d, J=8.7 Hz, 2H), 6.72 (tq, J=7.0, 1.3 Hz, 1H), 5.84 (ddt, J=17.0, 10.3, 6.3 Hz, 1H), 5.08–4.96 (m, 3H), 4.46 (d, J=11.0 Hz, 1H), 4.42 (d, J= 11.0 Hz, 1H), 3.89 (dd, J=6.0, 3.0 Hz, 1H), 3.80 (s, 3H), 3.77 (d, J= 6.3 Hz, 1H), 2.32–2.26 (m, 2H), 2.22–2.16 (m, 2H), 2.14 (s, 3H), 1.88–1.82 (m, 1H), 1.80 (d, J=1.3 Hz, 3H), 1.64–1.57 (m, 1H), 1.56–1.49 (m, 1H), 1.20 (d, J=6.2 Hz, 3H), 0.94 (t, J=7.8 Hz, 9H), 0.88 (d, J=6.5 Hz, 3H), 0.65–0.59 ppm (m, 6H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ= 210.0, 167.7, 160.5, 141.6, 138.6, 130.6, 130.5, 129.2, 115.6, 114.5, 89.0, 77.7, 73.1, 69.2, 55.5, 41.2, 33.6, 33.3, 28.7, 27.1, 21.2, 13.9, 12.6, 7.4, 5.9 ppm; IR (film): $\tilde{\nu}$=2954, 2876, 1707, 1514, 1249, 1078, 1005 cm^{-1}; MS (EI): m/z (%): 308 (2), 279 (3), 213 (28), 201 (14), 121 (100); HRMS (ESI): m/z: calcd for $C_{31}H_{50}O_6SiNa$ [M^++Na]: 569.32689, found: 569.32657.

Compound 107: Prepared analogously from acid **28** (90 mg, 0.64 mmol) and alcohol **106** (100 mg, 0.16 mmol) as a colorless oil (90 mg, 73 %). $[\alpha]_D^{20}$ = −7.1 (c=0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (m, 4H), 7.43–7.38 (m, 6H), 7.26 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 6.79 (td, J=7.3, 1.3 Hz, 1H), 5.85 (ddt, J=16.9, 11.4, 6.6 Hz, 1H), 5.17 (m, 1H), 5.03 (ddt, J=16.9, 1.8, 1.4 Hz, 1H), 5.00 (ddt, J=10.4, 1.4, 1.2 Hz, 1H), 4.45 (d, J=11.6 Hz, 1H), 4.41 (d, J=11.6 Hz, 1H), 3.81 (s, 3H), 3.67 (m, 2H), 3.66 (2d, J=10.6, 5.6 Hz, 1H), 3.65 (2d, J=10.6, 5.6 Hz, 1H), 2.27 (td, J=7.2, 6.9 Hz, 2H), 2.22 (td, J=6.8, 6.6 Hz, 2H), 2.12 (s, 3H), 1.84 (s(d), J=1.0 Hz, 3H), 1.82 (m, 1H), 1.44 (m, 2H), 1.05 (s, 9H), 1.02 (d, J=6.7 Hz, 3H), 0.89 (s, 9H), 0.03 ppm (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=209.0, 167.7, 164.5, 160.2, 145.6, 141.9, 138.1, 137.5, 136.3, 136.3, 134.2, 130.3, 130.0, 128.6, 128.4, 127.8, 114.3, 88.6, 78.6, 73.0, 72.5, 66.6, 55.0, 53.6, 49.5, 34.5, 33.2, 33.1, 32.9, 32.7, 28.8, 28.5, 26.8, 27.3, 27.0, 26.6, 26.8, 19.7, 18.2, 17.6, 13.0, 12.6, −3.5, −4.3 ppm; IR (film): $\tilde{\nu}$=3072, 2955, 2930, 2857, 1710, 1648, 1613, 1514, 1471, 1462, 1462, 1388, 1249, 1111, 1035, 913, 834, 740 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{47}H_{68}O_7Si_2Na$ [M^++Na]: 823.4396, found: 823.4398.

Methyl ketone 29: A solution of pyridinium *p*-toluenesulfonate (251 mg, 1 mmol) and **27** (1.0 g, 1.26 mmol) in EtOH (3 mL) was stirred for 1 h before the reaction was quenched with a sat. aq. $NaHCO_3$ (5 mL). A standard extractive work up followed by flash chromatography (hexanes/*tert*-butyl methyl ether 12:1) of the crude product gave the TES-deprotected alcohol as a colorless oil (480 mg, 56 %).

DCC (365 mg, 1.77 mmol) and DMAP (72 mg, 0.59 mmol) were added to a solution of this compound (480 mg, 0.70 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred for 30 min before acid **28** (393 mg, 2.8 mmol)[75] was introduced and stirring continued for 12 h at ambient temperature. For work up, all volatile materials were evaporated, the product adsorbed on silica and purified by flash chromatography (hexanes/*tert*-butyl methyl ether 12:1) to give product **29** as a colorless oil (405 mg, 75 %). $[\alpha]_D^{20}$ = +11.5 (c=0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.63 (m, 4H), 7.43–7.32 (m, 6H), 7.20 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 6.75 (td, J=6.9, 1.3 Hz, 1H), 5.82 (ddt, J=17.3, 10.4, 6.6 Hz, 1H), 5.10 (m, 1H), 5.03 (ddt, J=17.1, 1.8, 1.4 Hz, 1H), 4.98 (ddt, J=10.4, 1.4, 1.2 Hz, 1H), 4.38 (d, J=11.6 Hz, 1H), 3.78 (br.s, 5H), 3.72 (d, J=5.7 Hz, 1H), 3.66 (d, J=4.8 Hz, 2H), 2.25 (td, J=7.2, 6.9 Hz, 2H), 2.18 (td, J=6.8, 6.6 Hz, 2H), 2.09 (s, 3H), 1.94 (3d, J=14.2, 9.8, 4.2 Hz, 1H), 1.82 (s(d), J=1.0 Hz, 3H), 1.59 (m, 2H), 1.01 (s, 9H), 0.87 (s, 9H), 0.86 (d, J=6.7 Hz, 3H), 0.02 (s, 3H), −0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=210.1, 167.3, 159.0, 141.9, 137.2, 135.2, 133.0, 129.3, 129.0, 127.8, 127.3, 114.9, 113.4, 87.6, 76.6, 72.1, 71.8, 65.4, 54.9, 34.5, 32.5, 32.1, 27.8, 26.8, 26.3, 25.6, 18.83, 18.0, 13.4, 12.1, −4.5, −5.0 ppm; IR (film): $\tilde{\nu}$=3072, 2955, 2930, 2857, 1710, 1648, 1613, 1514, 1471, 1462, 1462, 1388, 1249, 1111, 1035, 913, 834, 740 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{47}H_{68}O_7Si_2Na$ [M^++Na]: 823.4396, found: 823.4398.

Compound 30: DDQ (797 mg, 3.51 mmol) was added to a solution of **29** (900 mg, 1.17 mmol) in CH_2Cl_2 (6 mL). After stirring for 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ (12 mL) and ice, the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/*tert*-butyl methyl ether 4:1) to give the corresponding alcohol as a colorless oil (400 mg, 52 %), which was immediately used in the next step.

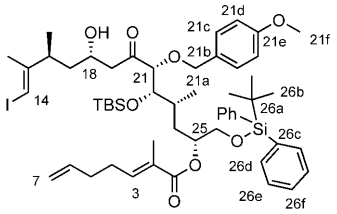
DMAP (100 mg, 0.77 mmol), imidazole (149 mg, 2.19 mmol) and TESCl (553 mg, 0.62 mL, 3.67 mmol) were added to a solution of this alcohol (400 mg, 587 mol) in DMF (7 mL) and the resulting mixture was stirred at 45 °C for 3 d. The reaction was quenched with sat. aq. NH_4Cl (3× 20 mL), the aqueous phase extracted with EtOAc (4×10 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 30:1) to give product **30** (370 mg, 79 %) as a colorless oil. $[\alpha]_D^{20}$ = +20.1 (c=0.2, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ=7.65 (m, 4H), 7.09 (m, 6H), 6.85 (td, J=6.9, 1.3 Hz, 1H), 5.54 (ddt, J=17.3, 10.4, 6.6 Hz, 1H), 5.33 (m, 1H), 4.87 (ddt, J=17.1, 1.8, 1.4 Hz, 1H), 4.79 (ddt, J=10.4, 1.4, 1.2 Hz, 1H), 4.09 (d, J=5.1 Hz, 1H), 3.70 (m, 3H), 1.97 (m, 1H), 1.94 (s, 3H), 1.88 (m, 3H), 1.76 (s(d), J=1.3 Hz, 3H), 1.51 (m, 1H), 1.033 (s, 9H), 0.89 (d, J=6.7 Hz, 3H), 0.86 (m, 2H), 0.83 (t, J=7.9 Hz, 9H), 0.825 (s, 9H), 0.39 (q, J=8 Hz, 6H), −0.02 (s, 3H), −0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=207.8, 167.7, 141.9, 138.0, 136.2, 134.1, 130.0, 129.0, 129.0, 128.0, 115.5, 82.1, 78.8, 72.6, 66.5, 35.8, 33.1, 32.9, 28.7, 28.0, 27.3, 26.5, 19.8, 18.7, 15.4, 7.3, 5.5, −3.5, −4.0 ppm; IR (film): $\tilde{\nu}$=2957, 1712, 1648, 1613, 1462, 1258, 1113, 1005, 837, 740, 702 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{45}H_{74}O_6Si_3Na$ [M^++Na]: 817.46785, found: 817.46854.

Compound 108: Prepared analogously from compound **107** as a colorless oil (34 mg, 65 % over two steps). $[\alpha]_D^{20}$ = −32.5 (c=0.9, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ=7.72 (m, 4H), 7.15 (m, 6H), 6.95 (td, J= 6.9, 1.3 Hz, 1H), 5.66 (ddt, J=17.1, 10.0, 6.9 Hz, 1H), 5.33 (m, 1H), 4.93 (ddt, J=16.9, 1.8, 1.1 Hz, 1H), 4.88 (ddt, J=10.4, 1.6, 1.2 Hz, 1H), 4.19 (d, J=5.0 Hz, 1H), 3.74 (m, 2H), 3.67 (dd, J=13.5, 4.8 Hz, 1H), 2.04 (s, 3H), 1.98 (m, 1H), 1.84 (s(d), J=1.3 Hz, 3H), 1.37 (m, 1H), 1.18 (m, 4H), 1.18 (s, 9H), 1.03 (d, J=6.7 Hz, 3H), 0.92 (s, 9H), 0.73 (t, J=

7.9 Hz, 9H), 0.52 (q, J=8 Hz, 6H), 0.07 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=208.2, 167.7, 141.8, 138.1, 136.2, 134.1, 130.2, 128.9, 128.5, 128.0, 115.5, 81.8, 79.4, 72.2, 66.7, 41.9, 36.6, 34.0, 33.1, 32.7, 32.2, 29.6, 28.7, 28.2, 27.4, 27.3, 26.6, 21.0, 19.8, 18.8, 17.5, 14.8, 14.6, 13.0, 11.9, 7.4, 5.5, −3.2, −4.0 ppm; HRMS (ESI): m/z: calcd for $C_{45}H_{74}O_6Si_3Na$ [M^++Na]: 817.46785, found: 817.46854.

Fragment couplings: **Aldol reactions and elaboration of the resulting adducts**

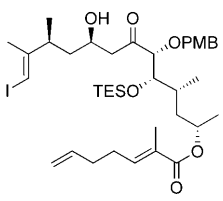
Aldol product 62: A solution of LDA (1 M in THF, 0.19 mL, 0.16 mmol) was added to a solution of methyl ketone **29** (100 mg, 0.13 mmol) in THF (0.5 mL) at −78 °C. After stirring for 2 h, a pre-cooled solution of aldehyde **41** (40 mg, 0.17 mmol) was added via cannula at −78 °C. Stirring was continued for 45 min at this temperature before the reaction was quenched with aq. phosphate buffer (pH 7, 10 mL). The mixture was extracted with EtOAc (3×5 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 4:1) gave aldol **62** as a colorless oil (90 mg, 70%, d.r. >10:1). $[\alpha]_D^{20}$ = +5 (c=0.2, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ=7.78 (m, 4H, H26d), 7.26 (m, 6H, H26e, H26f), 7.18 (d, J=8.5 Hz, 2H, H21c), 6.98 (tq, J=7.3, 1.4 Hz, 1H, H3), 6.75 (d, J=8.5 Hz, 2H, H21d), 5.86 (s(q), J=0.8, 1H, H14), 5.69 (ddt, J=17.0, 10.4, 6.3 Hz, 1H, H6), 5.43 (m, 1H, H25), 4.98 (ddt, J=17.7, 1.7, 1.6 Hz, 1H, $H7_Z$), 4.95 (ddt, J=10.2, 1.8, 1.2 Hz, 1H, $H7_E$), 4.29 (d, J=11.2 Hz, 1H, H21a), 4.24 (d, J=11.2 Hz, 1H, H21a′), 4.08 (m, 1H, H18), 4.01 (dd, J=6.1, 3.2 Hz, 1H, H22), 3.82 (dd, J=10.8, 4.2 Hz, 1H, H26a), 3.82 (d, J=6.1 Hz, 1H, H21), 3.79 (dd, J=10.8, 5.5 Hz, 1H, H26b), 3.26 (s, 3H, H21f), 2.86 (d, J=3.3 Hz, 1H, OH), 2.71 (dd, J=18.2, 9.2 Hz, 1H, H19a), 2.61 (ddq, J=9.2, 6.8, 5.5 Hz, 1H, H16), 2.51 (dd, J=18.2, 2.4 Hz, 1H, H19b), 2.14 (3d, J=14.2, 9.8, 4.2 Hz, 1H, H24a), 2.06 (m, 2H, H4), 2.01 (m, 2H, H5), 1.90 (s, 3H, H27), 1.86 (m, 1H, H23), 1.68 (s(d), J=1.0 Hz, 3H, H30), 1.68 (3d, J=14.2, 9.3, 3.4 Hz, 1H, H24b), 1.52 (3d, J=13.7, 9.5, 5.5 Hz, 1H, H17a), 1.16 (s, 9H, H26b), 1.11 (3d, J=13.6, 9.2, 3.6 Hz, 1H, H17b), 1.06 (d, J=6.7 Hz, 3H, H32), 0.99 (s, 9H, H22b), 0.90 (d, J=6.8 Hz, 3H, H31), 0.12 (s, 3H, H22c), 0.15 ppm (s, 3H, H22d); ^{13}C NMR (100 MHz, C_6D_6): δ=212.8 (s, C20), 167.6 (s, C1), 160.1 (s, C21e), 152.7 (s, C15), 141.6 (d, C3), 137.7 (d, C6), 136.0 (d, C26d), 135.9 (d, C26e), 133.8 (2 s, C26c), 130.0 (d, C21d), 129.6 (s, C21b), 128.7 (s, C2), 115.4 (t, C7), 114.2 (d, C21d), 88.0 (d, 21), 77.0 (d, C22), 75.6 (d, C14), 73.0 (t, C21a), 72.9 (d, C25), 66.4 (t, C26), 65.2 (d, C18), 54.8 (q, C21f), 47.2 (t, C19), 42.2 (t, C17), 39.5 (d, C16), 35.4 (t, C24), 33.8 (d, C23), 32.8 (t, C5), 28.4 (t, C4), 27.0 (q, C26b), 26.4 (q, C22b), 21.3 (q, C30), 19.5 (s, C26a), 18.6 (s, C22a), 18.5 (q, C31), 14.6 (q, C32), 12.8 (q, C27), −3.7 (q, C22c), −4.3 ppm (q, C22d); IR (film): $\tilde{\nu}$=3480, 2930, 2857, 1708, 1613, 1514, 1462, 1428, 1388, 1250, 1115, 1036, 834, 777, 741, 702 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{54}H_{79}O_8Si_2INa$ [M^++Na]: 1061.42504, found: 1061.42498.



