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Molecular Editing and Biological Evaluation of Amphidinolide X and Y

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Abstract: Deliberate deviations from the previously described total syntheses of amphidinolide X (**1**) and Y (**2**) allowed a collection of seven designed analogues of these extremely scarce marine natural products to be obtained. These fully synthetic "natural product-like" compounds enabled first insights into the previously unknown structure–activity relationships governing this series. Although the average cytotoxicity is moderate, it was found that certain bladder, colon and prostate cancer cell lines are fairly sensitive, and that the best synthetic analogues are more active than the natural products themselves. The syntheses rely on the 9-MeO-9-BBN variant of the Suzuki coupling for the formation of the carbon frameworks, as well as on Yamaguchi lactonization reactions for the cyclization of the macrocyclic rings.

Keywords: anticancer agents · cross-coupling · macrolides · natural products · structure–activity relationships

Introduction

Marine dinoflagellates of the *Amphidinium* sp. represent an exceptionally rich source of bioactive secondary metabolites of mixed polyketide origin.[1] To date, more than thirty different "amphidinolides", grouped together into sub-families ranging from A–Y, have been extracted from culture broths of such algae. These macrolides are distinguished by a set of rather unusual structural features and exhibit good to outstanding levels of cytotoxicity, even though they were tested only against a very small number of cancer cell lines. This is mainly due to the low isolation yields which limit the supply of material available from the natural sources and therefore constitute a serious handicap for a more detailed biological evaluation.[1]

Challenged by the diverse molecular architectures of the amphidinolides and inspired by their potential biological significance, the synthetic community has paid considerable attention to this family of natural products.[2,3] Our group has contributed to this venture, upon describing total syntheses of members of the amphidinolide B,[4] G,[4,5] H,[4,5] T,[6] V,[7,8] X[9,10] and Y[10] series. These campaigns served as a stringent testing ground for the methodology developed in this laboratory;[11–13] as the largely catalysis-based routes are inherently flexible, however, they might also qualify as basis for a synthesis-driven editing of the molecular framework of the individual targets as part of a more ambitious program at the chemistry/biology interface. The accompanying paper in this issue describes, among other things, such a "diverted total synthesis"[14] project modelled around amphidinolide V as one of the rarest members of this class.[8] Outlined below is a similar investigation on the sister compounds amphidinolide X and Y, which again focused on the preparation of such structural variants that cannot (or at least not easily) be obtain by functionalization or derivatization of the natural products themselves. This "molecular editing" exercise led to a collection of de-novo analogues with deep-seated structural modifications, that allowed us to obtain first insights into structure–activity relationships determining the cytotoxicity profile of this series.

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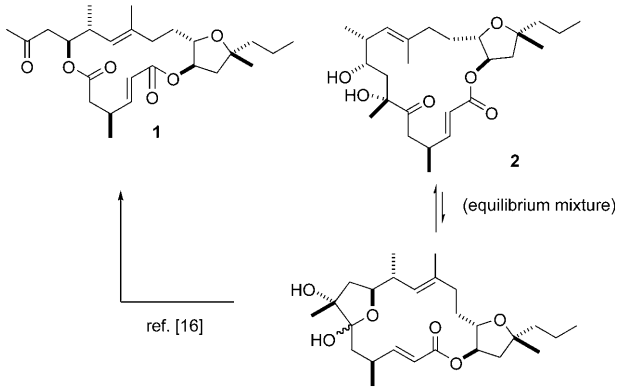
Results and Discussion

Design aspects: Amphidinolide X (**1**) was described by Kobayashi and co-workers as the first naturally occurring macrodiolide consisting of a diacid and a diol unit rather than of two hydroxy-acid segments.[15] It is closely related to amphidinolide Y (**2**),[16] since an oxidative cleavage of the hemiketal form of **2** contracts its *odd*-numbered lactone to the 16-membered macrodiolide core displayed by **1** (Scheme 1).[16]

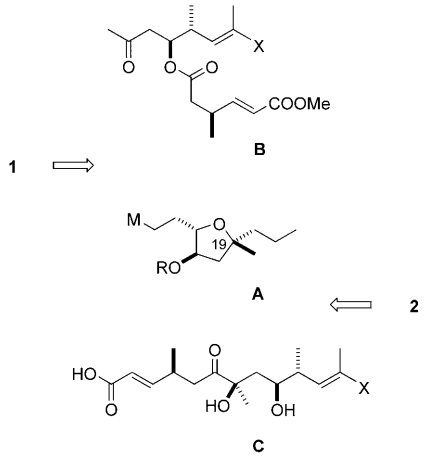
Both compounds are extremely rare (0.001 and 0.0007%, respectively, of the wet weight of the algae) and were described as moderately cytotoxic agents against murine lymphoma L1210 cells ($IC_{50}=0.6\ \mu g\,mL^{-1}$ and $0.8\ \mu g\,mL^{-1}$) and human epidermoid carcinoma KB cells ($IC_{50}=7.5\ \mu g\,mL^{-1}$ and $8.0\ \mu g\,mL^{-1}$).[15,16]



Scheme 1. Structures of and chemical relationship between amphidinolide X (**1**) and Y (**2**).

Our total syntheses dismantled **1** and **2** such that building block **A** representing the common tetrahydrofuran ring could be used en route to both targets (Scheme 2).[9,10,17] This fragment was successfully coupled to either vinyliodide **B** or the more sophisticated segment **C** by means of the 9-MeO-9-BBN variant of the Suzuki reaction.[18,19] The resulting compounds were then elaborated by productive Yamaguchi lactonization reactions[20–22] into the macrocyclic natural products.

The synthetically challenging tertiary ether motif in **A** was set in high optical purity by recourse to a relay strategy based on iron-catalyzed opening of a propargyl epoxide precursor, as previously described by our group.[23,24] This method also allowed for the preparation of the C-19 epimer of amphidinolide X (**3**).[10] Since the formal replacement of the quarternary stereocenter by a branched, yet achiral entity should be advantageous in preparative terms but may not compromise the activity profile, compounds **4** and **9**, respectively, were considered attractive analogues to be chased (Figure 1).



Scheme 2. Basic disconnections of the previous total syntheses of **1** and **2**.

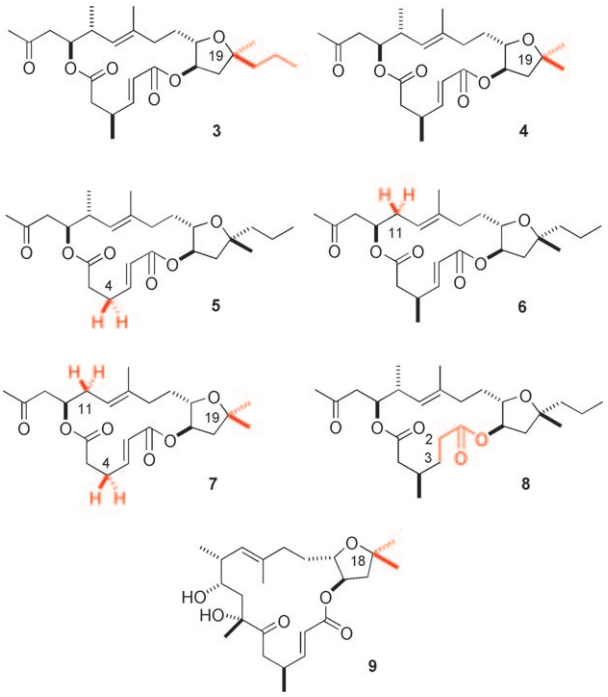
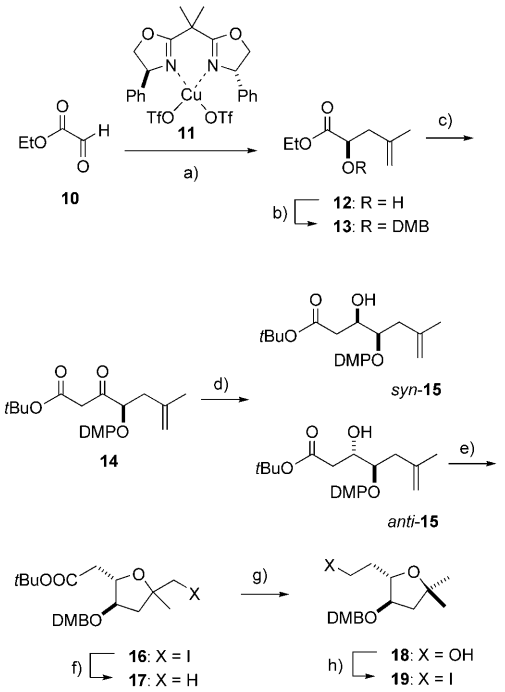


Figure 1. Envisaged analogues of amphidinolide X and Y for biological testing. Structural changes relative to the parent compounds are highlighted in red. It is of note that the tertiary center C-19 in **1** corresponds to C-18 in **2**.

Along the same lines, it was envisaged to formally eradicate the chiral centers at C-4 and/or C-11 on the macrocyclic frame (amphidinolide X numbering), which display no more but a methyl branch. It is a priori difficult to predict which consequences such modifications may entail for the chemical stability as well as the biological activity of the resulting compounds. A previous "diverted total synthesis" project pursued by our group had revealed a significant correlation between a seemingly innocent methyl substituent decorating the core of latrunculin B with the actin-binding capacity of this macrolide.[25] In this particular case, the fully synthetic *nor*-analogue turned out to be significantly more potent than the natural product itself; therefore, analogues **5**–**7** modelled around amphidinolide X were considered potentially interesting targets. Finally, it seemed necessary to address the role of the enoate moiety in **1**, which may serve as a Michael acceptor for biological nucleophiles. In order to probe this possible role, it was planned to replace the α,β-unsaturated ester of **1** by a saturated entity as shown in compound **8** (Figure 1).

Preparation of the building blocks: With the tableau of desirable analogues defined, efficient routes to the building

blocks required for their assembly had to be devised. To this end, ethyl glyoxalate **10** was subjected to a copper-catalyzed carbonyl-ene reaction with isobutene, which furnished gram quantities of alcohol **12** with 92% enantiomeric excess (Scheme 3).[26] The subsequent protection as a 3,4-dimethoxybenzyl (DMB) ether, however, was problematic, resulting in substantial loss in optical purity upon treatment of **12** with DMB-trichloroacetimidate under either mildly acidic conditions or by Finkelstein reaction. Only when the alkylation was performed in THF at −20 °C using strictly equimolar amounts of KH as the base and DMB-Br/TBAI as the alkylating agent could product **13** be obtained in appreciable yield and acceptable 83% *ee*. In contrast, the subsequent chain extension by a Claisen condensation occurred without incident using the lithium enolate derived from *tert*-butyl acetate as the nucleophile.



Scheme 3. a) Isobutene, complex **11** (10 mol%), CH_2Cl_2, 0 °C, 90% (92% *ee*); b) DMBBr, KH, $(n\text{Bu})_4\text{NI}$, THF, −40 → −20 °C, 62% (83% *ee*); c) $t\text{BuOC(O)CH}_3$, LiHMDS, THF, −78 °C, 96%; d) see Table 1; e) I_2, $NaHCO_3$, Et_2O/MeCN, 0 °C, 89% (dr 2.2:1); f) $NaBH_4$, $InCl_3$ (15 mol%), MeCN, 88%; g) Dibal-H, CH_2Cl_2, −15 °C → 0 °C, 85%; h) I_2, PPh_3, imidazole, Et_2O/MeCN, 89%; DMBBr = 3,4-dimethoxybenzyl bromide; LiHMDS = lithium hexamethyldisilazide.

A chelate-controlled reduction of the resulting product **14** was thought to produce the required *anti*-configured diol **15**.[27,28] Surprisingly, however, the use of either $Zn(BH_4)_2$, $LiAlH_4$ or K-Selectride invariably afforded *syn*-**15** as the major isomer, likely because of the competing influence of the ester carbonyl group which seems to outperform the guidance exerted by the -ODMB ether (Table 1). Attempted CBS-reduction of **14** was plagued by low yields and found virtually unselective.[29] Gratifyingly, $NaBH_4$ modified with L-tartaric acid in THF at −20 °C provided the desired product with respectable selectivity (entry 8).[30] The control experiments shown in entries 6 and 7 make clear that this reduction is ligand-controlled, as the use of $NaBH_4$ alone resulted in a very modest diastereomeric ratio, whereas the use of D-tartaric acid as the additive inverted the stereochemical course. Routine flash chromatography furnished *anti*-**15** in optically pure form, as it allowed to remove all diastereomers derived from the competing *syn* reduction or from the antipodal substrate, given the fact that **13** and hence also **14** had only been 83% optically pure.