Compound 58: Prepared analogously from methyl ketone **29** (25 mg, 31 μmol) and aldehyde **57** (10 mg, 38 μmol) as a colorless oil (13 mg, 40%, d.r. >20:1). $[\alpha]_D^{20}$ = +12.3 (c=0.4, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ=7.79 (m, 4H), 7.21 (m, 6H), 7.15 (m, 2H), 6.99 (tq, J=7.4, 1.4 Hz, 1H), 6.75 (d, AB, J=8.7, 2H), 5.73 (s 1H), 5.69 (ddt, J=17.0, 10.3, 6.3, 1H), 5.50 (3d, J=17.2, 10.4, 7.5, 1H), 5.44 (m, 1H), 5.29 (3d, J=17.2, 1.5, 0.5 Hz, 1H), 5.02 (3d, J=10.4, 1.6, 0.5 Hz, 1H), 5.00 (s, 1H), 4.99 (ddt, J=17.2, 1.7, 1.6 Hz, 1H), 4.95 (ddt, J=10.3, 1.9, 1.1 Hz, 1H), 4.93 (dd, J=2.4, 1.1 Hz, 1H), 4.37 (d, J=11.2 Hz, 1H), 4.26 (m, 1H), 4.24 (d, J=11.1 Hz, 1H), 4.03 (dd, J=6.1, 3.3 Hz, 1H), 3.86 (d, J=6.1 Hz, 1H), 3.82 (dd, J=10.8, 4.3 Hz, 1H), 3.79 (dd, J=10.8, 5.5 Hz, 1H), 3.27 (s, 3H), 2.91 (br d, J=3.4 Hz, 1H, OH), 2.91 (dd, J=7.4, 2.0 Hz, 1H), 2.89 (dd, J=17.9, 9.1 Hz, 1H), 2.68 (3d, J=6.4, 5.5, 2.1 Hz, 1H), 2.59 (dd, J=18.0, 2.6 Hz, 1H), 2.55 (m, 1H), 2.15 (3d, J=14.4, 10.0, 4.0 Hz, 1H), 2.09 (dd, J=13.6, 6.6 Hz, 1H), 2.07 (m, 2H), 2.03 (m, 2H), 1.93 (dd, J=13.6, 7.8 Hz, 1H), 1.91 (s(d), J=1.2 Hz, 3H), 1.88 (m, 1H), 1.80 (m, 1H), 1.79 (s(d), J=0.9 Hz, 3H), 1.76 (m, 1H), 1.69 (3d, J=14.4, 9.6, 3.2 Hz, 1H), 1.54 (3d, J=13.9, 6.4, 4.7 Hz, 1H), 1.35 (3d, J=13.2, 8.4, 4.0 Hz, 1H), 1.17 (s, 9H), 1.14 (m, 1H), 1.07 (d, J=6.7, 3H), 1.06 (d, J=6.8, 3H), 1.03 (s, 9H), 0.88 (d, J=6.6 Hz, 3H), 0.14 (s, 3H), 0.12 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=212.6, 167.5, 160.0, 144.8, 143.5, 137.7, 136.8, 136.0, 135.9, 133.9, 133.8, 130.1, 130.02, 130.01, 129.8, 128.8, 128.1, 125.5, 117.9, 115.4, 114.9, 114.1, 88.0, 77.0, 72.9, 72.8, 66.4, 65.8, 59.0, 58.9, 54.7, 47.3, 46.3, 42.7, 40.0, 39.2, 35.4, 33.7, 32.9, 29.9, 28.4, 27.0, 26.4, 19.7, 19.5, 19.2, 18.6, 14.9, 14.6, 12.8, −3.7, −4.3 ppm; IR (film): $\tilde{\nu}$= 3390, 2927, 2876, 1711, 1608, 1514, 1462, 1425, 1390, 1252, 1125, 834, 702, 691 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{64}H_{94}O_9Si_2Na$ [M^++Na]: 1085.63375, found: 1085.63386.

Compound 76: Prepared analogously from ketone **75** (300 mg, 0.55 mmol) and aldehyde **41** (170 mg, 0.71 mmol). Flash chromatography (5 → 10% v/v EtOAc in hexanes) of the crude product afforded (*R*)-**76** (59 mg, 14%) and (*S*)-**76** (191 mg, 44%) as a colorless oil each. Analytical and spectroscopic data of the major isomer (*S*)-**76**: $[\alpha]_D^{20}$ = +40.4 (c= 0.95, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ=7.20 (d, J=8.7 Hz, 2H), 6.95–6.91 (m, 1H), 6.77 (d, J=8.7 Hz, 2H), 5.87 (s, 1H), 5.67 (qt, J= 10.3, 6.2 Hz, 1H), 5.31–5.23 (m, 1H), 5.00–4.94 (m, 2H), 4.32 (d, J= 11.2 Hz, 1H), 4.27 (d, J=11.1 Hz, 1H), 4.13–4.06 (m, 1H), 4.01 (dd, J= 6.2, 3.4 Hz, 1H), 3.84 (d, J=6.2 Hz, 1H), 3.28 (s, 3H), 2.90 (d, J=3.4 Hz, 1H), 2.71 (dd, J=18.1, 9.1 Hz, 1H), 2.65–2.58 (m, 1H), 2.53 (dd, J=18.1, 2.5 Hz, 1H), 2.07–1.95 (m, 6H), 1.88–1.81 (m, 1H), 1.86 (d, J=1.1 Hz, 3H), 1.69 (d, J=1.0 Hz, 3H), 1.56–1.46 (m, 2H), 1.36–1.26 (m, 1H), 1.20 (d, J=6.2 Hz, 3H), 1.13–1.07 (m, 1H), 1.04 (d, J=6.7 Hz, 1H), 1.03 (t, J=7.8 Hz, 9H), 0.85 (d, J=6.9 Hz, 3H), 0.73–0.66 ppm (m, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ=213.1, 167.5, 160.2, 152.7, 141.3, 137.8, 130.1, 129.7, 129.0, 115.4, 114.2, 88.2, 77.2, 75.7, 73.2, 69.1, 65.3, 54.8, 47.2, 42.3, 40.8, 39.6, 33.7, 32.9, 28.4, 21.4, 21.2, 18.5, 14.4, 12.8, 7.4, 5.8 ppm; IR (film): $\tilde{\nu}$=3528, 2954, 2875, 1706, 1514, 1250, 1077 cm^{-1}; MS (EI): m/z (%): 517 (1), 439 (6), 421 (3), 279 (2), 213 (32), 121 (100); HRMS (ESI): m/z: calcd for $C_{38}H_{61}IO_7SiNa$ [M^++Na]: 807.31235, found: 807.31209.

Analytical and spectroscopic data of the minor isomer (*R*)-**76**: $[\alpha]_D^{20}$ = +21.4 (c=0.92, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ=7.15 (d, J= 8.4 Hz, 2H), 6.95–6.92 (m, 1H), 6.77 (d, J= 8.7 Hz, 2H), 5.97 (s, 1H), 5.68 (qt, J=10.3, 6.1 Hz, 1H), 5.31–5.24 (m, 1H), 5.01–4.94 (m, 2H), 4.31 (d, J=11.4 Hz, 1H), 4.19 (d, J=11.4 Hz, 1H), 3.99 (dd, J=6.8, 2.8 Hz, 1H), 3.92–3.85 (m, 1H), 3.82 (d, J=6.8 Hz, 1H), 3.30 (s, 3H), 2.80 (br s, 1H), 2.72–2.64 (m, 1H), 2.64 (dd, J=18.0, 2.9 Hz, 1H), 2.45 (dd, J=18.0, 8.9 Hz, 1H), 2.06–1.91 (m, 4H), 1.88 (s, 3H), 1.86–1.78 (m, 1H), 1.65 (d, J=1.0 Hz, 3H), 1.55–1.48 (m, 1H), 1.31–1.14 (m, 3H), 1.22 (d, J= 6.1 Hz, 3H), 1.07 (d, J=6.4 Hz, 3H), 1.04 (t, J=7.8 Hz, 9H), 0.82 (d, J= 7.0 Hz, 3H), 0.75–0.68 ppm (m, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ= 212.4, 167.5, 160.1, 151.2, 141.2, 137.8, 130.1, 129.6, 129.0, 115.4, 114.2, 89.2, 76.9, 76.4, 73.3, 69.0, 65.5, 54.9, 46.8, 42.1, 41.3, 40.1, 33.0, 32.9, 28.4, 21.1, 20.2, 20.1, 13.8, 12.8, 7.4, 5.8 ppm; IR (film): $\tilde{\nu}$=3528, 2955, 2932, 2875, 1705, 1514, 1249, 1075, 1036 cm^{-1}; MS (EI): m/z (%): 517 (1), 439 (8), 421 (3), 353 (1), 279 (2), 213 (33), 121 (100); HRMS (ESI): m/z: calcd for $C_{38}H_{61}IO_7SiNa$ [M^++Na]: 807.31235, found: 807.31198.



Compound 90: Prepared analogously from ketone **75** (140 mg, 0.26 mmol) and aldehyde **89** (123 mg, 0.33 mmol) as a colorless oil (106 mg, 45%). $[\alpha]_D^{20}$ = +38.5 (c=1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ=7.25 (d, J=8.7 Hz, 2H), 6.97–6.91 (m, 1H), 6.79 (d, J=8.7 Hz, 2H), 6.37 (d, J=0.8 Hz, 1H), 5.76–5.63 (m, 1H), 5.32–5.22 (m, 1H), 5.03–4.94 (m, 2H), 4.54–4.48 (m, 1H), 4.47 (d, J=11.0 Hz, 1H), 4.27 (d, J=11.0 Hz, 1H), 4.04 (dd, J=6.1, 3.0 Hz, 1H), 3.89 (d, J=6.4 Hz, 1H), 3.45 (d, J=2.0 Hz, 1H), 3.29 (s, 3H), 3.08 (dd, J=17.5, 8.0 Hz, 1H), 2.52

(dd, $J=17.5$, 4.3 Hz, 1H), 2.07–1.98 (m, 6H), 1.93–1.85 (m, 2H), 1.89 (s, 6H), 1.56–1.45 (m, 3H), 1.30 (s, 3H), 1.22 (d, $J=6.0$ Hz, 3H), 1.04–0.99 (m, 1H), 1.04 (t, $J=8.3$ Hz, 9H), 0.92 (t, $J=7.9$ Hz, 9H), 0.75–0.65 (m, 6H), 0.55–0.47 ppm (m, 6H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=211.4$, 167.4, 160.0, 152.8, 141.2, 137.8, 130.1, 130.0, 129.0, 115.4, 114.1, 88.4, 80.0, 79.2, 76.9, 73.0, 69.2, 64.9, 54.8, 48.7, 47.4, 40.7, 33.6, 32.9, 28.4, 26.6, 22.1, 21.1, 14.4, 12.8, 7.4, 7.3, 6.8, 5.8 ppm; IR (film): $\tilde{\nu}=2955$, 1707, 1515, 1250, 1077, 1009 cm^{-1}; MS (EI): m/z (%): 685 (1), 437 (2), 339 (6), 325 (6), 279 (3), 213 (34), 121 (100); HRMS (ESI): m/z: calcd for $C_{44}H_{75}IO_8Si_2Na$ [M^++Na]: 937.39374, found: 937.39384.

Compound 109: Prepared analogously from methyl ketone **108** (34 mg, 42 μmol) and aldehyde **57** (11 mg, 42 μmol) as a colorless oil (21 mg, 49%). $[\alpha]_D^{20}=+11.0$ ($c=0.1$, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): $\delta=$ 7.79 (m, 4H), 7.27–7.22 (m, 6H), 7.06 (tq, $J=7.3$, 1.4 Hz, 1H), 5.72 (ddt, $J=16.9$, 10.4, 6.3 Hz, 1H), 5.72 (s, 1H), 5.52 (3d, $J=17.2$, 10.3, 7.5 Hz, 1H), 5.52 (m, 1H), 5.29 (3d, $J=17.2$, 1.8, 1.6 Hz, 1H), 5.03 (3d, $J=10.4$, 1.6, 0.3 Hz, 1H), 5.00 (s(d), $J=2.5$ Hz, 1H), 5.00 (ddt, $J=17.0$, 1.6, 0.5 Hz, 1H), 4.96 (ddt, $J=10.2$, 1.9, 1.1 Hz, 1H), 4.92 (dd, $J=2.4$, 1.2 Hz, 1H), 4.36 (d, $J=5.4$ Hz, 1H), 4.25 (m, 1H), 3.87 (dd, $J=10.6$, 5.5 Hz, 1H), 3.85 (dd, $J=5.3$, 4.6 Hz, 1H), 3.83 (dd, $J=10.6$, 4.9 Hz, 1H), 2.91 (dd, $J=7.5$, 2.0 Hz, 1H), 2.90 (dd, $J=17.4$, 2.7 Hz, 1H), 2.87 (br. d, $J=$ 3.2 Hz, 1H, OH), 2.73 (dd, $J=17.4$, 9.3 Hz, 1H), 2.68 (3d, $J=6.3$, 5.4, 2.0 Hz, 1H), 2.49 (sext., $J=7.0$ Hz, 1H), 2.13 (3d, $J=14.2$, 10.4, 2.8 Hz, 1H), 2.10–2.07 (m, 5H), 2.03 (m, 1H), 1.95 (s(d), $J=1.3$ Hz, 3H), 1.93 (dd, $J=13.6$, 7.6 Hz, 1H), 1.81 (m, 1H), 1.78 (3d, $J=13.7$, 8.5, 7.0 Hz, 1H), 1.76 (s(d), $J=1.4$ Hz, 3H), 1.60 (3d, $J=14.1$, 10.9, 2.6 Hz, 1H), 1.55 (3d, $J=13.7$, 6.4, 4.8 Hz, 1H), 1.38 (3d, $J=13.7$, 7.6, 4.5 Hz, 1H), 1.18 (s, 9H), 1.15 (3d, $J=13.8$, 8.8, 5.3 Hz, 1H), 1.15 (d, $J=6.8$ Hz, 3H), 1.03 (d, $J=6.9$ Hz, 3H), 1.01 (s, 9H), 1.01 (t, $J=7.9$ Hz, 9H), 0.88 (d, $J=6.7$ Hz, 3H), 0.67 (q, $J=8.0$ Hz, 6H), 0.20 (s, 3H), 0.10 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=211.3$, 167.5, 144.7, 143.4, 141.5, 137.8, 136.8, 136.0, 135.9, 133.9, 133.8, 130.0, 128.7, 128.1, 128.0, 125.7, 118.0, 115.3, 115.0, 82.0, 79.0, 72.1, 66.5, 66.4, 59.0, 46.9, 46.2, 42.8, 40.2, 39.1, 33.7, 32.9, 32.6, 29.9, 28.5, 27.0, 26.4, 19.7, 19.5, 19.4, 18. 6, 17.3, 14.7, 12.8, 7.2, 5.3, −3.3, −4.2 ppm; IR (film): $\tilde{\nu}=3370$, 2950, 2872, 1705, 1610, 1514, 1462, 1423, 1381, 1252, 1125, 906, 699 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{62}H_{100}O_8Si_3$+NH_4 [M^++NH_4]: 1074.7049, found: 1074.7064.

Compounds 96: A solution of the ketone **30** (20 mg, 24.7 μmol) in Et_2O (0.8 mL) was added to a pre-mixed (0 °C) solution containing dicyclohexylborane (1 M in hexane, 37 μL, 37.1 μmol) and Et_3N (55.5 μL, 0.4 mmol) at 0 °C and the resulting mixture was stirred at this temperature for 1 h before it was cooled to −78 °C. A solution of aldehyde *ent*-**41** (6 mg, 25.2 μmol) in Et_2O (1 mL) was slowly introduced and stirring continued for 15 min at −78 °C and for 13 h at −20 °C. For work up, the mixture was partitioned between Et_2O (3×5 mL) and pH 7 buffer solution (10 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was taken up in MeOH (3 mL) and pH 7 buffer solution (3 mL) and stirred at 0 °C before aq. H_2O_2 (30% *w*/*w*, 20 μL) was added. After stirring for 1 h at room temperature, the mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with aq. sat. sodium thiosulfate solution (3×10 mL), dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/*tert*-butyl methyl ether 25:1) to give compound (*R*)-**96** as a colorless oil (12 mg, 46%) and a second fraction containing (*S*)-**96** (3 mg, 12%). The major diastereomer (*R*)-**96** analyzed as follows: ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.67$ (m, 4H), 7.12 (m, 6H), 6.88 (t, $J=7.0$ Hz, 1H), 5.75 (s, 1H), 5.57 (ddt, $J=16.9$, 10.7, 5.6 Hz, 1H), 5.33 (m, 1H), 4.85 (ddt, $J=17.2$, 1.5, 1.3 Hz, 1H), 4.83 (ddt, $J=10.9$, 1.5, 1.1 Hz, 1H), 4.17 (d, $J=5.3$ Hz, 1H), 3.96 (m, 1H), 3.74 (m, 2H), 3.60 (m, 1H), 2.90 (d, $J=2.8$ Hz, 1H), 2.80 (dd, $J=17.9$, 2.3 Hz, 1H), 2.45 (m, 1H), 2.37 (dd, $J=17.7$, 9.6 Hz, 1H), 1.99–1.87 (m, 5H), 1.79 (s, 3H), 1.66 (m, 1H), 1.53 (s(d), $J=1.0$ Hz, 3H), 1.16 (m, 3H), 1.04 (s, 9H), 0.91 (d, $J=6.6$ Hz, 3H), 0.84 (s, 9H), 0.72 (m, 9H), 0.66 (d, $J=$ 6.8 Hz, 3H), 0.49 (q, $J=7.8$ Hz, 6H), 0.05 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=211.6$, 167.5, 152.4, 141.6, 137.8, 136.0, 135.9, 135.2, 133.8, 133.7, 130.0, 129. 8, 128.7, 128.1, 128.0, 127.8, 127.6, 115.4, 82.0, 78.6, 75.7, 72.3, 66.2, 65.6, 47.3, 42.1, 39.7, 35.8, 32.9, 32.5, 32.3, 30.4, 30.2, 30.1, 29.6, 29.56, 29.55, 28.4, 27.0, 26.7, 26.3, 26.21, 26.18, 26.0, 23.8, 20.9, 19.5, 18.6, 18.4, 15.2, 14.6, 12.8, 7.19, 7.16, 5.22, 5.21, 5.18, 1.4, −3.7, −4.4 ppm.

Data of the minor diastereomer (*S*)-**96**: $[\alpha]_D^{20}=+11.0$ (0.1, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.63$ (m, 4H), 7.07 (m, 6H), 6.85 (t, $J=$ 6.1 Hz, 1H), 5.80 (s, 1H), 5.44 (ddt, $J=16.1$, 10.6, 5.5 Hz, 1H), 5.30 (m, 1H), 4.84 (ddt, $J=18.9$, 1.7, 1.6 Hz, 1H), 4.80 (ddt, $J=11.6$, 1.5, 1.0 Hz, 1H), 4.12 (d, $J=4.6$ Hz, 1H), 3.82 (m, 1H), 3.68 (m, 3H), 2.81 (d, $J=$ 2.0 Hz, 1H), 2.46 (dd, $J=17.9$, 9.1 Hz, 1H), 2.59 (m, 1H), 2.45 (dd, $J=$ 18.1, 2.5 Hz, 1H), 1.99–1.87 (m, 5H), 1.76 (s, 3H), 1.49 (s, 3H), 1.45 (m, 1H), 1.18 (m, 3H), 1.01 (s, 9H), 0.87 (d, $J=6.6$ Hz, 3H), 0.82 (s, 9H), 0.69 (t, $J=8.0$ Hz, 9H), 0.66 (d, $J=6.8$ Hz, 3H), 0.46 (q, $J=7.8$ Hz, 6H), 0.03 (s, 3H), −0.05 ppm (s, 3H).

Compound 63: A precooled solution of TBSOTf (39.6 mg, 0.15 mmol) and 2,6-lutidine (27.8 mg, 0.26 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of **62** (130 mg, 0.13 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C and the resulting mixture was slowly warmed to ambient temperature. After stirring for 1 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), the mixture extracted with CH_2Cl_2 (3×10 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 11:1) gave product **63** as a pale yellow oil (112 mg, 79%). ^{1}H NMR (400 MHz, C_6D_6): $\delta=$ 7.78 (m, 4H), 7.31 (d, $J=8.2$ Hz, 2H), 7.24 (m, 6H), 6.99 (tq, $J=7.1$, 1.4 Hz, 1H), 6.78 (d, $J=8.5$ Hz, 2H), 6.06 (s, 1H), 5.71 (ddt, $J=17.0$, 10.7, 6.2 Hz, 1H), 5.43 (m, 1H), 4.97 (m, 2H), 4.55 (d, $J=11.1$ Hz, 1H), 4.39 (m, 1H), 4.29 (d, $J=10.9$ Hz, 1H), 4.04 (dd, $J=10.8$, 3.3 Hz, 1H), 3.89 (d, $J=5.8$ Hz, 1H), 3.81 (dd, $J=10.8$, 5.5 Hz, 1H), 3.27 (s, 3H), 3.26 (m, 1H), 3.25 (m, 1H), 2.59 (dd, $J=18.2$, 7.7 Hz, 1H), 2.54 (ddq, $J=9.8$, 6.7, 5.5 Hz, 1H), 2.15 (m, 1H), 2.09 (m, 2H), 2.01 (m, 2H), 1.92 (s(d), $J=$ 1.3 Hz, 3H), 1.76 (s(d), $J=1.0$ Hz, 3H), 1.74 (m, 1H), 1.68–1.65 (m, 2H), 1.17 (s, 9H), 1.08 (d, $J=6.8$ Hz, 3H), 1.0 (s, 9H), 0.99 (d, $J=6.8$ Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.05 ppm (s, 3H); IR (film): $\tilde{\nu}=2926$, 2855, 1713, 1613, 1515, 1462, 1462, 1428, 1361, 1250, 1112, 1084, 1039, 1005, 914, 834, 775, 701 cm^{-1}.

Compound 77: Prepared analogously from alcohol **76** (146 mg, 0.186 mmol) as a colorless oil (136 mg, 81%). $[\alpha]_D^{20}=+42.5$ ($c=0.94$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.32$ (d, $J=8.6$ Hz, 2H), 6.96–6.92 (m, 1H), 6.82 (d, $J=8.7$ Hz, 2H), 6.05 (s, 1H), 5.68 (ddt, $J=16.9$, 10.4, 6.3 Hz, 1H), 5.32–5.24 (m, 1H), 5.01–4.92 (m, 2H), 4.57 (d, $J=$ 10.9 Hz, 1H), 4.43–4.38 (m, 1H), 4.33 (d, $J=10.9$ Hz, 1H), 4.05 (dd, $J=$ 6.1, 3.4 Hz, 1H), 3.90 (d, $J=6.2$ Hz, 1H), 3.29 (s, 3H), 3.26 (dd, $J=18.2$, 6.6 Hz, 1H), 2.59–2.53 (m, 2H), 2.07–1.98 (m, 5H), 1.90–1.83 (m, 2H), 1.88 (d, $J=1.1$ Hz, 3H), 1.77 (d, $J=1.0$ Hz, 3H), 1.68–1.61 (m, 2H), 1.58–1.51 (m, 2H), 1.36–1.27 (m, 1H), 1.22 (d, $J=6.2$ Hz, 3H), 1.06 (d, $J=$ 6.7 Hz, 3H), 1.03 (t, $J=7.8$ Hz, 9H), 0.95 (s, 9H), 0.75–0.66 (m, 6H), 0.15 (s, 3H), 0.13 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=210.1$, 167.4, 160.0, 152.2, 141.1, 137.7, 129.9, 129.0, 128.8, 115.3, 114.2, 88.4, 76.9, 75.8, 72.9, 69.2, 66.5, 54.7, 47.2, 43.7, 40.7, 39.8, 33.7, 32.8, 28.3, 26.1, 21.3, 21.1, 19.3, 18.2, 14.5, 12.8, 7.3, 5.7, −4.0, −4.6 ppm; IR (film): $\tilde{\nu}=2956$, 1709, 1515, 1251, 1079 cm^{-1}; MS (EI): m/z (%): 660 (3), 553 (19), 213 (79), 121 (100); HRMS (ESI): m/z: calcd for $C_{44}H_{75}IO_7Si_2Na$ [M^++Na]: 921.39883, found: 921.39895.

Compound 91: Prepared analogously from alcohol **90** (141 mg, 0.154 mmol) as a colorless oil (137 mg, 86%). $[\alpha]_D^{20}=+43.6$ ($c=1.4$, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6): $\delta=7.36$ (d, $J=8.6$ Hz, 2H), 6.95–6.91 (m, 1H), 6.82 (d, $J=8.6$ Hz, 2H), 6.44 (s, 1H), 5.68 (qt, $J=10.3$, 6.3 Hz, 1H), 5.37–5.26 (m, 1H), 5.01–4.93 (m, 2H), 4.62 (d, $J=10.8$ Hz, 1H), 4.51–4.43 (m, 1H), 4.32 (d, $J=10.8$ Hz, 1H), 4.06 (dd, $J=6.8$, 2.9 Hz, 1H), 3.90 (d, $J=6.8$ Hz, 1H), 3.35 (dd, $J=18.0$, 8.1 Hz, 1H), 3.29 (s, 3H), 2.72 (dd, $J=18.0$, 4.0 Hz, 1H), 2.08–1.85 (m, 8H), 1.94 (s, 3H), 1.88 (s, 3H), 1.61 (ddd, $J=13.8$, 8.9, 4.9 Hz, 1H), 1.27 (d, $J=6.9$ Hz, 3H), 1.26 (s, 3H), 1.10 (d, $J=6.6$ Hz, 3H), 1.07–0.97 (m, 18H), 0.94 (s, 9H), 0.77–0.68 (m, 6H), 0.65–0.57 (m, 6H), 0.19 (s, 3H), 0.18 ppm (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): $\delta=210.5$, 167.4, 160.0, 151.8, 141.1, 137.8, 130.1, 129.9, 129.1, 115.4, 114.1, 88.6, 79.1, 79.0, 76.4, 72.7, 69.1, 65.9, 54.8, 50.2, 47.4, 40.6, 33.6, 32.9, 28.5, 28.4, 26.3, 22.3, 21.1, 18.3, 14.5, 12.9, 7.5, 7.4, 7.1, 5.8, −3.8, −4.1 ppm; IR (film): $\tilde{\nu}=2955$, 2877, 1708, 1575, 1250, 1003 cm^{-1}; MS (EI): m/z (%): 790 (2), 683 (3), 551 (10), 325 (28), 213

(93), 121 (100); HRMS (ESI): *m/z*: calcd for $C_{50}H_{89}IO_8Si_3Na$ [M^++Na]: 1051.48045, found: 1051.48022.