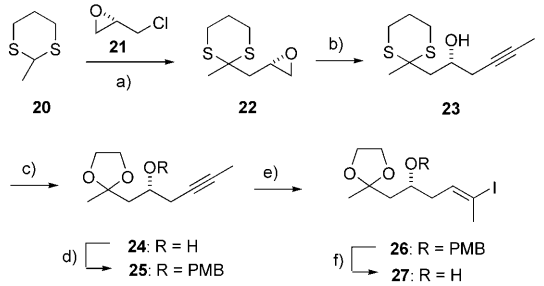
Table 1. Reduction of ketone **14** with different metal hydrides.

Entry	Reagents and conditions	*anti*/*syn*	Yield [%][a]
1	$Zn(BH_4)_2$, Et_2O, −78 °C	1:4	58 (85)
2	$LiAlH_4$, Et_2O, −78 °C	1:3.5	55 (79)
3	K-selectride, THF, −78 °C	1:5	21 (60)
4	CBS[b]	1:1.1	40
5	KBH_4, MeOH, −78 °C	1.6:1	78
6	$NaBH_4$, MeOH, −78 °C	1.5:1	83
7	$NaBH_4$, D-tartaric acid, THF, −20 °C	1:6	65 (72)
8	$NaBH_4$, L-tartaric acid, THF, −20 °C	7:1	65 (77)

[a] Isolated yields (yield based on recovered starting material). [b] BH_3-(SMe_2), (*S*)-3,3-diphenyl-1-methylpyrrolidino-[1,2-*c*]-1,3,2-oxazaborole, toluene, −15 °C, cf. ref. [29].

Iodo-etherification of *anti*-**15** effectively set the tertiary ether (Scheme 3).[31] The subsequent reduction of the neopentylic iodide in **16** was swiftly accomplished with $NaBH_4$ in the presence of catalytic amounts of $InCl_3$ in MeCN,[32] whereas conventional radical dehalogenation conditions were unsatisfactory. Reduction of the remaining ester in **17** followed by conversion of the resulting primary alcohol **18** into iodide **19** completed the synthesis of the required building block.

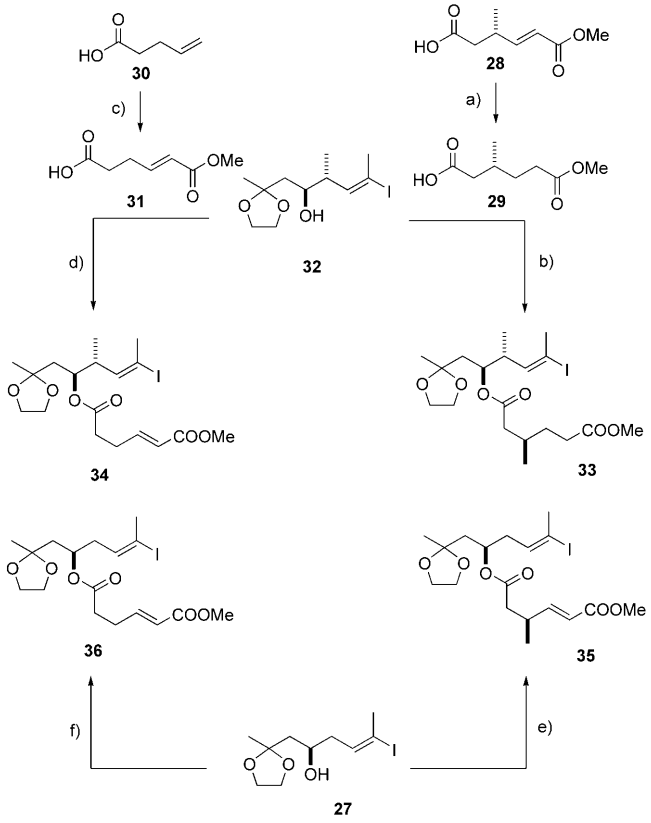
The vinyliodide fragment **27** lacking the C-11 methyl branch (amphidinolide X numbering) was obtained by alkylation of 2-methyl-1,3-dithiane **20** with (*S*)-**21** (>99% *ee*)[33] followed by opening of the epoxide in **22** with propynyl lithium in the presence of $BF_3(OEt_2)$ (Scheme 4).[34,35] Treatment of **23** with ethyleneglycol and iodine in MeCN gently swapped the thioketal for the corresponding 1,3-dioxolane **24**,[36,37] which served as the substrate for a subsequent hydrozirconation/iodination[38] sequence once the free hydroxy group had been protected as PMB-ether. For a regioselective hydrozirconation of a non-symmetrical alkyne to occur, it is believed that thermodynamic conditions need to be operative.[38,39] The acetal ring in **25**, however, turned out to be sensitive toward the Lewis-acidic Schwartz reagent, thus leading to rather poor yields of the desired product **26** if the mixture was allowed to stir for extended periods of time and/or at higher temperatures (≥40 °C). However, a workable compromise between selectivity (d.r. ≥ 96:4) and productivity (60%) was reached when **25** was treated with $[Cp_2Zr(H)Cl]$ in THF at +35 °C for 140 min, followed by addition of iodine to the reaction mixture at −78 °C. Cleavage of the -OPMB group with DDQ[40] afforded the desired building block **27** to be incorporated into the amphidinolide congeners **6** and **7** (Scheme 4). At this stage, the minor regioisomeric vinyl iodide formed in the hydrozirconation/io-



Scheme 4. a) i) *n*BuLi, THF, ii) epoxide **21**, −40 °C → RT, 86 %; b) propynyl lithium, $BF_3(OEt_2)$, THF, −78 °C 91 % (98 % *ee*); c) ethylene glycol, I_2, MeCN, 0 °C, 64 %; d) PMBCl, NaH, $(nBu)_4NI$, DMF, 81 %; e) i) $[Cp_2Zr(H)Cl]$, THF, 35 °C; ii) I_2, −78 °C, 60 % (d.r. 94:6); f) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 91 %; PMB = *p*-methoxybenzyl; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

dination step could be conveniently removed by flash chromatography.

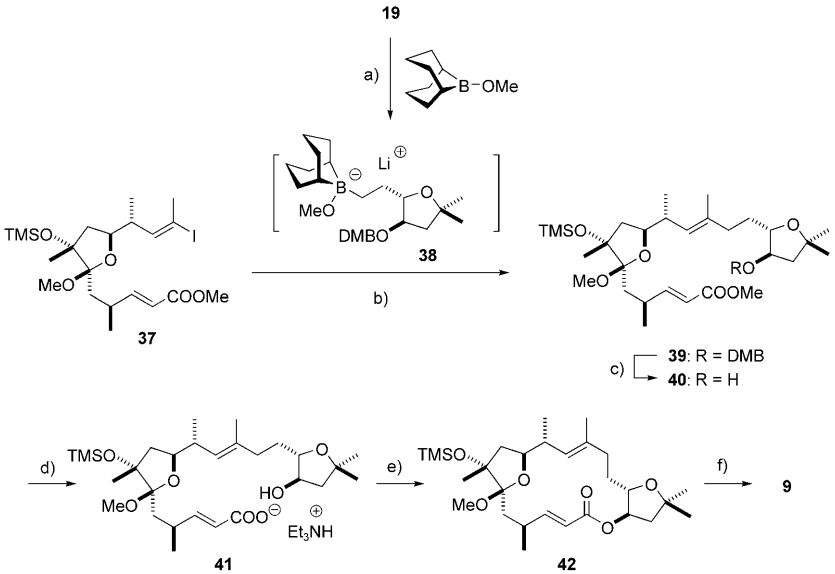
Acids **29** and **31** required for the preparation of the envisaged analogues were readily obtained by hydrogenation of the known compound **28** or by cross-metathesis of **30** with methyl acrylate, respectively.[41,42] They were attached in high yields to segments **27** or **32**[10] by intermolecular Yamaguchi esterification reactions as shown in Scheme 5.



Scheme 5. a) H_2 (1 atm), Pd/C (10 % *w*/*w*), MeOH, 94 %; b) **29**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP cat., 92 %; c) methyl acrylate, second generation Hoveyda–Grubbs catalyst (2 mol %), CH_2Cl_2, 69 %; d) **31**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP cat., 86 %; e) **28**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP cat., 91 %; f) **31**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP cat., 85 %.

A fully synthetic analogue of amphidinolide Y: The modified tetrahydrofuran **19** was coupled with segment **37**[10] previously used in the total synthesis of **2** upon metal-halogen exchange with *t*BuLi and trapping of the resulting organolithium reagent with 9-MeO-9-BBN; a subsequent alkyl-Suzuki reaction reliably transferred the functionalized alkyl residue from the resulting borate **38** to the organopalladium complex derived from **37** and $[(dppf)PdCl_2]$ (Scheme 6).[18,19,43]

The crude product **39** was immediately subjected to cleavage of the -ODMB ether with DDQ[40] to give **40** in 45 % unoptimized yield over both steps. Saponification of the methyl ester and conversion of the resulting acid into the corresponding triethylammonium salt **41** set the stage for the Yamaguchi macrolactonization[20–22,44] and final deprotection with the aid of dilute HOAc. Because of the sensitivity of the *seco*-acid and the ring closed product **42** in which the glycoside was still in place, these last steps were best performed without rigorous purification of the intermediates. Overall, this sequence provided compound **9** as a first fully synthetic conge-

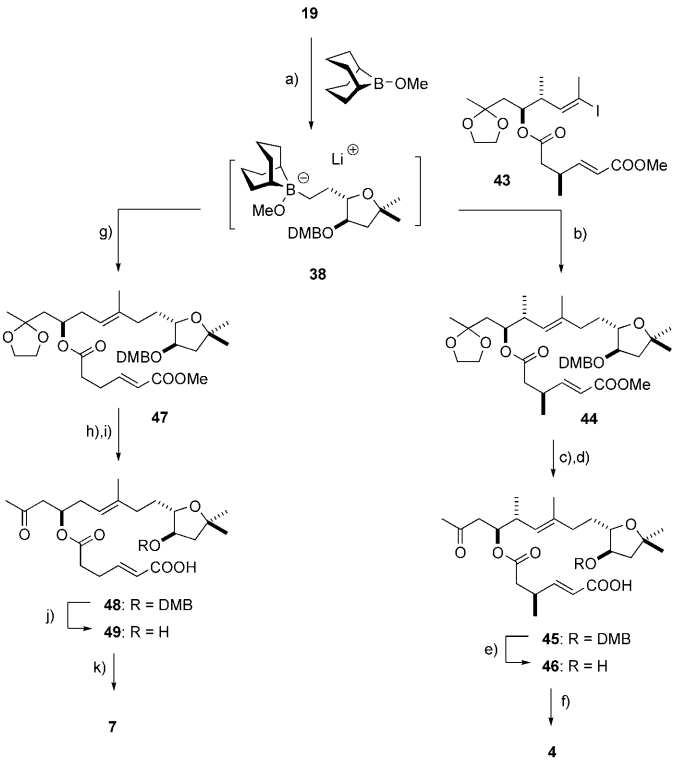


Scheme 6. a) *t*BuLi, Et_2O/THF, then 9-MeO-9-BBN, −78 °C → RT; b) $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol %), $AsPh_3$ (10 mol %), K_3PO_4, aq. DMF; c) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 0 °C, 45 % (over steps a)–c)); d) LiOH, MeOH/THF/H_2O 4:1:1, then Et_3N; e) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP cat., toluene; f) HOAc/THF/H_2O 4:1:1, 43 % (over three steps).

ner of amphidinolide Y, which—in analogy to the natural product[10,16]—exists as a mixture of the hydroxyketone- and the 6(9)-hemiketal form in $CDCl_3$ solution (4.8:1) (Scheme 6).

Analogues of the amphidinolide X series: In line with the results outlined above, the simplified tetrahydrofuran segment **19** could also be combined with vinyl iodide **43**[10] by recourse to the 9-MeO-9-BBN variant of the Suzuki coupling.[18,19] From there on, it sufficed to follow the blueprint of our previous total synthesis of amphidinolide X (Scheme 7).[9,10] Specifically, the selective cleavage of the methyl ester in **44** was effected with LiI in hot pyridine,[45] which left the sterically more encumbered ester group untouched. Although the aldol entity in **45** unmasked by acid catalyzed cleavage of the acetal ring turned out to be rather sensitive, it was possible to cleave the -ODMP ether with DDQ in buffered medium in high yield.[40] The macrocyclic ring of **4** was then closed by Yamaguchi lactonization of the resulting *seco*-acid **46** (Scheme 7).[20–22]

The same sequence of reactions also provided access to congener **5**, which solely lacks the methyl branch at C-4, as well as to product **8** incorporating a saturated ester in lieu of the enone moiety of **1** (Scheme 8). No significant changes to the experimental protocols were necessary in either case, thus attesting to the robustness of the chosen approach.



Scheme 7. a) *t*BuLi, Et_2O/THF, then 9-MeO-9-BBN, −78 °C → RT; b) $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol %), $AsPh_3$ (10 mol %), K_3PO_4, aq. DMF, 68 %; c) LiI, pyridine, reflux; d) aq. HOAc, 58 % (over both steps); e) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 81 %; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP cat., toluene, 56 %; g) iodide **36**, $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol %), $AsPh_3$ (10 mol %), K_3PO_4, aq. DMF, 67 %; h) LiI, pyridine, reflux; i) aq. HOAc, THF, 65 °C, 56 % (over both steps); j) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 82 %; k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP cat., toluene, 16 %.

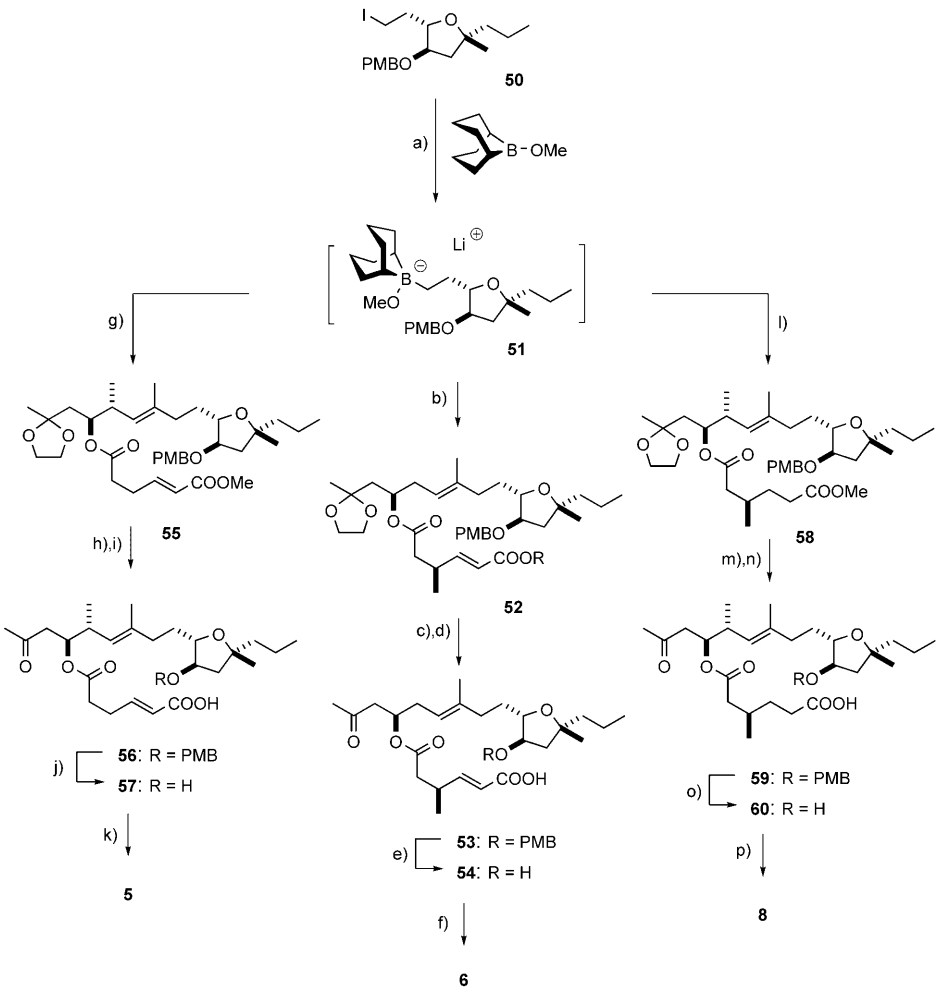
Even though the extension of this synthesis plan to analogues **6** and **7** was equally successful, it turned out that these compounds, deprived of the methyl group at C-11, are considerably more fragile in chemical terms (Scheme 7 and 8). Whereas the Suzuki cross-coupling reactions and the cleavage of the acetals were accomplished with ease, the *seco*-acid derivatives **54** and **49**, respectively, were found unusually labile and had to be handled with great care. As they tend to degrade the aldol subunit on their own backbones much faster than their relatives bearing a C-11 methyl group, they were immediately converted into the corresponding macrolactones. The yields obtained in the Yamaguchi reactions, however, were considerably lower than in the previous cases, again reflecting the stability issues mentioned above. Nevertheless, sufficient amounts of the targeted compounds could be secured for biological testing.

Assessment of the cytotoxicity profile: Amphidinolide X (**1**) and Y (**2**) were described as moderately active but roughly equipotent against murine lymphoma L1210 and human epidermoid carcinoma KB cells.[15,16] A more detailed inspection of their activity and selectivity profile, however, is missing. To this end, both compounds together with the synthetic analogues described above were assayed against a panel of human cancer cell lines. Relevant results of this investigation are compiled in Table 2.

Whereas our data confirm a moderate average cytotoxicity, it was surprising to find that **1** was considerably more active than **2**. Although this result contrast the literature reports,[15,16] it is internally calibrated because the amphidinolide Y analogue **9** was also by and large inactive, whereas congeners **4**–**8** reflect the level of activity as well as the selectivity profile characteristic of their parent compound amphidinolide X. The best results were recorded for analogue **5** lacking the C-4 methyl branch, which is slightly more active than the natural product itself. Compound **8** incorporating a saturated diacid segment comes next in terms of potency, which shows that the enone part of **1** is not an essential structural motif. In contrast, however, removal of the methyl group at C-11 as well as formal replacement of the chiral tertiary ether at C-18 by a seemingly closely related *gem*-dimethyl group results in diminished potency. Equally consistent throughout the series is the fact that the urothelial bladder carcinoma BXF 1218 L was found most sensitive to treatment with the drugs, followed by the colorectal carcinoma cell line HT29 and the prostate cancer cell line PC3 M.

Conclusion

Whereas the chemical derivatization of natural products has a long history as an exploratory tool for medicinal chemistry, this approach is very often not applicable to bioactive



Scheme 8. a) *t*BuLi, Et_2O/THF, then 9-MeO-9-BBN, −78 °C → RT; b) **35**, $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol %), $AsPh_3$ (10 mol %), K_3PO_4, aq. DMF, 79 %; c) LiI, pyridine, reflux; d) aq. HOAc, THF, 65 °C, 54 % (over both steps); e) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 71 %; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP cat., toluene, 32 %; g) **34**, $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol %), $AsPh_3$ (10 mol %), K_3PO_4, aq. DMF, 63 %; h) LiI, pyridine, reflux; i) aq. HOAc, THF, 65 °C, 52 % (over both steps); j) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 81 %; k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP cat., toluene, 58 %; l) **33**, $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol %), $AsPh_3$ (10 mol %), K_3PO_4, aq. DMF, 73 %; m) LiI, pyridine, reflux; n) aq. HOAc, THF, 65 °C, 68 % (over both steps); o) DDQ, CH_2Cl_2, phosphate buffer (pH 7), 71 %; p) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP cat., toluene, 59 %.

secondary metabolites of marine origin, simply because they are too scarce. In these cases, total synthesis has to fill the gap. Even though this may require considerable efforts, the undertaking may be rewarded by the fact that deliberate deviations from a successful synthesis plan can bring analogues with deep seated structural "point mutations" into reach that are not available otherwise. The synthesis campaign described above illustrates this notion. Specifically, a set of seven designed analogues of the macrolides amphidinolide X and Y has been prepared which exhibit such modifications in every segment of the macrocyclic frames of the parent compounds. The fact that these de novo syntheses were possible within a reasonable timeframe bears testimony to the inherent flexibility and chemical robustness of the underlying blueprint. Moreover, the acquired compound collection of fully synthetic "natural product-like" derivatives allowed first insights into the previously completely unknown SAR of these marine natural products. Although the average cytotoxicity against a panel of human cancer cell lines is moderate, it was found that certain bladder-, colon- and prostate cancer cell lines are reasonably sensitive. Moreover, the best analogues, which are either deprived of the methyl substituent at C-4 or incorporate a saturated ester rather than an enone into the macrodiolide skeleton, are somewhat more active than the natural product amphidinolide X itself.

Table 2. Antitumor activity of amphidinolide X and Y and their analogues against selected human tumor cell lines.

Cell line	Type	IC_{50} [$\mu g\,mL^{-1}$]							
		1	**2**	**4**	**5**	**6**	**7**	**8**	**9**
BXF 1218L	bladder	3.51	>10	4.70	3.21	7.82	>10	6.60	>10
HT29	colorectal	5.15	>10	8.11	3.70	>10	>10	6.90	>10
GXF 251L	gastric	>10	>10	9.34	7.68	>10	>10	5.48	>10
LXFA 629L	lung	7.89	>10	>10	8.58	>10	4.29	6.31	>10
MAXF 401NL	breast	7.33	>10	>10	>10	>10	>10	>10	>10
MEXF 462NL	melanoma	5.95	>10	>10	6.90	>10	>10	10.00	>10
PC3M	prostate	6.40	>10	>10	7.57	>10	>10	5.75	>10
22RV1	prostate	>10	>10	>10	9.28	>10	>10	7.46	>10
OVCAR3	ovarian	>10	>10	>10	>10	>10	>10	>10	>10
UXF 1138L	uterus	9.47	>10	>10	>10	>10	>10	9.12	>10

Experimental Section

General: All reactions were carried out under Ar. The solvents used were purified by distillation over the drying agents indicated and were transferred under Argon: THF, Et_2O (Mg/anthracene), $CHCl_3$ (P_4O_{10}), CH_2Cl_2, MeCN, Et_3N, pyridine (CaH_2), DMF (Desmodur, dibutyltin dilaurate), MeOH (Mg), hexanes, cyclohexane, toluene, benzene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a DPX 300, AV 400 or DMX 600 spectrometer (Bruker) 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 ($CDCl_3$: $\delta_C=77.1$ ppm, $\delta_H=7.26$ ppm; CD_2Cl_2: $\delta_C=54.0$ ppm, $\delta_H=5.32$ ppm; C_6D_6: $\delta_C=128.1$, $\delta_H=7.16$ ppm); IR (film): Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), (ESI) Finnigan MAT 95, accurate mass determination: Finnigan MAT 95, Bruker APEX III FT-ICR-MS (7 T magnet). Melting points: Büchi melting point apparatus (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. Unless stated otherwise, all commercially available compounds (Lancaster, Fluka, Aldrich) were used as received.

Preparation of the building blocks

Ethyl (2*R*)-2-hydroxy-4-methyl-4-pentenoate (12): A mixture of (*S,S*)-bis-(phenyloxazoline) (290 mg, 0.87 mmol) and $Cu(OTf)_2$ (320 mg, 0.87 mmol) in CH_2Cl_2 (26 mL) was stirred for 4 h at ambient temperature before it was cooled to −78 °C and transferred to a mixture of isobutylene in CH_2Cl_2 (1.1 M, 6.7 mL, 7.3 mmol) and freshly distilled ethyl glyoxalate in toluene (ethyl glyoxalate/toluene 1.5:1, 3.6 mL, 22 mmol) at 0 °C. The resulting green-blue solution was stirred for 18 h at 0 °C, before it was concentrated to a small volume and directly loaded onto a silica column. Eluation with pentanes/diethyl ether 3:1 gave alcohol **12** as a colorless oil (1.0 g, 90 %). The enantiomeric excess (*ee* 92 %) was determined by GC by comparison with the racemate (25 m Lipodex G 399, 220 °C, 0.5 bar H_2). $[\alpha]_D^{20}=9.3$ ($c=5.57$, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.89$ (d, $J=1.4$ Hz, 1H), 4.82 (d, $J=0.8$ Hz, 1H), 4.32 (dd, $J=8.3$, 4.2 Hz, 1H), 4.25 (q, $J=7.2$ Hz, 2H), 2.68 (br s, 1H), 2.53 (dd, $J=14.2$, 4.2 Hz, 1H), 2.37 (dd, $J=14.2$, 8.3 Hz, 1H), 1.79 (s, 3H), 1.30 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.7$, 140.9, 114.0, 69.1, 61.7, 42.7, 22.5, 14.2 ppm; IR (film): $\tilde{\nu}=3476$, 3077, 1736, 1649, 1205, 1100, 893 cm^{-1}; MS (EI): *m/z* (%): 158 (14) [M^+], 140 (68), 125 (6), 112 (49), 97 (10), 95 (12), 85 (62), 42 (75), 67 (17), 57 (77), 41 (73), 29 (100); HRMS (EI): *m/z*: calcd for $C_8H_{14}O_3$ [M^+]: 158.0943, found: 158.0942.