Compound 97: Prepared analogously from alcohol **96** (157 mg, 0.152 mmol) as a colorless oil (155 mg, 89%). $[\alpha]_D^{20} = -4.1$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.93$–7.89 (m, 4H), 7.41–7.34 (m, 6H), 7.13–7.09 (m, 1H), 6.13 (s, 1H), 5.81 (ddt, $J = 16.9$, 10.3, 6.3 Hz, 1H), 5.59 (sext., $J = 4.3$ Hz, 1H), 5.13–5.05 (m, 2H), 4.45 (quint., $J = 6.0$ Hz, 1H), 4.40 (d, $J = 5.3$ Hz, 1H), 4.05 (dd, $J = 5.0$, 3.7 Hz, 1H), 4.00 (s, 1H), 3.98 (d, $J = 0.8$ Hz, 1H), 3.20 (dd, $J = 18.8$, 6.3 Hz, 1H), 2.91 (dd, $J = 18.7$, 5.3 Hz, 1H), 2.70 (q, $J = 6.9$ Hz, 1H), 2.29 (brs, 1H), 2.22–2.11 (m, 5H), 2.03 (s, 3H), 1.88–1.82 (m, 1H), 1.85 (d, $J = 0.8$ Hz, 3H), 1.77–1.72 (m, 2H), 1.29 (s, 9H), 1.16–1.11 (m, 9H), 1.12 (s, 9H), 1.09 (s, 9H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.5$ Hz, 3H), 0.77 (q, $J = 3.7$ Hz, 6H), 0.32 (s, 3H), 0.30 (s, 3H), 0.27 (s, 3H), 0.23 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 207.6$, 167.4, 152.4, 141.4, 137.8, 136.1, 136.0, 133.9, 133.8, 130.1, 115.4, 81.2, 78.7, 75.7, 72.5, 66.3, 66.2, 49.2, 43.9, 40.1, 36.5, 33.0, 31.8, 28.5, 27.1, 26.3, 26.2, 21.3, 19.6, 19.1, 18.5, 18.3, 15.4, 12.9, 7.2, 5.4, −3.6, −3.9, −4.3, −4.4 ppm; IR (film): $\tilde{\nu} = 2955$, 2930, 2857, 1710, 1255, 1111 cm^{-1}; MS (EI): *m/z* (%): 1089 (1) [$M^+ - t$Bu], 957 (3), 721 (3), 467 (46), 185 (100); HRMS (ESI): *m/z*: calcd for $C_{58}H_{99}IO_7Si_4Na$ [M^++Na]: 1169.540481, found: 1169.541301.

Compound 64: DDQ (66 mg, 0.29 mmol) was added to a solution of **63** (110 mg, 97 μmol) in aq. CH_2Cl_2 (2 mL). After stirring for 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and ice, the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/*tert*-butyl methyl ether 9:1) gave the corresponding alcohol as a colorless oil (61 mg, 62%). DMAP (13 mg, 0.10 mmol), imidazole (21.8 mg, 0.32 mmol) and TESCl (48.2 mg, 53 μL, 0.32 mmol) were added to a solution of this compound (100 mg, 96.8 μmol) in DMF (4 mL) and the resulting mixture was stirred at 45 °C for 3 d. The reaction was quenched with sat. aq. NH_4Cl (20 mL), the aqueous phase extracted with EtOAc (4×10 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 20:1) to give product **64** as a colorless oil (86 mg, 79%). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.81$ (m, 4H), 7.26 (m, 6H), 7.01 (tq, $J = 7.1$, 1.5 Hz, 1H), 6.01 (s, 1H), 5.71 (ddt, $J = 16.7$, 10.8, 6.6 Hz, 1H), 5.50 (m, 1H), 4.97 (m, 2H), 4.36 (m, 1H), 4.30 (d, $J = 4.6$ Hz, 1H), 3.89 (m, 3H), 3.09 (dd, $J = 18.4$, 4.5 Hz, 1H), 2.74 (dd, $J = 18.4$, 7.6 Hz, 1H), 2.64 (m, 1H), 2.12–2.06 (m, 5H), 1.94 (s, 3H), 1.76 (s(d), $J = 1.0$ Hz, 3H), 1.67 (m, 1H), 1.57 (m, 2H), 1.19 (s, 9H), 1.0 (s, 9H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.93 (s, 9H), 0.89 (t, $J = 7.8$ Hz, 9H), 0.56 (q, $J = 7.8$ Hz, 6H), 0.19 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.09 ppm (s, 3H).

Compound 78: Prepared analogously from compound **77** by DDQ cleavage of the PMB ether (73%) followed by TES protection (81%). Colorless oil (122 mg); $[\alpha]_D^{20} = -15.1$ ($c = 1.2$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.98$–6.95 (m, 1H), 6.03 (s, 1H), 5.69 (qt, $J = 10.3$, 6.3 Hz, 1H), 5.36–5.30 (m, 1H), 5.00–4.94 (m, 2H), 4.40–4.35 (m, 1H), 4.29 (d, $J = 5.0$ Hz, 1H), 3.91 (dd, $J = 4.6$, 4.3 Hz, 1H), 3.13 (dd, $J = 18.3$, 4.3 Hz, 1H), 2.76 (dd, $J = 18.3$, 8.1 Hz, 1H), 2.66 (q, $J = 6.8$ Hz, 1H), 2.09–2.00 (m, 6H), 1.91 (s, 3H), 1.78 (d, $J = 0.7$ Hz, 3H), 1.61 (dd, $J = 6.7$, 6.0 Hz, 1H), 1.46–1.36 (m, 2H), 1.27 (d, $J = 6.1$ Hz, 3H), 1.06 (t, $J = 7.9$ Hz, 18H), 1.03 (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.98 (s, 9H), 0.76–0.66 (m, 12H), 0.16 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 208.1$, 167.3, 152.7, 141.0, 137.7, 129.0, 115.2, 81.9, 78.3, 75.5, 68.7, 66.5, 48.8, 43.6, 41.3, 39.7, 32.9, 32.4, 28.3, 26.1, 21.4, 20.9, 18.8, 18.2, 15.3, 12.7, 7.3, 7.2, 5.6, 5.5, −4.1, −4.6 ppm; IR (film): $\tilde{\nu} = 2955$, 2877, 1708, 1258, 1075, 1004 cm^{-1}; MS (EI): *m/z* (%): 654 (10), 540 (2), 453 (2), 353 (6), 213 (100); HRMS (ESI): *m/z*: calcd for $C_{42}H_{81}IO_6Si_3Na$ [M^++Na]: 915.42780, found: 915.42680.

Compound 92: Prepared analogously from compound **91** by DDQ cleavage of the PMB ether (92%) followed by TES protection (75%). Colorless oil (77 mg); $[\alpha]_D^{20} = -5.2$ ($c = 0.8$, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6): $\delta = 6.97$–6.92 (m, 1H), 6.36 (d, $J = 0.8$ Hz, 1H), 5.67 (qt, $J = 10.2$, 6.4 Hz, 1H), 5.38–5.28 (m, 1H), 5.00–4.91 (m, 2H), 4.35 (t, $J = 5.8$ Hz, 1H), 4.28 (d, $J = 5.3$ Hz, 1H), 3.91 (dd, $J = 5.1$, 4.2 Hz, 1H), 3.10 (dd, $J = 18.4$, 5.9 Hz, 1H), 2.82 (dd, $J = 18.4$, 6.1 Hz, 1H), 2.10–1.95 (m, 7H), 2.02 (s, 3H), 1.89–1.84 (m, 1H), 1.89 (s, 3H), 1.54–1.44 (m, 1H), 1.33 (s, 3H), 1.26 (d, $J = 6.1$ Hz, 3H), 1.09–0.96 (m, 30H), 0.98 (s, 9H), 0.77–0.66 (m, 12H), 0.63–0.55 (m, 6H), 0.18 (s, 3H), 0.17 ppm (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 207.9$, 167.4, 152.1, 141.0, 137.8, 129.1, 115.4, 81.8, 79.3, 78.9, 78.2, 68.8, 65.7, 50.2, 49.4, 41.2, 33.0, 32.5, 28.5, 28.4, 26.4, 22.2, 21.0, 18.3, 15.7, 12.9, 7.5, 7.4, 7.3, 7.1, 5.7, 5.5, −3.7, −4.0 ppm; IR (film): $\tilde{\nu} = 2954$, 2877, 1708, 1002 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{48}H_{95}IO_7Si_4Na$ [M^++Na]: 1045.50918, found: 1045.50828.

Stille–Migita cross-coupling reactions

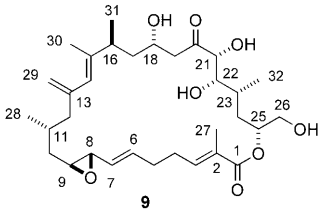
Compound 65: A degassed solution of stannane **55** (51 mg, 113 μmol) and vinyl iodide **64** (65 mg, 57 μmol) in DMF (0.6 mL) was added to a Schlenk tube containing flame-dried $[Ph_2PO_2^-][NBu_4^+]$ (105 mg, 230 μmol). Copper-thiophene carboxylate (CuTC, 33 mg, 170 μmol) was then introduced followed by $[Pd(PPh_3)_4]$ (46 mg, 40 μmol). The resulting mixture was stirred for 30 min before the reaction was quenched with water (1 mL). The aqueous phase was extracted with Et_2O (2×2 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 4:1) to afford product **65** as a pale yellow oil (58.6 mg, 89%). $[\alpha]_D^{20} = +12.3$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.81$ (tt, $J = 1.8$, 6.6 Hz, 4H), 7.26 (m, 6H), 7.01 (tq, $J = 7.4$, 1.1 Hz, 1H), 5.78 (s, 1H), 5.70 (ddt, $J = 16.9$, 10.3, 6.4 Hz, 1H), 5.53 (m, 1H), 5.02 (ddt, $J = 17.7$, 1.7, 1.4 Hz, 1H), 4.98 (ddt, $J = 11.0$, 1.8, 1.2 Hz, 1H), 4.96 (s, 1H), 4.94 (s, 1H), 4.42 (m, 1H), 4.34 (d, $J = 4.6$ Hz, 1H), 3.96 (dd, $J = 4.5$, 4.3 Hz, 1H), 3.89 (dd, $J = 10.7$, 5.5 Hz, 2H), 3.51 (ddd, $J = 12.1$, 5.4, 2.9 Hz, 1H), 3.34 (ddd, $J = 12.3$, 6.8, 4.7 Hz, 1H), 3.15 (dd, $J = 17.7$, 5.2 Hz, 1H), 2.85 (dd, $J = 18.2$, 7.2 Hz, 1H), 2.81 (ddd, $J = 7.2$, 6.4, 2.1 Hz, 1H), 2.58 (ddd, $J = 7.2$, 6.7, 2.7 Hz, 1H), 2.52 (dq, $J = 13.8$, 6.7 Hz, 1H), 2.16 (m, 1H), 2.14 (m, 1H), 2.08 (m, 3H), 2.04 (m, 2H), 1.94 (s(d), $J = 0.9$ Hz, 3H), 1.94 (m, 1H), 1.84 (s(d), $J = 1.3$ Hz, 3H), 1.81 (m, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.55 (m, 1H), 1.36 (ddd, $J = 13.2$, 8.4, 4.0 Hz, 1H), 1.18 (s, 9H), 1.10 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.03 (s, 9H), 1.02 (s, 9H), 0.89 (t, $J = 7.8$ Hz, 9H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.7 (q, $J = 7.8$ Hz, 6H), 0.45 (s, 3H), 0.20 (s, 3H), 0.17 (s, 3H), 0.16 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 208.1$, 167.5, 144.8, 143.2, 141.4, 137.8, 136.0, 135.9, 133.8, 129.9, 125.6, 115.3, 114.9, 81.8, 78.6, 72.5, 66.9, 66.3, 62.0, 58.8, 54.3, 48.7, 46.3, 39.8, 39.0, 35.8, 32.9, 32.4, 30.2, 30.0, 29.6, 28.4, 28.3, 28.2, 28.1, 26.0, 26.6, 26.3, 22.7, 19.7, 19.5, 19.4, 18.5, 18.4, 18.3, 18.2, 17.3, 16.3, 16.2, 16.1, 15.6, 15.0, 13.9, 13.7, 12.9, 10.0, 7.2, 5.4, −3.8, −4.1, −4.3, −4.5 ppm; IR (film): $\tilde{\nu} = 3390$, 2927, 2876, 1711, 1608, 1514, 1462, 1425, 1390, 1252, 11125, 834, 702, 691 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{67}H_{114}O_9Si_4Na$ [M^++Na]: 1197.74376, found: 1197.74369.

Compound 56: Prepared analogously as a yellow oil (390 mg, 83%). $[\alpha]_D^{20} = -3.6$ ($c = 0.95$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.80$–7.77 (m, 4H), 7.25–7.22 (m, 6H), 5.65 (brs, 1H), 5.00–4.99 (m, 1H), 4.88 (brs, 1H), 3.71–3.62 (m, 2H), 3.46 (brd, $J = 12.0$ Hz, 1H), 3.28 (brd, $J = 12.0$ Hz, 1H), 2.70 (ddd, $J = 7.5$, 5.6, 2.2 Hz, 1H), 2.51 (ddd, $J = 4.9$, 4.2, 2.8 Hz, 1H), 2.39 (qd, $J = 13.4$, 6.6 Hz, 1H), 2.08 (dd, $J = 13.4$, 6.6 Hz, 1H), 1.87 (dd, $J = 13.4$, 7.8 Hz, 1H), 1.75–1.66 (m, 2H), 1.62 (d, $J = 1.2$ Hz, 3H), 1.62–1.55 (m, 2H), 1.47 (ddd, $J = 11.4$, 6.6, 5.0 Hz, 1H), 1.19 (s, 9H), 1.09 (ddd, $J = 13.9$, 8.6, 5.4 Hz, 1H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.67$–7.65 (m, 4H), 7.44–7.36 (m, 6H), 5.67 (brs, 1H), 4.95–4.94 (m, 1H), 4.76 (brs, 1H), 3.83 (ddd, $J = 12.5$, 5.4, 2.6 Hz, 1H), 3.67–3.69 (m, 2H), 3.53 (ddd, $J = 11.8$, 7.5, 4.7 Hz, 1H), 2.84–2.77 (m, 2H), 2.38 (qd, $J = 13.4$, 6.6 Hz, 1H), 2.09 (dd, $J = 13.4$, 6.4 Hz, 1H), 1.91 (dd, $J = 13.5$, 7.8 Hz, 1H), 1.75–1.66 (m, 2H), 1.64 (d, $J = 1.3$ Hz, 3H), 1.61–1.56 (m, 3H), 1.22 (ddd, $J = 13.9$, 8.6, 5.5 Hz, 1H), 1.03 (s, 9H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.85 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 145.4$, 142.9, 136.5, 135.1, 129.2, 128.5, 126.5, 115.4, 63.3, 62.4, 59.2, 54.9, 46.8, 40.7, 39.5, 38.6, 30.6, 27.7, 20.5, 20.2, 20.1, 14.7 ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 144.6$, 142.5, 135.6, 134.2, 129.6, 129.5, 127.7; 125.4, 114.2, 62.5, 62.0, 58.0, 54.5, 45.9, 39.8, 38.6, 37.7, 29.7, 26.7, 19.5, 19.3, 19.1, 13.9 ppm; IR (film): $\tilde{\nu} = 2956$, 2921, 2855, 1428, 1110, 705 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{32}H_{46}NaO_3SiNa$ [M^++Na]: 529.3106, found: 529.3106.