Ethyl (2*R*)-2-((3,4-dimethoxybenzyl)oxy)-4-methyl-4-pentenoate (13): KH (330 mg, 8.3 mmol) was added in portions to a solution of **12** (1.30 g, 8.3 mmol), 3,4-dimethoxybenzyl bromide (3.8 g, 17 mmol), and tetra-*n*-butylammonium iodide (610 mg, 1.7 mmol) in THF (100 mL) at −40 °C. The reaction mixture was warmed to −20 °C over the course of 2 h and stirred for another 3 h at this temperature. The reaction was quenched with aq. sat. $NaHCO_3$ (40 mL), the mixture diluted with methyl *tert*-butyl ether (50 mL) and allowed to reach ambient temperature. The aqueous layer was repeatedly extracted with methyl *tert*-butyl ether and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 15:1) to give compound **13** as a colorless oil (1.60 g, 62 %). The enantiomeric excess (*ee* 83 %) was determined by HPLC by comparison with the racemate (250 mm Chiralpak AS-H, ∅ 4.6 mm, *n*-heptane/2-propanol 98:2, 0.5 mL min^{-1}, 2.4 MPa, 298 K, UV, 220 nm). $[\alpha]_D^{20}=53.6$ ($c=1.37$, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.92$ (d, $J=1.8$ Hz, 1H), 6.85 (dd, $J=8.1$, 1.8 Hz, 1H), 6.81, (d, $J=8.1$ Hz, 1H), 4.82–4.81 (m, 1H), 4.79–4.78 (m, 1H), 4.64 (d, $J=11.5$ Hz, 1H), 4.37 (d, $J=11.5$ Hz, 1H), 4.20 (dq, $J=7.1$, 1.3 Hz, 2H), 4.06 (dd, $J=7.7$, 5.7 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 2.47 (m, 2H), 1.72 (s, 3H), 1.28 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.5$, 149.0, 148.7, 141.0, 130.0, 120.6, 113.5, 111.3, 110.8, 76.7, 72.1, 60.8, 55.9, 55.8, 41.2, 22.5, 14.3 ppm; IR (film): $\tilde{\nu}=3076$, 1746, 1500, 1265, 1109, 893 cm^{-1}; MS (EI): *m/z* (%): 308 (21) [M^+], 208 (5), 167 (38), 151 (100); HRMS (ESI): *m/z*: calcd for $C_{17}H_{24}O_5Na$ [M^++Na]: 331.1516, found: 331.1515; elemental analysis calcd (%) for $C_{17}H_{24}O_5$: C 66.21, H 7.84; found: C 66.15, H 7.80.

***tert*-Butyl (4*R*)-4-((3,4-dimethoxybenzyl)oxy)-6-methyl-3-oxo-6-heptenoate (14)**: A solution of *tert*-butyl acetate (1.9 mL, 14 mmol) in THF (7.0 mL) was added over 15 min to a solution of LiHMDS (2.4 g, 14 mmol) in THF (38 mL) at −78 °C. The mixture was stirred for 30 min at this temperature before a solution of compound **13** (1.50 g, 4.7 mmol) in THF (7.0 mL) was introduced. After stirring for 4 h at −78 °C, the reaction was quenched at that temperature with aq. sat. NH_4Cl (20 mL) and the mixture allowed to reach ambient temperature. The aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the combined organic phases were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to provide compound **14** as a colorless oil (1.70 g, 96 %). Keto–enol tautomer ratio in $CDCl_3$: 5.6:1 (NMR). $[\alpha]_D^{20}=41.6$ ($c=1.12$, $CHCl_3$); ketone form: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.77$–6.74 (m, 1H), 6.71–6.65 (m, 2H), 4.70–4.69 (m, 1H), 4.65–4.64 (m, 1H), 4.41 (d, $J=11.3$ Hz, 1H), 4.26 (d, $J=11.3$ Hz, 1H), 3.87 (dd, $J=7.8$, 5.3 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.38 (d, $J=15.8$ Hz, 1H), 3.29 (d, $J=15.8$ Hz, 1H), 2.33–2.20 (m, 2H), 1.56 (s, 3H), 1.30 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=205.4$, 166.4, 149.0, 148.9, 140.8, 129.7, 120.6, 114.0, 111.3, 110.9, 82.8, 81.9, 72.6, 55.9, 55.8, 46.0, 40.1, 28.0, 22.5 ppm; enol form: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=12.00$ (br s, 1H), 5.05 (s, 1H), 6.77–6.65 (m, 3H), 4.66 (s, 1H), 4.63 (s, 1H), 4.45 (d, $J=11.7$ Hz, 1H), 4.18 (d, $J=11.7$ Hz, 1H), 3.92–3.86 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.33–2.20 (m, 2H), 1.53 (s, 3H), 1.36 ppm (s, 9H); IR (film): $\tilde{\nu}=3076$, 1742, 1717, 1593, 1517, 1368, 1264, 1159, 895 cm^{-1}; MS (EI): *m/z* (%): 378 (4) [M^+], 238 (5), 167 (9), 156 (9), 151 (100); HRMS (ESI): *m/z*: calcd for $C_{21}H_{30}O_6Na$ [M^++Na]: 401.1934, found: 401.1931; elemental analysis calcd (%) for $C_{21}H_{30}O_6$: C 66.65, H 7.99; found: C 66.57, H 8.08.

***tert*-Butyl (3*S*,4*R*)-4-((3,4-dimethoxybenzyl)oxy)-3-hydroxy-6-methyl-6-heptenoate (*anti*-15)**: $NaBH_4$ (720 mg, 19 mmol) was added in portions to a solution of L-(+)-tartaric acid (2.9 g, 19 mmol) in THF (35 mL) and the resulting suspension was stirred for 4 h at reflux temperature before it was cooled to −20 °C. A solution of compound **14** (1.2 g, 3.2 mmol) in THF (25 mL) was added over 30 min and stirring continued for 20 h at this temperature. The reaction was then quenched with aq. sat. NH_4Cl (40 mL), the mixture diluted with ethyl acetate (40 mL) and allowed to reach ambient temperature. The aqueous layer was repeatedly extracted with ethyl acetate and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 5:1) to give a mixture of the *anti*-configured alcohol and its *syn*-configured isomer (*anti*/*syn* 7:1, 780 mg, 65 %) as well as a second fraction of reisolated starting material **14** (190 mg, 16 %). The isomers can be separated by flash chromatography (hexanes/ethyl acetate 8:1) to provide *anti*-**15** (600 mg, 50 %) and *syn*-**15** (70 mg, 6 %) in pure form each. The enantiomeric excess of *anti*-**15** (*ee* > 99 %) and *syn*-**15** (*ee* 98 %) was determined by HPLC by comparison with the racemates (250 mm Chiralpak AD, ∅ 4.6 mm, *n*-heptane/2-propanol 90:10, 0.5 mL min^{-1}, 1.7 MPa, 298 K, UV, 220 nm). *anti*-**15**: $[\alpha]_D^{20}=-31.4$ ($c=1.03$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.91$ (d, $J=1.8$ Hz, 1H), 6.86 (dd, $J=8.1$, 1.8 Hz, 1H), 6.81 (d, $J=8.1$ Hz, 1H), 4.83 (s, 2H), 4.56 (s, 2H), 4.09–4.04 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.62 (dt, $J=7.7$, 4.7 Hz, 1H), 3.11 (br s, 1H), 2.50 (d, $J=4.5$ Hz, 1H), 2.49 (d, $J=8.0$ Hz, 1H), 2.34 (dd, $J=14.2$, 7.6 Hz, 1H), 2.24 (dd, $J=14.2$, 4.8, 1H), 1.76 (s, 3H), 1.45 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.4$, 148.9, 148.6, 142.5, 131.0, 120.3, 113.2, 111.3, 110.8, 81.2, 79.3, 72.4, 70.0, 55.9, 55.8, 39.1, 37.7, 28.1, 22.8 ppm; IR (film): $\tilde{\nu}=3530$, 3074, 1726, 1517, 1368, 1264, 1156, 889 cm^{-1}; MS (EI): *m/z* (%): 380 (3) [M^+], 323 (7), 235 (3), 205 (7), 167 (20), 151 (100), 57 (11); HRMS (EI): *m/z:* calcd for $C_{21}H_{32}O_6$ [M^+]: 380.2199, found: 380.2201; elemental analysis calcd (%) for $C_{21}H_{32}O_6$: C 66.29, H 8.48; found: C 66.19, H 8.42.

syn-**15** (*ee* 98 %): $[\alpha]_D^{20}=1.6$ ($c=2.9$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.90$ (d, $J=1.6$ Hz, 1H), 6.86 (dd, $J=8.1$, 1.6 Hz, 1H), 6.82 (d, $J=8.1$ Hz, 1H), 4.84 (s, 2H), 4.59 (d, $J=11.3$ Hz, 1H), 4.47 (d, $J=11.3$ Hz, 1H), 4.06–4.02 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.52 (dt, $J=6.5$, 3.5 Hz, 1H), 2.75 (br s, 1H), 2.48 (d, $J=8.3$ Hz, 1H), 2.45 (d, $J=4.8$ Hz, 1H), 2.40 (dd, $J=13.7$, 6.1 Hz, 1H), 2.30 (dd, $J=13.9$, 6.8 Hz, 1H), 1.76 (s, 3H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.7$, 149.0, 148.7, 142.3, 130.8, 120.5, 113.4, 111.4, 110.9, 81.0, 78.3, 72.1, 68.9, 55.9, 55.8, 39.4, 38.4, 28.1, 22.8 ppm.

***tert*-Butyl ((2*S*,3*R*,5*RS*)-3-((3,4-dimethoxybenzyl)oxy)-5-(iodomethyl)-5-methyltetrahydro-2-furanyl)acetate (16)**: A solution of iodine (700 mg, 2.8 mmol) in Et_2O was added over 25 min to a mixture containing *anti*-**15** (520 mg, 1.4 mmol) and $NaHCO_3$ (460 mg, 5.5 mmol) in MeCN (10 mL) at 0 °C. After reaching ambient temperature, the mixture was stirred for 15 min before the reaction was quenched with a mixture of $Na_2S_2O_3$ (5 mL) and aq. sat. $NaHCO_3$ (5 mL). The aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 8:1) to give product **16** as a mixture of diastereoisomers (d.r. 2.2:1, 620 mg, 89 %). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90–6.82 (m, 3H), 4.49–4.38 (m, 3H), 4.02–3.96 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.55 (d, J = 9.7 Hz, 1H), 3.39 (d, J = 9.7 Hz, 1H), 2.49–2.37 (m, 4H), 1.44 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 149.0, 148.6, 130.4, 120.2, 111.1, 110.9, 83.3, 83.0, 81.0, 80.5, 71.5, 55.914, 40.9, 40.5, 28.1, 27.6, 17.0 ppm. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90–6.82 (m, 3H), 4.49–4.38 (m, 3H), 4.02–3.96 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.26 (s, 1H), 3.25 (s, 1H), 2.22 (dd, J = 13.5, 7.0 Hz, 1H), 2.01–1.94 (m, 3H), 1.59 (s, 3H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 149.0, 148.6, 130.4, 120.2, 111.1, 110.9, 83.0, 81.8, 80.8, 80.8, 71.6, 55.8, 42.5, 40.5, 28.1, 26.2, 18.4; IR (film): $\tilde{\nu}$ = 2975, 2933, 1727, 1517, 1367, 1264, 1158 cm^{-1}; MS (EI): m/z (%): 506 (8) [M^+], 449 (24), 283 (13), 265 (6), 223 (8), 205 (8), 167 (78), 151 (100), 57 (9); HRMS (EI): m/z: calcd for $C_{21}H_{31}O_6I$ [M^+]: 506.1165, found: 506.1165; elemental analysis calcd (%) for $C_{21}H_{31}O_6I$: C 49.81, H 6.17; found: C 49.54, H 6.31.

***tert*-Butyl ((2*S*,3*R*)-3-((3,4-dimethoxybenzyl)oxy)-5,5-dimethyltetrahydro-2-furanyl)acetate (17)**: $NaBH_4$ (50 mg, 1.3 mmol) was added to a suspension of $InCl_3$ (17 mg, 0.08 mmol) in MeCN (1.0 mL) at −40 °C. The mixture was stirred for 5 min before it was allowed to reach ambient temperature. After 5 min, a solution of **16** (270 mg, 0.53 mmol) in MeCN (4.2 mL) was introduced and stirring continued for 1 h. The reaction was quenched with water (2.0 mL), the aqueous layer was repeatedly extracted with methyl *tert*-butyl ether and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 8:1) to provide compound **17** as a colorless oil (180 mg, 88 %). $[\alpha]_D^{20}$ = −22.8 (c = 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, J = 1.6 Hz, 1H), 6.86 (dd, J = 8.1, 1.8 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.44 (s, 2H), 4.32 (dt, J = 6.3, 4.2 Hz, 1H), 3.97 (dt, J = 6.9, 3.9 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.50–2.40 (m, 2H), 1.96 (dd, J = 13.1, 6.8 Hz, 1H), 1.89 (dd, J = 13.1, 3.8 Hz, 1H), 1.43 (s, 9H), 1.35 (s, 3H), 1.26 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 149.0, 148.6, 130.9, 120.1, 111.0, 110.9, 83.5, 80.9, 80.6, 79.5, 71.5, 55.9, 55.8, 44.0, 40.7, 30.0, 28.4, 28.1 ppm; IR (film): $\tilde{\nu}$ = 2972, 2934, 1729, 1517, 1367, 1263, 1158 cm^{-1}; MS (EI): m/z (%): 380 (8) [M^+], 324 (16), 235 (6), 167 (67), 151 (100), 57 (16); HRMS (EI): m/z: calcd for $C_{21}H_{32}O_6$ [M^+]: 380.2199, found: 380.2197; elemental analysis calcd (%) for $C_{21}H_{32}O_6$: C 66.29, H 8.48; found: C 66.20, H 8.56.

2-((2*S*,3*R*)-3-((3,4-Dimethoxybenzyl)oxy)-5,5-dimethyltetrahydro-2-furanyl)ethanol (18): A solution of Dibal-H (1.0 M in hexanes, 1.8 mL, 1.8 mmol) was added over 20 min to a solution of ester **17** (135 mg, 0.36 mmol) in CH_2Cl_2 (2.7 mL) at −15 °C and the resulting mixture was stirred for 2 h at this temperature and for 4 h at 0 °C. The reaction was quenched with aq. potassium/sodium tartrate (1 M, 2.7 mL) and stirring was continued until a clean phase separation was reached. The aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 1:1) to give alcohol **18** as a colorless oil (94 mg, 85 %). $[\alpha]_D^{20}$ = −50.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.81 (m, 3H), 4.47 (d, J = 11.3 Hz, 1H), 4.39 (d, J = 11.3 Hz, 1H), 4.11–4.06 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.88–3.83 (m, 1H), 3.77–3.74 (m, 2H), 2.26 (br s, 1H), 2.01 (dd, J = 12.9, 7.4 Hz, 1H), 1.87 (dd, J = 12.9, 4.9 Hz, 1H), 1.90–1.72 (m, 2H), 1.34 (s, 3H), 1.27 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.7, 130.4, 120.2, 111.1, 111.0, 83.7, 82.5, 80.9, 71.8, 61.3, 55.9, 55.8, 44.0, 36.3, 30.0, 28.3 ppm; IR (film): $\tilde{\nu}$ = 3442, 2967, 1593, 1517, 1465, 1265, 1158 cm^{-1}; MS (EI): m/z (%): 310 (19) [M^+], 235 (3), 167 (5), 151 (100); HRMS (EI): m/z: calcd for $C_{17}H_{26}O_5$ [M^+]: 310.1780, found: 310.1783; elemental analysis calcd (%) for $C_{17}H_{26}O_5$: C 65.78, H 8.44; found: C 65.70, H 8.38.

(4*R*,5*S*)-4-((3,4-Dimethoxybenzyl)oxy)-5-(2-iodoethyl)-2,2-dimethyl-tetrahydrofuran (19): PPh_3 (130 mg, 0.49 mmol) and imidazole (44 mg, 0.65 mmol) were added to a solution of **18** (100 mg, 0.25 mmol) in Et_2O/MeCN 1:1 (2.8 mL) at 0 °C. After stirring for 5 min, a solution of iodine (125 mg, 0.49 mmol) in Et_2O (1.4 mL) was added dropwise and the resulting mixture was stirred for 1 h. The reaction was quenched with aq. sat. NH_4Cl (3.0 mL), the aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 12:1) to give iodide **19** as a colorless oil (122 mg, 89 %). $[\alpha]_D^{20}$ = −43.0 (c = 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.86–6.82 (m, 3H), 4.44 (d, J = 11.4 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 3.94 (dt, J = 8.4, 4.4 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.79 (dt, J = 7.0, 4.5 Hz, 1H), 3.28–3.17 (m, 2H), 2.13–2.04 (m, 1H), 1.88 (dd, J = 13.1, 4.2 Hz, 1H), 2.00–1.92 (m, 2H), 1.31 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 149.8, 149.4, 131.4, 120.7, 112.0, 111.8, 84.2, 83.0, 81.2, 72.0, 56.4, 56.3, 44.7, 39.9, 30.3, 28.6, 2.9; IR (film): $\tilde{\nu}$ = 2967, 2930, 1593, 1516, 1464, 1264, 1158 cm^{-1}; MS (EI): m/z (%): 420 (27) [M^+], 235 (2), 166 (3), 151 (100); HRMS (ESI): m/z: calcd for $C_{17}H_{25}O_4INa$ [M^++Na]: 443.0690, found: 443.0685; elemental analysis calcd (%) for $C_{17}H_{25}O_4I$: C 48.58, H 6.00; found: C 48.60, H 6.08.

(2*S*)-2-((2-Methyl-1,3-dithian-2-yl)methyl)oxirane (22): A solution of *n*BuLi (1.6 M in hexanes, 13 mL, 21 mmol) was added over 5 min to a solution of 2-methyl-1,3-dithiane (2.8 g, 21 mmol) in THF (35 mL) at 0 °C (exothermic!). Once the addition was complete, the solution was stirred for 3 min at ambient temperature before its was cooled to −40 °C and treated with a solution of (*S*)-**21** (1.9 g, 21 mmol) in THF (10 mL). After 20 min at −40 °C and 4 h at ambient temperature, the reaction was quenched with aq. sat. NH_4Cl (50 mL), the aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the combined extracts were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 6:1) to afford epoxide **22** as a colorless oil (3.4 g, 86 %). $[\alpha]_D^{20}$ = −6.4 (c = 4.2, CH_2Cl_2) [lit.:[36] $[\alpha]_D^{22}$ = −4.9 (c = 4.7, CH_2Cl_2)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20–3.16 (m, 1H), 2.95–2.79 (m, 5H), 2.52 (dd, J = 5.0, 2.7 Hz, 1H), 2.23 (dd, J = 14.7, 4.8 Hz, 1H), 2.10 (dd, J = 14.7, 6.3 Hz, 1H), 2.06–1.87 (m, 2H), 1.71 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.7, 47.4, 46.3, 44.0, 28.1, 26.3, 26.2, 24.6 ppm; IR (film): $\tilde{\nu}$ = 3045, 2920, 1446, 1422, 1277, 1258, 864 cm^{-1}; MS (EI): m/z (%): 190 (41) [M^+], 133 (100); HRMS (EI): m/z: calcd for $C_8H_{14}OS_2$ [M^+]: 190.0486, found: 190.0488.

(2*R*)-1-(2-Methyl-1,3-dithian-2-yl)-4-hexyn-2-ol (23): An excess of propyne was condensed into THF (120 mL) at −78 °C and treated dropwise with a solution of *n*BuLi (1.6 M in hexanes, 13 mL, 21 mmol). After stirring for 30 min, $BF_3{\cdot}OEt_2$ (2.7 mL, 21 mmol) was introduced and stirring continued for 20 min at −78 °C before a solution of epoxide **22** (3.1 g, 16 mmol) in THF (25 mL) was slowly added. The mixture was stirred for 1 h at −78 °C before the reaction was quenched with aq. sat. NH_4Cl (50 mL). The aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the combined organic phases were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to afford alcohol **23** as a colorless oil (3.4 g, 91 %). The enantiomeric excess (*ee* 98 %) was determined by GC by comparison with the racemate. $[\alpha]_D^{20}$ = −76.4 (c = 1.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04–3.99 (m, 1H), 3.26 (br s, 1H), 3.03–2.92 (m, 2H), 2.79–2.73 (m, 2H), 2.40–2.26 (m, 3H), 2.12 (dd, J = 15.0, 1.8 Hz, 1H), 2.07–1.99 (m, 1H), 1.92–1.82 (m, 1H), 1.78 (t, J = 2.6 Hz, 3H), 1.64 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.1, 75.2, 67.9, 47.6, 46.3, 28.4, 28.0, 26.7, 26.5, 24.6, 3.5 ppm; IR (film): $\tilde{\nu}$ = 3439, 2916, 2231, 1439, 1423, 1276, 1102, 867 cm^{-1}; MS (EI): m/z (%): 230 (24) [M^+], 177 (7), 156 (53), 133 (100), 53 (25); HRMS (EI): m/z: calcd for $C_{11}H_{18}OS_2$ [M^+]: 230.0799, found: 230.0798; elemental analysis calcd (%) for $C_{11}H_{18}OS_2$: C 57.35, H 7.87; found: C 57.42, H 7.81.

(2*R*)-1-(2-Methyl-1,3-dioxolan-2-yl)-4-hexyn-2-ol (24): Iodine (2.4 g, 9.6 mmol) was added in portions to a solution of dithiane **23** (740 mg, 3.2 mmol) and ethylene glycol (1.0 mL, 18 mmol) in MeCN (15 mL) at 0 °C. After stirring for 10 min, the reaction was quenched by pouring the

cold solution into a mixture of vigorously stirred aq. sat. $NaHCO_3$ and aq. sat. $Na_2S_2O_3$ 1:1 (50 mL). The aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the combined organic phases were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 8:1) to afford compound **24** as a colorless oil (380 mg, 64%). $[\alpha]_D^{20} = -8.8$ ($c = 1.2$, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 4.00$–3.89 (m, 5H), 3.44 (d, $J = 1.3$ Hz, 1H), 2.35–2.15 (m, 2H), 1.99 (dd, $J = 14.6$, 2.0 Hz, 1H), 1.82–1.74 (m, 1H), 1.77 (t, $J = 2.6$ Hz, 3H), 1.35 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta =$ 110.7, 77.9, 76.1, 67.6, 65.3, 64.9, 44.5, 27.9, 24.5, 3.7 ppm; IR (film): $\tilde{\nu} =$ 3512, 2920, 2234, 1219, 1106, 1054, 949, 820 cm^{-1}; MS (EI): *m/z* (%): 169 (4) [M^+–Me], 131 (7), 87 (100), 53 (4); HRMS (CI): *m/z:* calcd for $C_{10}H_{17}O_3$ [M^++H]: 185.1178, found: 185.1180; elemental analysis calcd (%) for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 65.07, H 8.64.

2-((2*R*)-2-((4-Methoxybenzyl)oxy)-4-hexynyl)-2-methyl-1,3-dioxolane (25): NaH (39 mg, 1.6 mmol) was added to a solution of **24** (250 mg, 1.4 mmol) in DMF (9.0 mL) at 0°C. The mixture was stirred for 10 min at 0°C and for 30 min at ambient temperature before *p*-methoxybenzyl chloride (240 μL, 1.6 mmol) and tetra-*n*-butylammonium iodide (50 mg, 0.14 mmol) were introduced. After stirring for 14 h, the reaction was quenched with aq. sat. $NaHCO_3$ (20 mL), the aqueous layer was repeatedly extracted with methyl *tert*-butyl ether, the extracts were washed with water, dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 12:1 + 1% Et_3N) to afford product **25** as a colorless oil (330 mg, 81%). $[\alpha]_D^{20} = -26.6$ ($c = 1.24$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 4.55 (d, $J = 11.1$ Hz, 1H), 4.46 (d, $J =$ 11.1 Hz, 1H), 3.97–3.89 (m, 4H), 3.80 (s, 3H), 3.70–3.64 (m, 1H), 2.44–2.40 (m, 2H), 2.01–1.99 (m, 2H), 1.79 (t, $J = 2.5$ Hz, 3H), 1.37 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.1$, 130.7, 129.4, 113.7, 109.1, 77.1, 75.9, 74.3, 70.8, 64.4, 64.4, 55.3, 42.8, 25.0, 24.5, 3.6 ppm; IR (film): $\tilde{\nu} = 2984$, 2920, 2233, 1514, 1253, 1053, 820 cm^{-1}; MS (EI): *m/z* (%): 304 (0.6) [M^+], 202 (6), 121 (100), 87 (22); HRMS (ESI): *m/z:* calcd for $C_{18}H_{24}O_4Na$ [M^++Na]: 327.1567, found: 327.1563.