Compound 79: Prepared analogously from vinyl iodide **78** (122 mg, 0.137 mmol) as a pale yellow oil (107 mg, 85%). $[\alpha]_D^{20} = -28.4$ ($c = 1.1$,

CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6): δ = 6.99–6.96 (m, 1H), 5.81 (s, 1H), 5.74–5.64 (m, 1H), 5.39–5.33 (m, 1H), 5.05–4.94 (m, 4H), 4.49–4.43 (m, 1H), 4.34 (d, J = 4.9 Hz, 1H), 3.95 (t, J = 4.4 Hz, 1H), 3.54 (ddd, J = 12.4, 5.4, 3.1 Hz, 1H), 3.37 (ddd, J = 11.5, 7.0, 4.3 Hz, 1H), 3.19 (dd, J = 18.0, 4.8 Hz, 1H), 2.86 (dd, J = 18.0, 7.0 Hz, 1H), 2.82 (td, J = 5.8, 2.1 Hz, 1H), 2.61–2.59 (m, 1H), 2.58–2.53 (m, 1H), 2.17–2.12 (m, 2H), 2.08–2.00 (m, 5H), 1.98–1.94 (m, 1H), 1.91 (s, 3H), 1.86 (d, J = 1.2 Hz, 3H), 1.84–1.70 (m, 4H), 1.60–1.54 (m, 1H), 1.51–1.45 (m, 1H), 1.36 (t, J = 6.7 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 5.3 Hz, 3H), 1.08–1.05 (m, 18H), 1.02 (s, 9H), 0.91 (d, J = 6.6 Hz, 3H), 0.76–0.70 (m, 12H), 0.20 (s, 3H), 0.19 ppm (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ = 208.5, 167.5, 144.9, 143.3, 141.1, 137.8, 129.1, 125.7, 115.4, 115.0, 82.0, 78.3, 68.8, 67.0, 62.0, 58.8, 54.4, 48.6, 46.3, 44.1, 41.2, 39.9, 39.1, 32.9, 32.6, 30.1, 28.4, 26.2, 21.0, 19.8, 19.3, 18.3, 15.5, 15.2, 12.8, 7.4, 7.3, 5.7, 5.6, −4.0, −4.4 ppm; IR (film): $\tilde{\nu}$ = 2956, 2876, 1708, 1257, 1075 cm^{-1}; MS (EI): m/z (%): 788 (1), 682 (4), 550 (1), 419 (1), 353 (8), 213 (100); HRMS (ESI): m/z: calcd for $C_{51}H_{96}O_8Si_3Na$ [M^++Na]: 943.63052, found: 943.63086.

Table 1. Compilation of the NMR data of synthetic **9** in C_6D_6; numbering scheme as shown in the insert.



9

Position	^{13}C NMR (150 MHz)	^{1}H NMR (600 MHz)[a]
1	168.3 (s)	
2	128.6 (s)	
3	140.5 (d)	6.98 (t, J = 7 Hz)
4	27.7 (t)	2.07 (m)/1.82 (m)
5	31.1 (t)	1.93 (m)/1.77 (m)
6	130.1 (d)	5.49 (m)
7	129.1 (d)	5.02 (dd, J = 15.4, 8.4 Hz)
8	60.8 (d)	2.83 (dd, J = 8.4, 2.2 Hz)
9	59.4 (d)	2.78 (dt, J = 9.6, 2.2 Hz)
10	39.9 (t)	1.20 (m)/0.97 (m)
11	29.4 (d)	1.76 (m)
12	47.4 (t)	2.03 (m)/1.81 (m)
13	144.8 (s)	
14	127.2 (d)	5.80 (s)
15	141.4 (s)	
16	40.2 (d)	2.77 (m)
17	41.9 (t)	1.41 (m)/1.33 (m)
18	67.8 (d)	4.05 (dd, J = 9.4, 2.4 Hz)
19	46.7 (t)	2.69 (dd, J = 14.1, 9.4 Hz), 2.26 (dd, J = 14.1, 2.4 Hz)
20	212.5 (s)	
21	78.5 (d)	4.21 (d, J = 3 Hz)
22	76.1 (d)	3.62 (t, J = 9 Hz)
23	33.4 (d)	2.00 (m)
24	34.1 (t)	1.95 (m)/1.11 (m)
25	73.4 (d)	5.19 (m)
26	65.9 (t)	3.45 (m)
27	12.8 (q)	1.86 (s)
28	17.8 (q)	0.98 (d, J = 5.8 Hz)
29	114.5 (t)	5.05 (s)/4.96 (d, J = 1 Hz)
30	13.1 (q)	1.68 (d, J = 1.1 Hz)
31	20.1 (q)	0.98 (d, J = 6.8 Hz)
32	16.0 (q)	1.02 (d, J = 6.5 Hz)

[a] The -OH protons were found to resonate at: δ = 1.57 (brs, 26-OH), 2.99 (d, J = 9.7 Hz, 22-OH), 3.39 (s, 18-OH), 4.02 (brs, 21-OH).

Compound 93: Prepared analogously as a pale yellow oil (85 mg, 87%) which was immediately used in the next step without further characterization.

Compound 98: Prepared analogously as a pale yellow oil (17 mg, 87%). $[\alpha]_D^{20}$ = −13.3 (c = 0.8, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ = 7.81–7.79 (m, 4H), 7.29–7.22 (m, 6H), 7.04–6.99 (m, 1H), 5.76 (s, 1H), 5.70 (ddt, J = 17.0, 10.3, 6.5 Hz, 1H), 5.51 (sext., J = 4.8 Hz, 1H), 5.03–5.02 (m, 1H), 5.00 (dq, J = 17.1, 1.6 Hz, 1H), 4.97–4.95 (m, 2H), 4.46–4.42 (m, 1H), 4.31 (d, J = 5.2 Hz, 1H), 3.97 (dd, J = 5.2, 3.0 Hz, 1H), 3.91–3.85 (m, 2H), 3.62–3.59 (m, 1H), 3.48–3.44 (m, 1H), 3.16 (dd, J = 18.9, 4.5 Hz, 1H), 2.90 (td, J = 6.0, 2.2 Hz, 1H), 2.67–2.65 (m, 1H), 2.40 (sext., J = 6.6 Hz, 1H), 2.29–2.25 (m, 1H), 2.14 (dd, J = 13.2, 6.5 Hz, 1H), 2.10–2.02 (m, 4H), 2.01–1.98 (m, 1H), 1.96–1.92 (m, 1H), 1.93 (d, J = 0.8 Hz, 3H), 1.87–1.76 (m, 3H), 1.81 (d, J = 1.2 Hz, 3H), 1.68–1.63 (m, 2H), 1.19 (s, 9H), 1.16–1.13 (m, 1H), 1.11 (d, J = 6.9 Hz, 3H), 1.10–1.07 (m, 2H), 1.05 (d, J = 6.5 Hz, 3H), 1.04 (t, J = 8.1 Hz, 9H), 1.02 (s, 9H), 1.01 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.71–0.66 (m, 6H), 0.25 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.17 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 207.7, 167.5, 144.6, 142.2, 141.5, 137.8, 136.0, 133.8, 133.7, 129.7, 128.8, 126.1, 115.4, 115.2, 80.9, 78.8, 72.3, 66.1, 62.3, 58.9, 54.6, 49.2, 46.3, 43.8, 40.4, 38.9, 36.8, 32.9, 31.0, 29.8, 28.4, 27.0, 26.3, 26.2, 20.0, 19.8, 19.5, 18.4, 18.2, 14.8, 14.6, 12.8, 7.2, 5.3, −3.6, −3.9, −4.3, −4.5 ppm; IR (film): $\tilde{\nu}$ = 3483, 2955, 2929, 2857, 1710, 1255, 1112 cm^{-1}; MS (EI): m/z (%): 607 (7), 467 (49), 295 (27), 185 (100); HRMS (ESI): m/z: calcd for $C_{67}H_{114}O_9Si_4Na$ [M^++Na]: 1197.74322, found: 1197.74356.

Alkenyl epoxide formation

Compound 66: A mixture containing compound **65** (45 mg, 38 μmol) and $NaHCO_3$ (32 mg, 380 μmol) in CH_2Cl_2 (0.5 mL) was stirred at 0°C for 0.5 h before Dess–Martin periodinane (21 mg, 49 μmol) was introduced. Stirring was continued for 1.5 h at 0°C before the solvent was removed

Table 2. Comparison between reported ^{13}C NMR data ($CDCl_3$) of amphidinolide H1 and the data recorded for synthetic **9**.

Position	Synthetic **9**	Lit.[10]
1	168.7	168.7
2	127.9	127.9
3	141.0	141
4	30.9	30.9
5	27.0	26.9
6	135.7	135.7
7	128.6	128.6
8	60.4	60.3
9	59.5	59.5
10	39.8	39.8
11	29.1	29.1
12	47.2	47.1
13	144.2	144.1
14	126.1	126.1
15	141.7	141.7
16	40.8	40.7
17	40.9	40.9
18	67.6	67.5
19	45.2	45.2
20	212.2	212.2
21	77.7	77.7
22	75.4	75.4
23	33.0	33
24	33.4	33.5
25	73.4	73.4
26	66.2	66.1
27	12.6	12.5
28	18.0	18.0
29	114.7	114.7
30	13.1	13.1
31	20.3	20.3
32	15.6	15.6

Table 3. Comparison between the well resolved ^{1}H NMR signals ($CDCl_3$) of amphidinolide H1 reported in the literature and the data recorded for synthetic **9**.

Position	Lit.[10] (MHz not specified)	J [Hz]	Synthetic **9**[a] (600 MHz)	J [Hz]
3	6.81 (t)	7.2	6.78 (ddq)	8.4, 5.6, 1.6
6	5.88 (ddd)	15.5, 9.0, 4.7	5.87 (ddd)	15.4, 9.2, 4.6
7	5.13 (dd)	15.5, 8.2	5.14 (dd)	15.4, 8.4
8	3.12 (dd)	8.2, 2.3	3.13 (dd)	8.6, 2.2
9	2.94 (dt)	9.7, 2.3	2.97 (dt)	9.7, 2.2
14	5.57 (s)		5.58 (s)	
18	3.92 (m)		3.85 (m)	
19	2.73 (dd)	15.8, 8.6	2.88 (dd)	13.7, 9.9
	2.61 (dd)	15.8, 1.6	2.34 (dd)	13.8, 1.6
21	4.30 (m)		4.23 (dd)	5.8, 1.4
25	5.07 (ddd)	11.4, 5.7, 3.0	5.07 (dddd)	11.5, 5.7, 2.9, 1
27	1.82 (s)		1.82 (s)	
28	0.84 (d)	6.4	0.89 (d)	6.5
29	4.97 (s), 4.80 (s)		4.96 (s), 4.79 (s)	
30	1.71 (s)		1.66 (d)	1.2
31	1.05 (d)	6.7	1.06 (d)	6.7
32	1.00 (d)	6.7	1.01 (d)	6.7

[a] The OH protons were found to resonate at: $\delta = 3.10$ (d, $J = 9.1$ Hz, 22-OH), 3.47 (d, $J = 3.6$ Hz, 18-OH), 3.92 (d, $J = 5.8$ Hz, 21-OH).

under reduced pressure and the residue was suspended in pentane (3 mL). The precipitates were filtered off through a pad of Florisil which was carefully rinsed with Et_2O (5×5 mL). Evaporation of the combined filtrates gave the corresponding epoxy-aldehyde as a pale yellow oil, which was immediately used in the next step.

A solution of NaHMDS in THF (1 M, 95 μL, 0.40 mmol) was added dropwise to a suspension of (methyl) triphenylphosphonium bromide (53 mg, 95 μmol) in THF (0.5 mL) at 0 °C. The resulting yellow suspension was stirred for 45 min at this temperature before a solution of the crude aldehyde prepared above in THF (0.2 mL) was slowly added. After stirring for 1 h, the reaction was quenched with sat. aq. NH_4Cl, the aqueous phase was extracted with EtOAc (2×3 mL), the combined extracts were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/*tert*-butyl methyl ether 15:1) to afford product **66** as a colorless oil (28 mg, 65% over two steps). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.67$ (m, 4H), 7.13 (m, 6H), 6.89 (tq, $J = 7.4$, 1.1 Hz, 1H), 5.65 (s, 1H), 5.57 (ddt, $J = 16.9$, 10.3, 6.4 Hz, 1H), 5.39 (m, 3H), 5.15 (3d, $J = 17.5$, 1.7, 0.5 Hz, 1H), 4.86 (m, 4H), 4.30 (m, 1H), 4.21 (d, $J = 6.3$ Hz, 1H), 3.82 (dd, $J = 4.5$, 4.3 Hz, 1H), 3.76 (dd, $J = 10.7$, 5.5 Hz, 2H), 3.0 (dd, $J = 14.4$, 4.8 Hz, 1H), 2.76 (dd, $J = 13.2$, 2.4 Hz, 1H), 2.69 (dd, $J = 7.8$, 2.2 Hz, 1H), 2.58 (ddd, $J = 6.8$, 5.7, 2.2 Hz, 1H), 2.39 (m, 1H), 2.16–1.98 (m, 7H), 1.94 (m, 1H), 1.91 (s(d), $J = 0.9$ Hz, 3H), 1.81 (s, 3H), 1.80 (m, 1H), 1.79 (m, 2H), 1.71 (m, 1H), 1.55 (m, 1H), 1.18 (s, 9H), 1.13 (m, 1H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.03 (s, 9H), 1.0 (s, 9H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.87 (t, $J = 7.8$ Hz, 9H), 0.8 (q, $J = 7.8$ Hz, 6H), 0.45 (s, 3H), 0.20 (s, 3H), 0.17 (s, 3H), 0.16 ppm (s, 3H).

Compound 80: Prepared analogously from compound **79** (74 mg, 0.08 mmol) as a colorless oil (32 mg, 44% over two steps). $[\alpha]_D^{20} = -17.1$ ($c = 0.7$, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): $\delta = 6.98$ (td, $J = 7.3$, 1.4 Hz, 1H), 5.80 (s, 1H), 5.71–5.65 (m, 1H), 5.52 (ddd, $J = 17.3$, 10.4, 7.6 Hz, 1H), 5.37–5.34 (m, 1H), 5.30 (ddd, $J = 17.2$, 1.5, 0.5 Hz, 1H), 5.04 (d, $J = 1.4$, 0.4 Hz, 1H), 5.02–4.93 (m, 2H), 4.46–4.43 (m, 1H), 4.34 (d, $J = 4.8$ Hz, 1H), 3.95 (t, $J = 4.5$ Hz, 1H), 3.17 (dd, $J = 17.9$, 4.9 Hz, 1H), 2.91 (dd, $J = 7.6$, 2.0 Hz, 1H), 2.87 (dd, $J = 18.0$, 7.1 Hz, 1H), 2.72 (td, $J = 5.9$, 2.0 Hz, 1H), 2.56 (sext, $J = 6.8$ Hz, 1H), 2.14–2.10 (m, 2H), 2.07–1.98 (m, 7H), 1.96–1.92 (m, 1H), 1.91 (d, $J = 1.3$ Hz, 3H), 1.88–1.82 (m, 1H), 1.85 (d, $J = 1.3$ Hz, 3H), 1.79–1.72 (m, 2H), 1.62–1.56 (m, 1H), 1.49–1.44 (m, 1H), 1.27 (d, $J = 6.2$ Hz, 3H), 1.19 (d, $J = 6.8$ Hz, 3H), 1.18–1.11 (m, 1H), 1.09–1.04 (m, 18H), 1.04 (d, $J = 6.7$ Hz, 3H), 1.02 (s, 9H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.77–0.68 (m, 12H), 0.19 (s, 3H), 0.17 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 208.4$, 167.3, 144.7, 143.3, 141.1, 137.7, 136.9, 128.9, 125.5, 118.0, 115.3, 115.0, 81.9, 78.1, 68.7, 66.9, 59.0, 58.9, 48.3, 46.3, 43.8, 41.0, 39.8, 32.9, 32.5, 29.9, 28.3, 26.1, 21.0, 19.6, 19.2, 18.3, 15.4, 15.0, 12.8, 7.3, 5.5, −4.1, −4.5 ppm; IR (film): $\tilde{\nu} = 2956$, 1710, 1460, 1258, 1078 cm^{-1}; MS (EI): m/z (%): 678 (3), 353 (6), 213 (100), 115 (14); HRMS (ESI): m/z: calcd for $C_{52}H_{96}O_7Si_3Na$ [M^++Na]: 939.63561, found: 939.63597.

Compound 94: Prepared analogously from compound **93** (41 mg, 0.039 mmol), using preformed $Ph_3P{=}CH_2$ (11 mg, 0.05 mmol) in the olefination step. Flash chromatography (1% *v*/*v* EtOAc in hexanes) of the crude material gave compound **94** as a colorless oil (13 mg, 32%). $[\alpha]_D^{20} = -21.2$ ($c = 0.6$, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ 6.97 (tq, $J = 5.8$, 1.4 Hz, 1H), 6.02 (s, 1H), 5.66 (qt, $J = 10.3$, 6.6 Hz, 1H), 5.58 (ddd, $J = 17.3$, 10.5, 7.6 Hz, 1H), 5.43–5.37 (m, 1H), 5.33 (ddd, $J = 17.2$, 1.4, 0.4 Hz, 1H), 5.09–5.06 (m, 2H), 5.05 (dd, $J = 10.5$, 1.5 Hz, 1H), 4.97 (dq, $J = 17.3$, 1.7, 1H), 4.96–4.93 (m, 1H), 4.47 (quint, $J = 1.6$ Hz, 1H), 4.31 (d, $J = 5.2$ Hz, 1H), 3.99 (dd, $J = 5.2$, 4.0 Hz, 1H), 3.22 (dd, $J = 18.4$, 7.1 Hz, 1H), 3.02 (dd, $J = 18.4$, 5.0 Hz, 1H), 2.97 (dd, $J = 7.6$, 1.9 Hz, 1H), 2.88 (td, $J = 6.0$, 2.0 Hz, 1H), 2.20 (dd, $J = 12.8$, 7.4 Hz, 1H), 2.18–2.14 (m, 1H), 2.05–2.04 (m, 5H), 1.99–1.96 (m, 4H), 1.99 (s, 3H), 1.90 (s, 3H), 1.71 (ddd, $J = 14.0$, 6.5, 4.5 Hz, 1H), 1.60 (ddd, $J = 13.7$, 8.8, 4.5 Hz, 1H), 1.46 (s, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.22–1.17

Table 4. Comparison between reported ^{13}C NMR data ($CDCl_3$) of amphidinolide B1 and the data recorded for synthetic **1**. The assignments of the signals follow the original literature, cf. ref. [14].

Position	Lit.[14] (125 MHz)	Synthetic **1** (150 MHz)
1	167.7	167.7
2	128.3	128.3
3	139.9	139.9
4	26.8	26.7
5	30.8	30.8
6	135.4	135.5
7	128.5	128.4
8	60.0	60.1
9	59.3	59.3
10	39.4	39.4
11	29.1	29.1
12	46.7	46.9
13	144.4	144.3
14	124.3	124.2
15	143.1	143.0
16	75.9	76.0
17	45.2	45.1
18	66.5	66.6
19	45.9	45.9
20	212.4	212.4
21	77.7	77.7
22	75.5	75.6
23	33.2	33.1
24	39.3	39.2
25	68.3	68.3
26	28.3	28.3
27	12.4	12.4
28	18.2	18.0
29	114.8	114.8
30	15.0	15.1
31	21.0	20.9
32	15.6	15.6

(m, 1H), 1.11 (t, J=7.9 Hz, 9H), 1.09 (d, J=8.1 Hz, 3H), 1.09 (t, J=7.9 Hz, 9H), 1.07 (t, J=7.9 Hz, 9H), 1.03 (s, 9H), 0.97 (d, J=6.6 Hz, 3H), 0.81–0.73 (m, 12H), 0.72–0.67 (m, 6H), 0.25 (s, 3H), 0.24 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ=208.4, 167.3, 144.9, 142.6, 140.9, 137.8, 136.9, 129.0, 126.0, 118.1, 115.5, 115.3, 81.5, 78.1, 78.0, 68.8, 66.0, 59.2, 58.9, 50.2, 49.2, 46.5, 41.0, 39.6, 32.9, 32.3, 29.7, 28.6, 28.3, 26.3, 21.0, 19.6, 18.2, 15.8, 15.2, 12.8, 7.6, 7.4, 7.3, 7.2, 5.6, 5.4, −3.8, −4.2 ppm; IR (film): $\tilde{\nu}$=2954, 2877, 1709, 1257, 1128, 1005 cm^{-1}; MS (EI): m/z (%): 1046 (1) [M^+], 653 (1), 444 (5), 349 (28), 213 (100); HRMS (ESI): m/z: calcd for $C_{58}H_{110}O_8Si_4Na$ [M^++Na]: 1069.71700, found: 1069.71705.

Compound 99: Prepared analogously from compound **98** (35 mg, 0.03 mmol), using preformed $Ph_3P{=}CH_2$ (8 mg, 0.06 mmol) in the olefination step. Flash chromatography (1% v/v EtOAc in hexanes) of the crude material gave compound **99** as a colorless oil (20 mg, 57%). $[\alpha]_D^{20}$ = −12.2 (c=1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ=7.83–7.79 (m, 4H), 7.29–7.25 (m, 6H), 6.99–6.96 (m, 1H), 5.79 (s, 1H), 5.77–5.67 (m, 1H), 5.57 (ddd, J=17.3, 10.6, 7.8 Hz, 1H), 5.54–5.49 (m, 1H), 5.32 (dd, J=17.3, 1.4 Hz, 1H), 5.05 (dd, J=10.4, 1.5 Hz, 1H), 5.03 (s, 1H), 4.99–4.95 (m, 3H), 4.45 (quint., J=5.7 Hz, 1H), 4.32 (d, J=5.2 Hz, 1H), 3.98 (dd, J=5.1, 3.2 Hz, 1H), 3.90–3.89 (m, 1H), 3.17 (dd, J=18.9, 5.0 Hz, 1H), 2.94 (dd, J=7.4, 1.8 Hz, 1H), 2.85 (dd, J=18.7, 6.6 Hz, 1H), 2.77 (td, J=5.7, 1.9 Hz, 1H), 2.44 (q, J=6.9 Hz, 1H), 2.25 (brs, 1H), 2.16–2.01 (m, 7H), 1.98 (d, J=8.0 Hz, 2H), 1.94 (s, 3H), 1.88–1.75 (m, 3H), 1.83 (d, J=1.0 Hz, 3H), 1.72–1.62 (m, 2H), 1.19 (s, 9H), 1.13 (d, J=6.6 Hz, 3H), 1.07 (d, J=5.4 Hz, 3H), 1.05 (t, J=8.0 Hz, 9H), 1.03 (s, 18H), 0.93 (d, J=6.5 Hz, 3H), 0.68 (q, J=7.8 Hz, 6H), 0.26 (s, 3H), 0.23 (s, 6H), 0.18 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=207.5, 167.4, 144.6, 142.7, 141.4, 137.8, 137.0, 136.1, 132.7, 132.6, 131.3, 130.1, 128.9, 126.1, 118.0, 115.4, 115.1, 81.1, 78.7, 72.5, 66.3, 66.2, 59.1, 59.0, 49.1, 46.3, 44.1, 40.4, 39.4, 39.3, 36.7, 33.0, 31.5, 30.0, 28.5, 27.1, 26.4, 26.3, 19.9, 19.8, 19.6, 18.5, 18.3, 15.2, 14.8, 12.9, 7.3, 5.4, −3.5, −3.8, −4.2, −4.3 ppm; IR (film): $\tilde{\nu}$=2956, 2926, 2860, 1711, 1256, 1105 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{68}H_{114}O_8Si_4Na$ [M^++Na]: 1193.74830, found: 1193.74933.

Table 5. Comparison between reported ^{1}H NMR data ($CDCl_3$) of amphidinolide B1 and the data recorded for synthetic **1**.

Position	Lit.[14] (500 MHz)[a]	Lit.[9] (400 MHz)	J [Hz]	Synthetic **1** (600 MHz)	J [Hz]
3	6.77 (td)	6.78 (t)	7.8	6.76 (td)	7.3
4	2.42 (m), 2.20 (m)	2.43 (m), 2.25 (m)		2.43 (m), 2.23 (m)	
5	2.40 (m), 2.15 (m)	2.38 (m), 2.17 (m)		2.37 (m), 2.12 (m)	
6	5.92 (ddd)	5.93 (ddd)	4.8, 8.5, 15.2	5.92 (ddd)	4.9, 8.7, 15.4
7	5.16 (dd)	5.18 (dd)	8.6, 15.8	5.15 (dd)	8.7, 15.6
8	3.14 (dd)	3.16 (dd)	2.0, 8.3	3.14 (dd)	2.2, 8.5
9	2.93 (dt)	2.94 (ddd)	2.2, 2.6, 8.9	2.93 (dt)	2.4, 9.0
10	1.49 (ddd), 1.27 (m)	[b]		1.49 (ddd), 1.26 (m)	2.8, 10.8, 13.6
11	1.65 (m)	[b]		1.63 (m)	
12	2.19 (m)	2.20 (m)		2.18 (m)	
13	1.95 (m)	[b]		1.93 (m)	
14	5.97 (s)	5.99 (s)		5.97 (s)	
16-OH	1.42 (s)	[b]		1.44 (s)	
17	1.95 (m), 1.78 (dd)	[b]		1.93 (m), 1.76 (dd)	5.3, 14.6
18	4.19 (m)	4.20 (m)		4.18 (m)	
18-OH	3.91 (d)	3.92 (d)	3.3	3.95 (d)	3.1
19	2.87 (dd), 2.79 (dd)	2.86 (d), 2.80 (dd)	7.3, 3.2, 15.9	2.87 (dd), 2.79 (dd)	7.5, 15.9, 3.1, 16.2
21	4.33 (dd)	4.34 (dd)	1.4, 4.8	4.33 (dd)	1.9, 5.0
21-OH	3.87 (d)	3.88 (d)	5.0	3.89 (d)	5.0
22	3.71 (td)	3.73 (ddd)	1.5, 8.8, 10.3	3.71 (td)	10.2, 10.2
22-OH	3.16 (d)	3.19 (d)	10.0	3.23 (s)	
23	1.85 (m)	[b]		1.87 (m)	
24	1.95 (m), 1.28 (m)	[b]		1.93 (m), 1.28 (m)	
25	5.06 (ddd)	5.06 (m)		5.05 (m)	
26	1.26 (d)	1.30 (d)	6.1	1.27 (d)	6.1
27	1.82 (brs)	1.80 (s)		1.82 (s)	
28	0.89 (d)	0.90 (d)	6.4	0.87 (d)	6.5
29	5.03 (s), 4.83 (s)	5.05 (s), 4.84 (s)		5.03 (s), 4.82 (s)	
30	1.83 (brs)	1.80 (s)		1.83 (s)	
31	1.42 (s)	1.44 (s)		1.38 (s)	
32	1.01 (d)	1.03 (d)	6.6	1.00 (d)	6.7

[a] No coupling constants (J) reported. [b] The remaining signals were tabulated as follows: δ = 1.98–1.91 (m, 4H), 1.76 (dd, J=14.5, 5.2 Hz), 1.64 (m, 1H), 1.49 (ddd, J=13.6, 10.9, 3.0 Hz), 1.31 (m, 1H), 1.26 ppm (m, 1H).