2-((2*R*,4*E*)-2-((4-Ethylbenzyl)oxy)-5-iodo-4-hexenyl)-2-methyl-1,3-dioxolane (26): A mixture containing **25** (140 mg, 0.45 mmol) and $[Cp_2Zr(H)Cl]$ (290 mg, 1.1 mmol) in THF (4.8 mL) was stirred in the dark for 140 min at 30–35°C before it was cooled to −78°C. A solution of iodine (290 mg, 1.1 mmol) in THF (2.0 mL) was slowly added and stirring continued for 5 min at this temperature before the mixture was poured into aq. sat. $NaHCO_3$ (10 mL). Extraction with methyl *tert*-butyl ether (10 mL), washing of the organic layer with aq. sat. $Na_2S_2O_3$ and brine, drying over Na_2SO_4, filtration and evaporation of the solvent afforded a residue which was purified by flash chromatography (hexanes/ethyl acetate 15:1 + 2% Et_3N) to give product **26** as a pale yellow oil (mixture of regioisomers, d.r. 96:4, 117 mg, 60%). $[\alpha]_D^{20} = -2.7$ ($c = 3.30$, $CHCl_3$). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J =$ 8.7 Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 6.22 (dt, $J = 7.4$, 1.5 Hz, 1H), 4.47 (d, $J = 11.1$ Hz, 1H), 4.42 (d, $J = 11.1$ Hz, 1H), 3.98–3.85 (m, 4H), 3.80 (s, 3H), 3.62–3.56 (m, 1H), 2.38–2.23 (m, 2H), 2.36 (d, $J = 1.6$ Hz, 3H), 1.99 (dd, $J = 14.7$, 5.6 Hz, 1H), 1.78 (dd, $J = 14.7$, 5.4 Hz, 1H), 1.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.1$, 137.6, 130.6, 129.4, 113.8, 109.0, 95.2, 74.3, 70.6, 64.5, 64.4, 55.3, 43.1, 36.2, 27.8, 24.5 ppm; IR (film): $\tilde{\nu} = 2957$, 2876, 1514, 1249, 1039, 820 cm^{-1}; MS (EI): *m/z* (%): 417 (0.3) [M^+–Me], 305 (4), 121 (100), 87 (25); HRMS (ESI): *m/z:* calcd for $C_{18}H_{25}O_4INa$ [M^++Na]: 455.0690, found: 455.0691; elemental analysis calcd (%) for $C_{18}H_{25}O_4I$: C 50.01, H 5.83; found: C 49.86, H 5.72.

2-((2*R*,4*E*)-2-((4-Ethylbenzyl)oxy)-5-iodo-4-hexenyl)-2-methyl-1,3-dioxolane (27): DDQ (210 mg, 0.92 mmol) was added in portions to a vigorously stirred solution of compound **26** (265 mg, 0.61 mmol) in CH_2Cl_2 (6.1 mL) and aq. phosphate buffer solution (pH 7, 6.1 mL) at 0°C. The mixture was stirred for 14 h at ambient temperature, diluted with CH_2Cl_2 (12 mL) and the reaction quenched with aq. sat. $NaHCO_3$ (12 mL). The aqueous layer was repeatedly extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 12:1 + 1% Et_3N) to give alcohol **27** as a colorless oil (174 mg, 91%). $[\alpha]_D^{20} = 4.1$ ($c =$ 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 6.24$ (tq, $J = 7.5$, 1.5 Hz, 1H), 4.02–3.89 (m, 5H), 3.46 (brs, 1H), 2.38 (d, $J = 1.4$ Hz, 3H), 2.22–2.10 (m, 2H), 1.81 (dd, $J = 14.6$, 2.3 Hz, 1H), 1.74 (dd, $J = 14.6$, 9.4 Hz, 1H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 138.2$, 110.7, 95.8, 67.6, 65.3, 64.9, 44.9, 38.8, 28.2, 24.5 ppm; IR (film): $\tilde{\nu} = 3518$, 2982, 2885, 1636, 1377, 1053, 818 cm^{-1}; MS (EI): *m/z* (%): 312 (0.2) [M^+], 297 (3), 181 (1), 131 (10), 87 (100); HRMS (ESI): *m/z:* calcd for $C_{10}H_{17}O_3INa$ [M^++Na]: 335.0117, found: 335.0115; elemental analysis calcd (%) for $C_{10}H_{17}O_3I$: C 38.48, H 5.49; found: C 38.39, H 5.43.

(3*R*)-6-Methoxy-3-methyl-6-oxohexanoic acid (29): Pd on charcoal (10% *w/w*, 6 mg) was added to a solution of **28** (61 mg, 0.35 mmol) in MeOH (3.5 mL). H_2 was bubbled through the suspension for 5 min before the mixture was stirred for 4 h under a H_2 atmosphere (≈1 atm). For work up, the mixture was filtered through a pad of silica which was rinsed with ethyl acetate, and the filtrates were evaporated to give product **29** as a colorless oil (58 mg, 94%). $[\alpha]_D^{20} = 4.7$ ($c = 1.2$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.17$ (brs, 1H), 3.66 (s, 3H), 2.40–2.27 (m, 3H), 2.16 (dd, $J = 15.1$, 7.7 Hz, 1H), 2.01–1.92 (m, 1H), 1.77–1.68 (m, 1H), 1.57–1.48 (m, 1H), 0.96 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.8$, 174.1, 51.6, 41.7, 31.6, 31.4, 29.7, 19.3; IR (film): $\tilde{\nu} = 3010$, 2957, 2933, 1732, 1707 cm^{-1}; MS (EI): *m/z* (%): 175 (0.2) [M^++H], 143 (35), 128 (54), 115 (81), 101 (6), 96 (20), 87 (36), 83 (47), 74 (63), 69 (49), 59 (48), 55 (100); HRMS (CI): *m/z:* calcd for $C_8H_{15}O_4$ [M^++H]: 175.0970, found: 175.0968; elemental analysis calcd (%) for $C_8H_{14}O_4$: C 55.16, H 8.15; found: C 55.16, H 8.10.

(4*E*)-6-Methoxy-6-oxo-4-hexenoic acid (31): Second generation Grubbs-Hoveyda catalyst (62 mg, 0.10 mmol)[42] was added to a solution of 4-pentenoic acid **30** (500 mg, 5.0 mmol) and methyl acrylate (2.3 mL, 25.0 mmol) in CH_2Cl_2 (50 mL). The solution was stirred for 16 h at ambient temperature before it was filtered through a pad of silica which was rinsed with hexanes/ethyl acetate (2:1). The combined filtrates were concentrated and the residue was purified by flash chromatography (hexanes/ethyl acetate 4:1 → 2:1) to afford acid **31** as a white solid (540 mg, 69%). M.p. 39–40°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.51$ (brs, 1H), 6.98–6.91 (m, 1H), 5.86 (d, $J = 15.6$ Hz, 1H), 3.71 (s, 3H), 2.52–2.51 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.0$, 166.8, 146.6, 121.9, 51.5, 32.1, 26.8 ppm; IR (film): $\tilde{\nu} = 3007$, 2956, 2626, 1713, 1700, 1660, 1319, 1157 cm^{-1}; MS (EI): *m/z* (%): 158 (0.2) [M^+], 140 (34), 127 (32), 113 (18), 108 (100), 99 (29), 81 (75), 45 (22); HRMS (CI): *m/z:* calcd for $C_7H_{11}O_4$ [M^++H]: 159.0657, found: 159.0655.

Compound 34: Et_3N (60 μL, 0.43 mmol) and 2,4,6-trichlorobenzoyl chloride (25 μL, 0.16 mmol) were successively added to a solution of acid **31** (25 mg, 0.16 mmol) in toluene (1.3 mL) and the resulting mixture was stirred for 1 h at ambient temperature. A solution of alcohol **32** (47 mg, 0.14 mmol) in toluene (1.3 mL) was introduced, followed by DMAP (18 mg, 0.14 mmol), and stirring was continued for 1 h. The mixture was filtered through a pad of Celite, which was carefully rinsed with toluene. The combined filtrates were concentrated and the residue was purified by flash chromatography (hexanes/ethyl acetate 10:1 + 1% Et_3N) to give ester **34** as a colorless oil (58 mg, 86%). $[\alpha]_D^{20} = 5.9$ ($c = 0.95$, CH_3OH); ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 6.94$ (dt, $J = 15.7$, 6.4 Hz, 1H), 6.05 (dd, $J = 10.0$, 1.5 Hz, 1H), 5.86 (dt, $J = 15.7$, 1.5 Hz, 1H), 5.08–5.03 (m, 1H), 3.93–3.82 (m, 4H), 3.69 (s, 3H), 2.72–2.60 (m, 1H), 2.56–2.41 (m, 4H), 2.40 (d, $J = 1.5$ Hz, 3H), 1.89 (dd, $J = 14.9$, 8.0 Hz, 1H), 1.77 (dd, $J = 14.9$, 3.3 Hz, 1H), 1.27 (s, 3H), 0.94 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta = 172.2$, 167.1, 147.7, 142.3, 122.2, 109.2, 95.9, 73.0, 65.1, 65.0, 51.8, 41.2, 40.4, 33.2, 28.4, 27.8, 24.5, 16.6 ppm; IR (film): $\tilde{\nu} = 2976$, 1726, 1659, 1267, 1152 cm^{-1}; MS (EI): *m/z* (%): 451 (0.5) [M^+–Me], 293 (5), 185 (7), 113 (11), 109 (7), 87 (100); HRMS (ESI): *m/z*: calcd for $C_{18}H_{27}O_6INa$ [M^++Na]: 489.0745, found: 489.0749; elemental analysis calcd (%) for $C_{18}H_{27}O_6I$: C 46.36, H 5.84; found: C 46.28, H 5.76.

Compound 33: Prepared analogously from acid **29** (19 mg, 0.11 mmol) and alcohol **32** (30 mg, 92 μmol) as a colorless oil (41 mg, 92%). $[\alpha]_D^{20} =$ −1.4 ($c = 0.9$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.25$ (dd, $J = 9.9$, 1.5 Hz, 1H), 5.30–5.26 (m, 1H), 3.61–3.44 (m, 4H), 3.36 (s, 3H), 2.51 (ddd, $J = 9.9$, 6.9, 4.3 Hz, 1H), 2.20 (d, $J = 1.5$ Hz, 3H), 2.14–2.09 (m, 3H), 2.00–1.94 (m, 3H), 1.76 (dd, $J = 14.9$, 3.3 Hz, 1H), 1.71–1.62 (m, 1H), 1.48–1.39 (m, 1H), 1.27 (s, 3H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.82 ppm

(d, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=173.2$, 171.8, 142.3, 109.0, 95.6, 72.2, 64.6, 64.6, 51.0, 41.7, 41.3, 40.2, 31.8 (2C), 30.0, 28.0, 24.5, 19.5, 16.4 ppm; IR (film): $\tilde{\nu}=2960$, 2879, 1732, 1258, 1154, 1041 cm^{-1}; MS (EI): *m/z* (%): 482 (0.2) [M^+], 380 (0.3), 293 (9), 201 (4), 157 (47), 125 (37), 97 (6), 87 (100); HRMS (ESI): *m/z*: calcd for $C_{19}H_{31}O_6INa$ [M^++Na]: 505.1058, found: 505.1059.

Compound 35: Prepared analogously from acid **28** (43 mg, 0.25 mmol) and alcohol **27** (65 mg, 0.21 mmol) as a colorless oil (88 mg, 91%). $[\alpha]_D^{20}=-0.24$ ($c=3.6$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta=6.90$ (dd, $J=15.7$, 7.1 Hz, 1H), 6.13 (tq, $J=7.5$, 1.4 Hz, 1H), 5.83 (dd, $J=15.7$, 1.4 Hz, 1H), 5.14–5.08 (m, 1H), 3.92–3.85 (m, 4H), 3.70 (s, 3H), 2.88–2.77 (m, 1H), 2.39 (dd, $J=15.4$, 6.8 Hz, 1H), 2.37 (d, $J=1.5$ Hz, 3H), 2.29 (dd, $J=15.4$, 7.3 Hz, 1H), 2.33–2.30 (m, 2H), 1.96 (dd, $J=14.8$, 7.3 Hz, 1H), 1.82 (dd, $J=14.8$, 4.4 Hz, 1H), 1.29 (s, 3H), 1.12 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta=171.4$, 167.3, 152.7, 136.7, 120.5, 109.0, 96.8, 69.9, 65.1, 65.0, 51.9, 42.6, 41.1, 36.4, 33.5, 28.2, 24.6, 19.5 ppm; IR (film): $\tilde{\nu}=2955$, 1725, 1656, 1272, 1153, 1053 cm^{-1}; MS (EI): *m/z* (%): 451 (0.8) [M^+−Me], 364 (2), 294 (4), 279 (9), 210 (5), 155 (1), 123 (6), 87 (100); HRMS (ESI): *m/z:* calcd for $C_{18}H_{27}O_6INa$ [M^++Na]: 489.0745, found: 489.0747; elemental analysis calcd (%) for $C_{18}H_{27}O_6I$: C 46.36, H 5.84; found: C 46.30, H 5.78.