Macrocyclization and deprotection

Compound 67: Ruthenium complex **60** (1.0 mg, 1.6 μmol) was added to a solution of compound **66** (19 mg, 16 μmol) in C_6H_6 (20 mL) and the resulting mixture was stirred at 20 °C for 2 h. The reaction was quenched with ethyl vinyl ether (20 μL, 216 μmol) and stirring was continued for 10 min before all volatile materials were evaporated under reduced pressure at 20 °C. The crude product was then adsorbed onto Celite and purified by flash chromatography (hexanes/*tert*-butyl methyl ether 15:1) to afford **67** as a yellow oil (12 mg, 68%). ^{1}H NMR (400 MHz, C_6D_6): δ= 7.80 (m, 4H), 7.24 (m, 6H), 6.92 (tq, J=7.2, 1.1 Hz, 1H), 5.68 (s, 1H), 5.77 (m, 1H), 5.51 (m, 1H), 5.17 (dd, J=16.7, 8.3 Hz, 1H), 5.06 (d, J= 1.6 Hz, 1H), 5.06 (d, J=1.6 Hz, 1H), 4.92 (d, J=1.7 Hz, 1H), 4.50 (d, J= 3.1 Hz, 1H), 4.22 (m, 1H), 3.96 (dd, J=9.8, 4.1 Hz, 1H), 3.88 (m, 3H), 3.0 (m, 2H), 2.92 (dd, J=16.1, 2.8 Hz, 1H), 2.86 (dd, J=16.8, 4.6 Hz,

Table 6. Comparison between reported ^{13}C NMR data ($CDCl_3$) of amphidinolide B4 and the data recorded for synthetic **4**.

Position	Lit.[15] (150 MHz)	Synthetic **4** (150 MHz)
1	167.8	167.8
2	128.5	128.3
3	139.8	139.7
4	26.8	26.9
5	31.2	31.0
6	135.9	136.0
7	128.7	128.5
8	60.6	60.5
9	59.5	59.4
10	39.8	39.8
11	29.4	29.2
12	47.1	47.1
13	144.2	144.1
14	126.5	126.1
15	141.7	141.7
16	40.9	40.8
17	40.8	40.7
18	67.4	67.6
19	45.1	45.2
20	212.9	212.3
21	77.9	77.7
22	75.8	75.6
23	33.2	33.3
24	39.2	39.0
25	68.3	68.2
26	21.2	21.2
27	12.4	12.5
28	18.0	17.8
29	114.8	114.7
30	13.1	13.1
31	20.5	20.3
32	15.8	15.6

Table 7. Comparison between reported ^{1}H NMR data ($CDCl_3$) of amphidinolide B4 and the data recorded for synthetic **4**.

Position	Lit.[15] (600 MHz)	J [Hz]	Synthetic **4** (600 MHz)	J [Hz]
3	6.73 (m)		6.73 (m)	
4a	2.42 (m)		2.43 (m)	
5a	2.34 (m)		2.35 (m)	
6	5.89 (m)		5.89 (m)	
7	5.16 (dd)	15.6, 8.2	5.12 (dd)	15.6, 8.4
8	3.14 (br d)	8.0	3.13 (dd)	8.7, 2.4
9	2.94 (br d)	9.7	2.94 (br d)	9.6
10	1.15 (m), 1.48 (m)		1.14 (m), 1.50 (m)	
11	1.56 (m)		1.56 (m)	
14	5.56 (s)		5.56 (s)	
17a	1.42 (m)		1.41 (m)	
18	3.92 (m)		3.91 (m)	
19	2.61 (br d), 2.74 (dd)	16.0, 16.0, 8.9	2.60 (br d), 2.74 (dd)	16.0, 16.0, 8.9
21	4.31 (br s)		4.31 (s)	
22	3.71 (m)		3.70 (m)	
24a	1.20 (m)		1.20 (m)	
25	5.08 (m)		5.04 (m)	
26	1.24 (d)	6.7	1.25 (d)	6.3
27	1.82 (s)		1.80 (s)	
28	0.85 (d)	6.5	0.83 (d)	6.5
29	4.81 (s), 4.97 (s)		4.79 (s), 4.96 (s)	
30	1.71 (s)		1.71 (d)	1.4
31	1.06 (d)	6.7	1.04 (d)	6.8
32	0.98 (d)	6.7	0.97 (d)	6.7
12a, 17b, 23	1.84–1.92 (m)		1.83–1.96 (m)	
5b, 12b, 24b	2.05–2.16 (m)		2.03–2.20 (m)	
4b, 16	2.18–2.28 (m)		2.21–2.25 (m)	
3×-OH	3.27, 3.55, 3.86 (br s)		3.30 (s), 3.61 (s), 3.87 (d)	5.5

1H), 2.58 (3d, J=16.8, 6.7, 3.2 Hz, 1H), 2.39 (m, 1H), 2.22 (m, 2H), 2.18 (m, 1H), 1.92 (m, 2H), 1.90 (s, 3H), 1.81 (m, 1H), 1.79 (m, 2H), 1.76 (s, 3H), 1.71 (m, 1H), 1.60 (m, 1H), 1.21 (s, 9H), 1.07 (m, 1H), 1.06 (d, J= 6.8 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H), 1.01 (s, 9H), 1.0 (s, 9H), 0.98 (d, J=6.7 Hz, 3H), 0.89 (t, J=7.8 Hz, 9H), 0.81 (q, J=7.6 Hz, 6H), 0.3 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.10 ppm (s, 3H).

Compound 81: Prepared analogously as a colorless oil (7.6 mg, 84%). $[\alpha]_D^{20}$ = −35.9 (c=0.95, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ=6.84–6.82 (m, 1H), 5.71 (s, 1H), 5.64–5.60 (m, 1H), 5.30–5.24 (m, 1H), 5.08–5.02 (m, 1H), 5.06 (s, 1H), 4.93 (s, 1H), 4.56 (d, J=2.9 Hz, 1H), 4.33 (br s, 1H), 4.08–4.04 (m, 1H), 3.10 (dd, J=15.6, 6.5 Hz, 1H), 2.94 (dd, J= 8.6, 2.0 Hz, 1H), 2.87–2.84 (m, 1H), 2.79–2.77 (m, 1H), 2.66–2.60 (m, 1H), 2.25–2.16 (m, 3H), 2.12 (dd, J=12.1, 3.2 Hz, 1H), 2.09–1.96 (m, 4H), 1.90–1.81 (m, 3H), 1.88 (s, 3H), 1.75 (s, 3H), 1.71–1.66 (m, 1H), 1.35–1.30 (m, 2H), 1.33 (d, J=6.0 Hz, 1H), 1.27–1.21 (m, 2H), 1.13 (t, J=8.0 Hz, 9H), 1.09 (d, J=7.0 Hz, 3H), 1.06 (t, J=8.0 Hz, 9H), 1.05 (d, J=7.9 Hz, 3H), 0.99 (s, 9H), 0.87 (d, J=6.4 Hz, 3H), 0.86–0.79 (m, 6H), 0.72 (q, J=8.2 Hz, 6H), 0.15 (s, 3H), 0.12 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ=208.5, 167.7, 144.3, 142.6, 139.6, 134.7, 130.0, 129.7, 125.9, 115.0, 82.2, 68.8, 68.7, 59.8, 58.4, 47.3, 40.7, 40.4, 33.9, 31.8, 29.8, 27.5, 26.0, 21.3, 19.8, 18.6, 18.2, 15.4, 14.1, 12.7, 7.5, 7.4, 6.1, 5.4, 1.4, −4.5, −4.7 ppm; IR (film): $\tilde{\nu}$=2955, 2930, 2876, 1706, 1085 cm^{-1}; MS (EI): m/z (%): 888 (2) [M^+], 756 (2), 437 (1), 371 (3), 213 (100); HRMS (ESI): m/z: calcd for $C_{50}H_{92}O_7Si_3Na$ [M^++Na]: 911.60431, found: 911.60457.

Compound 95: Prepared analogously as a colorless oil (6 mg, 91%). $[\alpha]_D^{20}$ = −26.0 (c=0.3, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ=6.89–6.87 (m, 1H), 6.06 (s, 1H), 5.76–5.72 (m, 1H), 5.35–5.30 (m, 1H), 5.24 (dd, J= 15.4, 8.3 Hz, 1H), 5.07 (d, J=2.3 Hz, 1H), 4.96 (s, 1H), 4.38 (d, J= 5.2 Hz, 1H), 4.31–4.27 (m, 1H), 4.00 (br s, 1H), 3.17–3.08 (m, 2H), 3.05–3.03 (m, 1H), 2.33–2.29 (m, 1H), 2.24–2.19 (m, 1H), 2.11–2.05 (m, 1H), 2.04–1.90 (m, 8H), 1.89 (s, 3H), 1.88 (s, 3H), 1.78–1.66 (m, 2H), 1.38 (s, 3H), 1.35–1.29 (m, 2H), 1.28 (d, J=6.1 Hz, 3H), 1.14–1.07 (m, 27H), 1.03 (d, J=6.9 Hz, 3H), 1.02 (s, 9H), 1.00 (d, J=6.0 Hz, 3H), 0.84–0.67 (m, 18H), 0.23 (s, 3H), 0.19 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ= 208.0, 167.4, 145.0, 142.3, 140.1, 133.8, 130.4, 129.2, 125.8, 115.6, 82.0, 78.1, 68.5, 66.4, 58.9, 58.8, 47.0, 40.2, 31.5, 29.8, 28.8, 27.6, 26.2, 21.2, 19.6, 18.2, 15.8, 14.8, 12.8, 7.6, 7.5, 7.4, 7.3, 5.8, 5.6, −3.8, −4.4 ppm; IR (film): $\tilde{\nu}$=2954, 2876, 1708, 1123, 1016 cm^{-1}; MS (EI): m/z (%): 1018 (2) [M^+], 886 (2), 754 (2), 558 (1), 444 (11), 213 (100); HRMS (ESI): m/z: calcd for $C_{56}H_{106}O_8Si_4Na$ [M^++Na]: 1041.68571, found: 1041.68577.

Compound 100: Prepared analogously as an E/Z 5.2:1 mixture of isomers. The major E isomer could be obtained in pure form by flash chromatography (hexanes/*tert*-butyl methyl ether 15:1) as a colorless oil (11 mg, 56%). $[\alpha]_D^{20}$ = −8.7 (c=0.55, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ= 7.78–7.76 (m, 4H), 7.24–7.21 (m, 6H), 6.87–6.84 (m, 1H), 5.71 (s, 1H), 5.59 (ddd, J=15.4, 8.0, 5.2 Hz, 1H), 5.54–5.50 (m, 1H), 5.49 (dd, J=15.2, 8.0 Hz, 1H), 5.05 (d, J=2.2 Hz, 1H), 4.94 (s, 1H), 4.46–4.42 (m, 1H), 4.26 (d, J=5.5 Hz, 1H), 3.82–3.80 (m, 3H), 3.42 (ddd, J=8.6, 3.4, 2.4 Hz, 1H), 3.13 (dd, J=19.0, 2.3 Hz, 1H), 3.02 (dd, J=8.2, 1.8 Hz, 1H), 2.72 (dd, J=18.7, 8.9 Hz, 1H), 2.33–2.24 (m, 2H), 2.20–2.16 (m, 2H), 2.14–2.11 (m, 2H), 2.06–1.98 (m, 4H), 1.91–1.85 (m, 4H), 1.87 (s, 3H), 1.84–1.79 (m, 3H), 1.77 (d, J=1.0 Hz, 3H), 1.17 (s, 3H), 1.17–1.16 (m, 1H), 1.07 (t, J=8.0 Hz, 9H), 1.06 (d, J=8.7 Hz, 3H), 1.03–1.02 (m, 3H), 1.02 (s, 9H), 0.98 (s, 9H), 0.92 (d, J=6.5 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H), 0.69–0.64 (m, 6H), 0.28 (s, 3H), 0.25 (s, 3H), 0.15 (s, 3H), 0.12 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ=206.4, 167.0, 144.8, 141.1, 140.6, 136.0, 133.8, 133.7, 133.6, 131.1, 130.0, 129.9, 129.0, 126.3, 115.2, 80.4, 79.1, 71.2, 66.6, 65.6, 59.8, 59.5, 49.7, 47.4, 43.1, 41.2, 39.6, 37.5, 31.7, 30.2, 29.8, 29.6, 27.7, 27.1, 26.9, 26.2, 26.1, 13.7, 13.0, 12.9, 7.3, 5.2, 1.4, −3.5, −3.9, −4.3, −4.7 ppm; IR (film): $\tilde{\nu}$=2955, 2930, 2857, 1721, 1707, 1254, 1112 cm^{-1}; MS (EI): m/z (%): 1142 (3) [M^+], 1085 (2), 1010 (3), 953 (2), 467 (27), 295 (27), 185 (100); HRMS (ESI): m/z: calcd for $C_{66}H_{110}O_8Si_4Na$ [M^++Na]: 1165.71700, found: 1165.71685.