Compound 36: Prepared analogously from acid **31** (36 mg, 0.23 mmol) and alcohol **27** (59 mg, 0.19 mmol) as a colorless oil (74 mg, 85%). $[\alpha]_D^{20}=-14.1$ ($c=2.5$, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta=6.94$ (dt, $J=15.7$, 6.4 Hz, 1H), 6.14 (dt, $J=7.6$, 1.5 Hz, 1H), 5.86 (dt, $J=15.7$, 1.6 Hz, 1H), 5.15–5.09 (m, 1H), 3.93–3.83 (m, 4H), 3.69 (s, 3H), 2.54–2.48 (m, 2H), 2.44 (dd, $J=6.5$, 1.0 Hz, 1H), 2.42 (dd, $J=6.5$, 2.0 Hz, 1H), 2.37 (d, 3H, $J=1.4$ Hz), 2.33–2.30 (m, 2H), 1.96 (dd, $J=14.8$, 7.5 Hz, 1H), 1.82 (dd, $J=14.8$, 4.2 Hz, 1H), 1.29 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.0$, 167.1, 147.6, 136.6, 122.3, 109.1, 96.8, 69.9, 65.1, 65.1, 51.8, 42.6, 36.4, 33.3, 28.2, 27.8, 24.6 ppm; IR (film): $\tilde{\nu}=2949$, 1724, 1659, 1267, 1151, 1041 cm^{-1}; MS (EI): *m/z* (%): 437 (0.8) [M^+−Me], 350 (2), 294 (4), 279 (9), 210 (6), 171 (3), 141 (1), 109 (5), 87 (100); HRMS (ESI): *m/z:* calcd for $C_{17}H_{25}O_6INa$ [M^++Na]: 475.0588, found: 475.0590; elemental analysis calcd (%) for $C_{17}H_{25}O_6I$: C 45.14, H 5.57, found: C 45.19, H 5.64.

9-MeO-9-BBN-mediated Suzuki coupling reactions

Compound 39: A solution of *t*BuLi (2.2 M in pentane, 180 μL, 0.39 mmol) was added to a mixture of Et_2O (90 μL) and THF (90 μL) at −78 °C before a solution of iodide **19** (30 mg, 71 μmol) in THF (520 μL) was added dropwise. The mixture was stirred for 5 min at this temperature before 9-MeO-9-BBN (53 μL, 0.39 mmol) was added causing an immediate color change from bright yellow to colorless. Stirring was continued for 5 min at −78 °C and for 1 h at ambient temperature, leading to the formation of a white precipitate. Aq. K_3PO_4 (3 M, 130 μL, 0.39 mmol) was added followed by a solution of vinyl iodide **37** (35 mg, 65 μmol) in DMF (520 μL) and a suspension of [(dppf)$PdCl_2$]·CH_2Cl_2 (2.4 mg, 3.2 μmol) and $AsPh_3$ (2.0 mg, 6.4 μmol) in DMF (100 μL). The resulting mixture was stirred for 90 min at ambient temperature before it was diluted with hexanes/ethyl acetate 10:1 (2.0 mL) and filtered through a pad of basic alumina, which was carefully rinsed (hexanes/ethyl acetate 10:1). The combined filtrates were washed with aq. sat. $NaHCO_3$, water, and brine, before they were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 15:1 + 1% Et_3N) to give compound **39** which contained traces of boron-containing impurities. This material was used in the next step without further purification; MS (EI): *m/z* (%): 690 (0.5) [M^+], 361 (1), 329 (22), 207 (6), 151 (100); HRMS (ESI): *m/z*: calcd for $C_{38}H_{62}O_9SiNa$ [M^++Na]: 713.4055, found: 713.4060.

Compound 44: Prepared analogously from alkyl iodide **19** (43 mg, 0.10 mmol) and vinyl iodide **43** (45 mg, 0.1 mmol) as a colorless oil (41 mg, 68%). $[\alpha]_D^{20}=-20.0$ ($c=1.0$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta=6.91$ (dd, $J=15.8$, 7.1 Hz, 1H), 6.87–6.82 (m, 3H), 5.82 (dd, $J=15.8$, 1.4 Hz, 1H), 5.07–5.03 (m, 1H), 5.01 (dd, $J=9.4$, 1.1 Hz, 1H), 4.43 (d, $J=11.4$ Hz, 1H), 4.37 (d, $J=11.4$ Hz, 1H), 3.90–3.76 (m, 6H), 3.82 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 2.88–2.78 (m, 1H), 2.65–2.56 (m, 1H), 2.39 (dd, $J=15.4$, 6.8 Hz, 1H), 2.28 (dd, $J=15.4$, 7.4 Hz, 1H), 2.13–2.06 (m, 1H), 2.04–1.98 (m, 1H), 1.94 (dd, $J=13.0$, 7.0 Hz, 1H), 1.88–1.82 (m, 2H), 1.75 (dd, $J=15.0$, 2.7 Hz, 1H), 1.63 (d, $J=1.2$ Hz, 3H), 1.65–1.55 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.11 (d, $J=6.8$ Hz, 3H), 0.88 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta=171.7$, 167.4, 153.0, 149.7, 149.3, 137.2, 131.7, 125.8, 120.6, 120.3, 112.0, 111.8, 109.5, 84.8, 83.0, 80.6, 74.0, 71.9, 65.0, 64.9, 56.4, 56.3, 51.8, 44.8, 41.2, 40.6, 37.4, 36.5, 34.1, 33.5, 30.4, 28.5, 24.5, 19.4, 16.9, 16.7 ppm; IR (film): $\tilde{\nu}=2967$, 2933, 1727, 1657, 1517, 1453, 1266, 1158 cm^{-1}; MS (EI): *m/z* (%): 646 (4) [M^+], 474 (5), 151 (100); HRMS (ESI): *m/z*: calcd for $C_{36}H_{54}O_{10}Na$ [M^++Na]: 669.3609, found: 669.3611.

Compound 47: Prepared analogously from alkyl iodide **19** (53 mg, 0.13 mmol) and vinyl iodide **36** (57 mg, 0.13 mmol) as a colorless oil (52 mg, 67%). $[\alpha]_D^{20}=-35.3$ ($c=0.9$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta=6.96$ (dt, $J=15.7$, 6.4 Hz, 1H), 6.92 (d, $J=1.8$ Hz, 1H), 6.89 (dd, $J=8.0$, 1.9 Hz, 1H), 6.67 (d, $J=8.0$ Hz, 1H), 5.81 (dt, $J=15.7$, 1.5 Hz, 1H), 5.48–5.42 (m, 1H), 5.32 (dt, $J=7.2$, 1.0 Hz, 1H), 4.40 (d, $J=11.6$ Hz, 1H), 4.32 (d, $J=4.32$ Hz, 1H), 4.16 (dt, $J=7.6$, 4.9 Hz, 1H), 3.74 (dt, $J=7.2$, 4.2 Hz, 1H), 3.62–3.48 (m, 4H), 3.53 (s, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 2.34–2.11 (m, 8H), 2.05 (dd, $J=14.8$, 8.0 Hz, 1H), 1.89 (dd, $J=14.8$, 3.4 Hz, 1H), 1.82 (dd, $J=12.9$, 3.9 Hz, 1H), 1.78–1.68 ppm (m, 3H), 1.58 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=171.3$, 166.4, 150.4, 150.0, 147.3, 138.3, 131.7, 122.1, 120.4, 119.7, 112.5, 112.3, 109.1, 84.7, 82.7, 80.1, 71.7, 70.7, 64.6 (2C), 55.8, 55.8, 50.9, 44.8, 42.9, 36.5, 34.3, 34.1, 33.0, 30.3, 28.4, 27.5, 24.6, 16.5 ppm; IR (film): $\tilde{\nu}=2934$, 1725, 1659, 1593, 1516, 1263, 1155, 1030 cm^{-1}; MS (EI): *m/z* (%): 618 (5) [M^+], 573 (2), 460 (2), 207 (3), 151 (100), 112 (42), 87 (75); HRMS (ESI): *m/z:* calcd for $C_{34}H_{50}O_{10}Na$ [M^++Na]: 641.3296, found: 641.3299.

Compound 52: Prepared analogously from alkyl iodide **50** (60 mg, 0.14 mmol) and vinyl iodide **35** (67 mg, 0.14 mmol) as a colorless oil (71 mg, 79%). $[\alpha]_D^{20}=-32.3$ ($c=1.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta=7.24$ (d, $J=8.4$ Hz, 2H), 6.90 (dd, $J=15.8$, 8.7 Hz, 1H), 6.87 (d, $J=8.4$ Hz, 2H), 5.81 (dd, $J=15.8$, 1.3 Hz, 1H), 5.14–5.06 (m, 2H), 4.43 (d, $J=11.2$ Hz, 1H), 4.36 (d, $J=11.2$ Hz, 1H), 3.90–3.82 (m, 5H), 3.79 (s, 3H), 3.75–3.71 (m, 1H), 3.69 (s, 3H), 2.85–2.78 (m, 1H), 2.37 (dd, $J=15.4$, 6.7 Hz, 1H), 2.29–2.23 (m, 3H), 2.12–1.90 (m, 3H), 1.92 (dd, $J=15.4$, 7.8 Hz, 1H), 1.83 (dd, $J=14.8$, 3.5 Hz, 1H), 1.77 (dd, $J=13.1$, 3.8 Hz, 1H), 1.60 (s, 3H), 1.60–1.30 (m, 6H), 1.28 (s, 3H), 1.26 (s, 3H), 1.10 (d, $J=6.8$ Hz, 3H), 0.91 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta=171.5$, 167.4, 159.8, 152.9, 138.8, 131.3, 129.8, 120.3, 119.4, 114.2, 109.3, 84.7, 83.0, 82.6, 71.7, 71.2, 65.0, 65.0, 55.8, 51.8, 45.9, 43.1, 42.6, 41.2, 36.5, 34.3, 33.9, 33.5, 26.6, 24.6, 19.4, 18.4, 16.7, 15.1 ppm; IR (film): $\tilde{\nu}=2960$, 2932, 1726, 1656, 1613, 1514, 1248, 1173, 1036 cm^{-1}; MS (EI): *m/z* (%): 630 (0.3) [M^+], 140 (41), 121 (100), 87 (83); HRMS (ESI): *m/z:* calcd for $C_{36}H_{54}O_9Na$ [M^++Na]: 653.3660, found: 653.3662.

Compound 55: Prepared analogously from **50** (48 mg, 0.12 mmol) and vinyl iodide **34** (54 mg, 0.12 mmol) as a colorless oil (46 mg, 63%). $[\alpha]_D^{20}=-26.8$ ($c=1.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta=7.25$ (d, $J=8.7$ Hz, 2H), 6.95 (dt, $J=15.7$, 6.4 Hz, 1H), 6.87 (d, $J=8.7$ Hz, 2H), 5.85 (dt, $J=15.7$, 1.6 Hz, 1H), 5.07 (ddd, $J=8.5$, 4.5, 2.6 Hz, 1H), 5.01 (dd, $J=9.4$, 1.3 Hz, 1H), 4.44 (d, $J=11.2$ Hz, 1H), 4.36 (d, $J=11.2$ Hz, 1H), 3.91–3.81 (m, 5H), 3.79 (s, 3H), 3.75–3.71 (m, 1H), 3.69 (s, 3H), 2.65–2.56 (m, 1H), 2.53–2.47 (m, 2H), 2.47–2.40 (m, 2H), 2.13–1.94 (m, 2H), 1.97 (dd, $J=13.1$, 7.3 Hz, 1H), 1.87 (dd, $J=15.0$, 8.6 Hz, 1H), 1.79–1.74 (m, 2H), 1.64 (d, $J=1.3$ Hz, 3H), 1.62–1.49 (m, 2H), 1.48–1.42 (m, 2H), 1.40–1.30 (m, 2H), 1.27 (s, 3H), 1.26 (s, 3H), 0.92 (t, $J=7.2$ Hz, 3H), 0.90 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta=172.2$, 167.2, 159.8, 147.867, 137.3, 131.3, 129.8, 125.8, 122.2, 114.2, 109.5, 84.7, 83.0, 82.5, 74.1, 71.7, 65.1, 64.9, 55.8, 51.8, 45.9, 43.1, 40.7, 37.5, 36.5, 34.0, 33.4, 27.9, 26.6, 24.5, 18.4, 17.0, 16.8, 15.1 ppm; IR (film): $\tilde{\nu}=2959$, 2932, 1726, 1660, 1514, 1248, 1267, 1152 cm^{-1}; MS (EI): *m/z* (%): 615 (0.2) [M^+−Me], 140 (39), 121 (100), 87 (56); HRMS (ESI): *m/z*: calcd for $C_{36}H_{54}O_9Na$ [M^++Na]: 653.3660, found: 653.3665.