Compound 110: Prepared analogously as a pale yellow oil (10.5 mg, 54%). $[\alpha]_D^{20}$ = +35.6 (c=0.1, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ= 7.78 (m, 4H), 7.26–7.22 (m, 6H), 7.00 (m, 1H), 5.89 (dm, J=15.4 Hz, 1H), 5.71 (s 1H), 5.43 (ddt, J=10.1, 2.7, 5.2 Hz, 1H), 5.29 (dd, J=15.5, 7.7 Hz, 1H), 5.02 (m, 1H), 4.91 (dd, J=2.4, 1.0 Hz, 1H), 4.34 (d, J= 6.2 Hz, 1H), 4.20 (m, 1H), 3.86 (dd, J=10.6, 5.3 Hz, 1H), 3.86 (dd, J= 6.2, 3.3 Hz, 1H), 3.82 (dd, J=10.6, 5.0 Hz, 1H), 3.03 (dd, J=7.7, 2.0 Hz, 1H), 2.94 (br. d, J=3.6 Hz, 1H, OH), 2.91 (dd, J=17.2, 2.7 Hz, 1H), 2.88 (3d, J=6.6, 5.2, 2.1 Hz, 1H), 2.76 (dd, J=17.2, 9.5 Hz, 1H), 2.61 (m, 1H), 2.17 (dd, J=13.2, 5.6 Hz, 1H), 2.09 (3d, J=14.0, 10.2, 2.6 Hz, 1H), 2.01–2.00 (m, 5H), 1.91 (dd, J=13.2, 8.8 Hz, 1H), 1.91 (s(d), J=1.2 Hz, 3H), 1.81 (dt, J=13.7, 7.9 Hz, 1H), 1.80 (m, 1H), 1.74 (s(d), J=1.3 Hz, 3H), 1.70 (3d, J=14.0, 10.8, 2.6 Hz, 1H), 1.67 (3d, J=13.8, 6.3, 5.5 Hz, 1H), 1.39 (dt, J=13.7, 5.9 Hz, 1H), 1.19 (m, 1H), 1.17 (s, 9H), 1.13 (d, J=6.8 Hz, 3H), 1.01 (t, J=8.0 Hz, 9H), 1.01 (s, 9H), 0.98 (d, J=6.9 Hz, 3H), 0.90 (d, J=6.5 Hz, 3H), 0.66 (q, J=8.0 Hz, 6H), 0.20 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=210.8, 167.5, 144.9, 144.7, 141.4, 136.0, 135.9, 133.9, 133.8, 133.5, 130.2, 130.0, 129.0, 128.1, 125.9, 115.0, 82.2, 78.6, 72.3, 66.6, 66.5, 59.0, 58.5, 46.7, 46.2, 42.9, 40.8, 39.7, 33.1, 32.5, 31.1, 30.3, 28.3, 27.0, 26.4, 20.2, 20.0, 19.5, 18.5, 17.9, 14.5, 12.9, 7.2, 5.3, −3.2, −4.3 ppm; HRMS (ESI): m/z: calcd for $C_{60}H_{96}O_8Si_3Na$ [M^++Na]: 1051.62998, found: 1051.63022.

Amphidinolides H1 (9) and G1 (14): A solution of TASF (16.4 mg, 59.3 μmol) in aq. DMF (0.2 mL + 4 μL H_2O) was added to a solution of compound **67** (12 mg, 9.9 μmol) in THF (2 mL) at 0°C. The mixture was slowly warmed to ambient temperature over a period of 30 min and stirring was continued for 2 h. For work up, the mixture was extracted with cold (5°C) phosphate buffer solution (pH 7, 3×2 mL), the aqueous phases were extracted with EtOAc (2×1 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (EtOAc/hexane 9:1) to afford compound **9** as a white solid (3 mg, 55%). HRMS (ESI): m/z: calcd for $C_{32}H_{50}O_8Na$ [M^++Na]: 585.33979, found: 585.33996. A solution of **9** in acidic $CDCl_3$

equilibrates with amphidinolide G1 (**14**) by transesterification as previously reported in the literature.[11,56] The two isomers can be separated by preparative HPLC. For a compilation of the NMR data and a comparison with the reported spectra, see Tables 1–3.

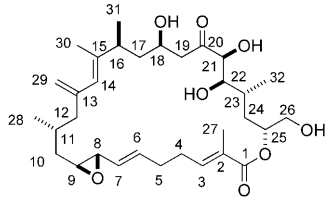
Amphidinolide B1 (1): Prepared analogously as a colorless solid (3.6 mg, 93%). For a compilation of the NMR data, see Tables 4 and 5.

Amphidinolide B4 (4): Prepared analogously as a colorless oil (7.6 mg, 58%). For a compilation of the NMR data, see Tables 6 and 7.

Compound 10: Prepared analogously as a colorless oil (3.1 mg, 46%). For a compilation of the NMR data, see Tables 8 and 9.

Compound 102: Prepared analogously as a white solid (4 mg, 80%). $[\alpha]_D^{20} = -79.8$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 6.77$ (dd, $J =$ 9.2, 4.8 Hz, 1H), 5.84 (3d, $J = 15.4$, 10.0, 4.4 Hz, 1H), 5.50 (s, 1H), 5.21 (dd, $J = 15.4$, 9.0 Hz, 1H), 5.10 (m, 1H), 4.93 (s, 1H), 4.78 (s, 1H), 4.21 (d, $J = 1.2$ Hz, 1H), 4.05 (t, $J = 9.2$ Hz, 1H), 3.69 (m, 2H), 3.59 (m, 1H), 3.06 (dd, $J = 8.8$, 2.2 Hz, 1H), 3.03 (dd, $J = 18.0$, 2.3 Hz, 1H), 2.94 (dt, $J =$ 9.6, 2.2 Hz, 1H), 2.51 (dd, $J = 18.0$, 9.8 Hz, 1H), 2.46 (m, 1H), 2.38 (m, 1H), 2.36 (m, 1H), 2.26 (m, 1H), 2.21 (m, 1H), 2.20 (m, 1H), 2.12 (m, 1H), 1.88 (m, 1H), 1.81 (s, 3H), 1.80 (m, 1H), 1.70 (s, 3H), 1.70 (m, 1H), 1.64 (m, 1H), 1.59 (m, 1H), 1.41 (m, 1H), 1.23 (m, 1H), 1.04 (d, $J =$ 6.7 Hz, 3H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.91 (m, 1H), 0.86 ppm (d, $J =$ 6.4 Hz, 3H); ^{1}H NMR (600 MHz, C_6D_6): $\delta = 6.93$ (ddq, $J = 9.6$, 4.8, 1.6 Hz, 1H, H3), 5.67 (s, 1H, H14), 5.43 (3d, $J = 15.2$, 9.8, 4.6 Hz, 1H, H6), 5.26 (4d, $J = 12.4$, 5.8, 4.6, 2.8 Hz, 1H, H25), 5.26 (dd, $J = 15.2$, 9.2 Hz, 1H, H7), 5.02 (s, 1H, H29a), 4.92 (s(d), $J = 2.4$ Hz, 1H, H29b), 4.15 (m, 1H, H18), 3.85 (t, $J = 2.5$ Hz, 1H, H21), 3.82 (d, $J = 12.1$, 1H, OH-22), 3.68 (d, $J = 2.6$ Hz, 1H, OH-21), 3.51 (dt, $J = 11.6$, 5.8 Hz, 1H, H26a), 3.46 (3d, $J = 11.6$, 5.6, 4.4 Hz, 1H, H26b), 3.40 (3d, $J = 12.0$, 11.0, 2.4 Hz, 1H, H22), 2.96 (dt, $J = 9.9$, 2.0 Hz, 1H, H9), 2.94 (dd, $J = 17.6$, 1.8 Hz, 1H, H19a), 2.78 (dd, $J = 9.0$, 2.3 Hz, 1H, H8), 2.51 (ddm, $J = 12.4$, 3.6 Hz, 1H, H12a), 2.50 (3d, $J = 14.0$, 12.4, 3.0 Hz, 1H, H24a), 2.17 (dd, $J = 17.6$, 9.7 Hz, 1H, H19b), 2.13 (br. s, 1H, OH-18), 2.13 (m, 1H, H16), 2.11 (m, 1H, H23), 2.02 (m, 1H, H4a), 1.93 (m, 1H, H5a), 1.83 (s, 3H, Me-27), 1.82 (m, 1H, H17a), 1.79 (m, 1H, OH-26), 1.73 (m, 1H, H11), 1.71 (s(d), $J = 1.4$ Hz, 3H, Me-30), 1.70 (m, 1H, H5b), 1.69 (m, 1H, H4b), 1.68 (m, 1H, H12b), 1.54 (3d, $J = 14.2$, 5.9, 1.7 Hz, 1H, H10a), 1.35 (3d, $J = 14.0$, 10.4, 4.0 Hz, 1H, H17b), 1.05 (3d, $J = 14.0$, 12.0, 2.8 Hz, 1H, H24b), 0.96 (d, $J = 6.8$ Hz, 3H, Me-31), 0.95 (d, $J = 6.2$ Hz, 3H, Me-28), 0.87 (d, $J = 6.6$ Hz, 3H, Me-32), 0.79 ppm (3d, $J = 14.1$, 9.9, 5.8 Hz, 1H, H10b); for the ^{13}C NMR data in $CDCl_3$ and a comparison with natural amphidinolide H2, see Table 8; ^{13}C NMR (100 MHz, C_6D_6): $\delta = 211.6$, 168.5, 145.0, 140.7, 140.3, 135.8, 130.4, 128.1, 127.4, 115.2, 78.7, 76.7, 73.1, 66.2, 65.7, 60.2, 59.7, 46.8, 43.9, 41.1, 40.7, 40.7, 34.3, 32.7, 31.2, 30.2, 26.8,

Table 8. Comparison of the ^{13}C NMR data ($CDCl_3$) of amphidinolide H2 reported by Kobayashi et al.[12] with those of synthetic **10** and synthetic **102**.



102

Position	Amphidinolide H2	**102**	δΔ	10	δΔ
1	168.7	168.8	−0.1	168.7	0
2	127.6	127.5	0.1	127.9	−0.3
3	140.8	140.8	0	141.4	−0.6
4	26.9	26.8	0.1	27.0	−0.1
5	31.0	31.0	0	30.8	0.2
6	136.1	136.1	0	135.2	0.9
7	129.7	129.7	0	128.7	1.0
8	59.8	59.8	0	60.6	−0.8
9	60.1	60.2	−0.1	59.4	0.7
10	40.4	40.4	0	38.8	1.6
11	29.8	29.8	0	28.3	1.5
12	46.6	46.5	0.1	47.4	−0.8
13	144.3	144.2	0.1	143.5	0.8
14	126.7	126.7	0	125.6	1.1
15	140.6	140.5	0.1	140.8	−0.2
16	40.8	40.8	0	41.3	−0.5
17	40.2	40.0	0.2	40.8	−0.6
18	65.9	65.8	0.1	66.9	−1.0
19	43.8	43.7	0.1	44.8	−1.0
20	211.3	211.3	0	211.6	−0.3
21	78.4	78.4	0	78.2	0.2
22	76.2	76.2	0	76.1	0.1
23	32.3	32.2	0.1	32.5	−0.2
24	33.9	33.8	0.1	33.6	0.3
25	73.3	73.3	0	73.4	−0.1
26	66.6	66.7	−0.1	66.2	0.4
27	12.7	12.7	0	12.5	0.2
28	19.5	19.5	0	18.6	0.9
29	115.0	115.0	0	114.8	0.2
30	12.3	12.2	0.1	12.8	−0.5
31	20.4	20.4	0	20.0	0.4
32	15.1	15.1	0	15.6	−0.5

Table 9. Compilation of the NMR data of synthetic **10** in C_6D_6; numbering Scheme analogous to that shown in the Insert of the previous Table.

Position	^{13}C NMR (150 MHz)	^{1}H NMR (600 MHz)[a]
1	168.3 (s)	
2	129.2 (s)	
3	141.0 (d)	6.99 (ddq, $J = 8.3$, 7.5, 1.4 Hz)
4	27.0 (t)	2.00 (m)/1.87 (m)
5	31.2 (t)	1.93 (m)/1.73 (m)
6	134.9 (d)	5.50 (ddd, $J = 15.4$, 9.4, 4.5 Hz)
7	129.2 (d)	4.86 (dd, $J = 15.5$, 8.4 Hz)
8	60.8 (d)	2.93 (dd, $J = 8.4$, 2.2 Hz)
9	59.2 (d)	2.70 (dd, $J = 9.2$, 5.2 Hz)
10	39.5 (t)	1.10 (m)
11	28.3 (d)	1.87 (m)
12	47.7 (t)	1.98 (m)/1.87 (m)
13	144.2 (s)	
14	126.2 (d)	5.77 (s)
15	140.5 (s)	
16	41.3 (d)	2.15 (ddq, $J = 11.4$, 6.8, 4.4 Hz)
17	41.2 (t)	1.72 (m),
		1.37 (ddd, $J = 13.6$, 9.6, 4.3 Hz)
18	66.1 (d)	4.23 (m)
19	44.6 (t)	2.85 (dd, $J = 16.9$, 1.0 Hz),
		2.37 (dd, $J = 17.0$, 9.2 Hz)
20	211.1 (s)	
21	78.4 (d)	3.97 (dd, $J = 4.4$, 1.9 Hz)
22	76.7 (d)	3.49 (ddd, $J = 11.0$, 9.0, 1.9 Hz)
23	32.8 (d)	2.10 (m)
24	34.0 (t)	2.02 (m),
		0.99 (ddd, $J = 13.4$, 11.8, 2.3 Hz)
25	73.1 (d)	5.25 (m)
26	65.9 (t)	3.58 (m)
27	12.7 (q)	1.88 (d, $J = 1.3$ Hz)
28	18.3 (q)	0.86 (d, $J = 6.0$ Hz)
29	115.0 (t)	5.00 (d, $J = 2.7$ Hz),
		4.92 (dd, $J = 2.6$, 1.1 Hz)
30	12.7 (q)	1.70 (d, $J = 1.3$ Hz)
31	20.1 (q)	0.95 (d, $J = 6.8$ Hz)
32	15.9 (q)	1.17 (d, $J = 6.6$ Hz)

[a] The -OH protons were found to resonate at: $\delta = 2.46$ (brs, 18-OH), 1.95 (brs, 26-OH), 3.95 (d, $J = 4.4$ Hz, 21-OH), 4.05 (d, $J = 11.1$ Hz, 22-OH).

20.5, 20.1, 15.2, 12.9, 12.3 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{32}H_{50}O_8Na$ [M^++Na]: 585.33979, found: 585.33996.

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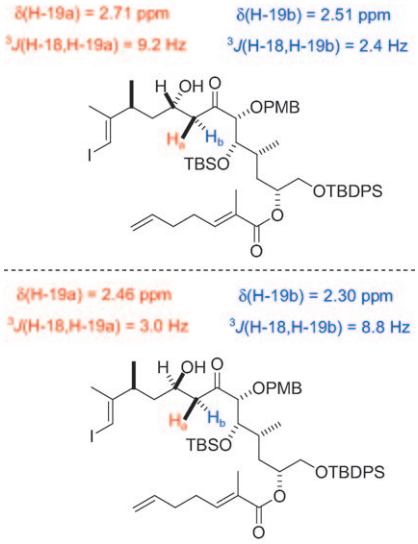

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