Compound 58: Prepared analogously from alkyl iodide **50** (38 mg, 91 μmol) and vinyl iodide **33** (40 mg, 83 μmol) as a colorless oil (39 mg, 73%). $[\alpha]_D^{20}=-25.2$ ($c=1.9$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.25$ (d, $J=8.6$ Hz, 2H), 6.84 (d, $J=8.6$ Hz, 2H), 5.43 (ddd, $J=7.1$, 4.4, 2.6 Hz, 1H), 5.28 (dd, $J=9.3$, 1.0 Hz, 1H), 4.36 (d, $J=11.5$ Hz, 1H), 4.29 (d, $J=$

11.5 Hz, 1H), 4.14 (dt, J=7.4, 5.0 Hz, 1H), 3.70–3.61 (m, 3H), 3.56–3.49 (m, 2H), 3.35 (s, 3H), 3.34 (s, 3H), 2.77–2.69 (m, 1H), 2.34–1.98 (m, 8H), 1.91 (dd, J=14.9, 2.5 Hz, 1H), 1.80–1.57 (m, 3H), 1.79 (dd, J=13.0, 7.3 Hz, 1H), 1.72 (dd, J=13.0, 4.1 Hz, 1H), 1.66 (d, J=1.2 Hz, 3H), 1.51–1.33 (m, 5H), 1.38 (s, 3H), 1.35 (s, 3H), 1.01 (d, J=6.9 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H), 0.86 ppm (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ=173.3, 171.9, 159.8, 136.9, 131.2, 129.4, 126.2, 114.2, 109.4, 84.5, 82.4, 82.2, 73.2, 71.5, 64.6, 64.6, 54.9, 51.0, 45.7, 43.2, 41.9, 41.0, 37.4, 36.5, 33.9, 31.9, 31.9, 30.0, 26.4, 24.6, 19.5, 18.2, 17.0, 16.6, 15.0 ppm; IR (film): $\tilde{\nu}$=2959, 2932, 1734, 1514, 1452, 1249, 1171 cm^{-1}; MS (EI): m/z (%): 646 (0.3) [M^+], 472 (6), 370 (4), 157 (11), 140 (36), 121 (100); HRMS (ESI): m/z: calcd for $C_{37}H_{58}O_9Na$ [M^++Na]: 669.3973, found: 669.3969.

Preparation of the *seco*-acids

Compound 40: DDQ (28 mg, 120 μmol) was added in portions to a vigorously stirred solution of **39** in CH_2Cl_2 (1.4 mL) and aq. phosphate buffer solution (pH 7, 1.4 mL) at 0°C and the resulting mixture was stirred for 3 h at this temperature. CH_2Cl_2 (3.0 mL) was introduced and the reaction quenched with aq. sat. $NaHCO_3$ (2.5 mL). The aqueous phase was repeatedly extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 25:1 + 1% Et_3N → 5:1 + 1% Et_3N) to give compound **40** as a colorless oil (11 mg, 45% over two steps). $[\alpha]_D^{20}$=−36.5 (c=0.84, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 7.00 (dd, J=15.8, 7.2 Hz, 1H), 5.74 (dd, J=15.8, 1.3 Hz, 1H), 5.10 (dd, J=9.3, 1.2 Hz, 1H), 4.12–4.07 (m, 1H), 3.94–3.88 (m, 1H), 3.74–3.68 (m, 1H), 3.68 (s, 3H), 3.14 (s, 3H), 2.70–2.60 (m, 1H), 2.45 (d, J=4.5 Hz, 1H), 2.41–2.31 (m, 1H), 2.18–2.04 (m, 2H), 1.99 (dd, J=13.0, 7.2 Hz, 1H), 1.94 (dd, J=12.8, 5.7 Hz, 1H), 1.84–1.72 (m, 4H), 1.70–1.54 (m, 2H), 1.63 (d, J=1.3 Hz, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.07 (d, J=6.9 Hz, 3H), 0.83 (d, J=6.8 Hz, 3H), 0.19 ppm (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=168.1, 157.3, 134.7, 129.3, 118.6, 110.7, 85.8, 85.3, 82.8, 80.3, 76.9, 51.7, 48.7, 47.6, 44.2, 39.5, 36.3, 35.8, 32.7, 32.6, 30.6, 29.0, 22.7, 20.4, 17.4, 16.4, 2.5 ppm; IR (film): $\tilde{\nu}$=3454, 2965, 2930, 1726, 1654, 1251, 841 cm^{-1}; MS (EI): m/z (%): 420 (27), 235 (2), 166 (3), 151 (100); HRMS (ESI): m/z: calcd for $C_{29}H_{52}O_7SiNa$ [M^++Na]: 563.3374, found: 563.3371.

Compound 46: LiI (220 mg, 1.6 mmol) was added to a solution of ester **44** (42 mg, 65 μmol) in pyridine (2 mL) and the resulting mixture was stirred for 30 h at 125°C. After cooling to 0°C, the mixture was diluted with CH_2Cl_2 (10 mL) and acidified with aq. HCl (2 M) to pH ≈2. The aqueous phase was repeatedly extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was rapidly passed through a pad of silica (hexanes/ethyl acetate 1:1 + 1% HOAc) and the acid **45** thus formed was used in the next step without further purification.

H_2O (1.0 mL) was added to a solution of **45** in HOAc (1.0 mL) and the resulting mixture was stirred for 30 min at 65°C. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (3 mL) and H_2O (3 mL), the aqueous phase was repeatedly extracted with ethyl acetate, the combined extracts were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 2:1 + 1% HOAc) to afford the corresponding carboxylic acid as a colorless oil (22 mg, 58% over two steps). $[\alpha]_D^{20}$=−30.2 (c=1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=6.99 (dd, J=15.7, 7.2 Hz, 1H), 6.87–6.82 (m, 3H), 5.78 (dd, J=15.7, 1.3 Hz, 1H), 5.21–5.16 (m, 1H), 5.01 (dd, J=9.7, 1.0 Hz, 1H), 4.45 (d, J=11.3 Hz, 1H), 4.37 (d, J= 11.3 Hz, 1H), 3.93–3.87 (m, 1H), 3.83–3.78 (m, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.13–3.07 (m, 1H), 3.13–3.07 (m, 1H), 2.87–2.78 (m, 1H), 2.68–2.49 (m, 3H), 2.53 (dd, J=16.8, 5.0 Hz, 1H), 2.36 (d, J=6.9 Hz, 1H), 2.14–2.01 (m, 1H), 2.08 (s, 3H), 1.97 (dd, J=13.0, 7.0 Hz, 1H), 1.88 (dd, J= 13.0, 4.0 Hz, 1H), 1.68–1.56 (m, 2H), 1.59 (d, J=1.3 Hz, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 1.11 (d, J=6.8 Hz, 3H), 0.91 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=206.4, 177.6, 171.5, 155.1, 149.7, 149.4, 137.8, 132.0, 125.4, 120.7, 120.3, 112.0, 111.8, 84.6, 83.0, 81.1, 74.0, 71.9, 56.4, 56.3, 45.8, 44.7, 41.1, 36.4, 36.2, 33.8, 30.7, 30.2, 28.5, 21.1, 19.2, 17.1, 16.7 ppm; IR (film): $\tilde{\nu}$=3422, 2968, 2933, 1716, 1654, 1515, 1260, 1157 cm^{-1}; MS (EI): m/z (%): 588 (<0.5) [M^+], 430 (8), 151 (100); HRMS (ESI): m/z: calcd for $C_{33}H_{48}O_9Na$ [M^++Na]: 611.3191, found: 611.3196.

An aqueous phosphate buffer solution (pH 7, 0.85 mL) was added to a solution of this carboxylic acid (20 mg, 34 μmol) in CH_2Cl_2 (1.0 mL) before DDQ (23 mg, 0.10 mmol) was introduced in portions at 0°C. The resulting mixture was vigorously stirred for 5 h before it was diluted with water (2.5 mL) and CH_2Cl_2 (3 mL). The aqueous layer was repeatedly extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 2:1 + 1% HOAc → 1:1 + 1% HOAc) to afford **46** as a colorless oil (12 mg, 81%). $[\alpha]_D^{20}$=−25.8 (c=0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.98 (dd, J=15.7, 7.4 Hz, 1H), 5.80 (d, J=15.7 Hz, 1H), 5.36–5.22 (m, 1H), 5.93 (d, J=9.3 Hz, 1H), 4.72 (brs, 2H), 4.12–4.08 (m, 1H), 3.83–3.73 (m, 1H), 3.14–3.01 (m, 1H), 2.86–2.79 (m, 1H), 2.67–2.31 (m, 4H), 2.15–2.06 (m, 3H), 2.12 (s, 3H), 1.83–1.79 (m, 1H), 1.70–1.57 (m, 2H), 1.59 (d, J=0.8 Hz, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.12 (d, J=6.8 Hz, 3H), 0.92 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.9, 171.1, 169.2, 153.8, 136.8, 125.1, 120.3, 84.1, 84.0, 80.5, 73.7, 47.3, 46.0, 41.0, 35.9, 35.6, 33.3, 32.3, 30.3, 30.2, 28.7, 19.2, 17.4, 16.3 ppm; IR (film): $\tilde{\nu}$=3384, 2969, 2933, 1715, 1652 cm^{-1}; MS (EI): m/z (%): 438 (< 0.5) [M^+], 280 (10), 128 (76), 97 (30), 71 (40), 55 (22), 43 (100); HRMS (ESI): m/z: calcd for $C_{24}H_{38}O_7Na$ [M^++Na]: 461.2510, found: 461.2510.

Compound 48: Prepared analogously from ester **47** (43 mg, 70 μmol) as a colorless oil (22 mg, 56% over two steps). $[\alpha]_D^{20}$=−40.9 (c=1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=7.00 (dt, J=15.7, 6.5 Hz, 1H), 6.87–6.82 (m, 3H), 5.83 (dt, J=15.7, 1.5 Hz, 1H), 5.26–5.20 (m, 1H), 5.12 (dt, J= 7.4, 1.1 Hz, 1H), 4.45 (d, J=11.4 Hz, 1H), 4.37 (d, J=11.4 Hz, 1H), 3.92–3.77 (m, 2H), 3.82 (s, 3H), 3.82 (s, 3H), 2.70 (dd, J=16.7, 7.7 Hz, 1H), 2.60 (dd, J=16.7, 5.0 Hz, 1H), 2.53–2.23 (m, 6H), 2.13–1.99 (m, 2H), 2.01 (s, 3H), 1.95 (dd, J=13.0, 6.9 Hz, 1H), 1.87 (dd, J=13.0, 4.0 Hz, 1H), 1.66–1.53 (m, 2H), 1.60 (s, 3H), 1.32 (s, 3H), 1.25 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=206.1, 172.0, 170.321, 149.8, 149.7, 149.4, 139., 131.7, 122.1, 120.8, 118.8, 112.1, 111.9, 84.6, 83.0, 81.0, 72.0, 70.959, 56.4, 56.3, 47.5, 44.8, 36.4, 33.8, 33.1, 32.9, 30.7, 30.3, 28.6, 28.0, 16.6 ppm; IR (film): $\tilde{\nu}$=2968, 2934, 1716, 1656, 1593, 1515, 1420, 1260, 1156 cm^{-1}; MS (EI): m/z (%): 560 (<0.4) [M^+], 416 (6), 151 (100).

Compound 49: Prepared analogously from compound **48** (20 mg, 36 μmol) as a colorless oil (12 mg, 82%). $[\alpha]_D^{20}$=−30.7 (c=1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=7.00 (dt, J=15.7, 6.4 Hz, 1H), 5.83 (dt, J=15.7, 1.5 Hz, 1H), 5.28–5.22 (m, 1H), 5.13 (dt, J=15.7, 1.2 Hz, 1H), 4.53 (brs, 1H), 4.05 (dt, J=7.3, 5.2 Hz, 1H), 3.71 (dt, J=7.3, 5.2 Hz, 1H), 2.72 (dd, J=16.7, 7.6 Hz, 1H), 2.61 (dd, J=16.7, 5.2 Hz, 1H), 2.53–2.42 (m, 4H), 2.31–2.28 (m, 2H), 2.17–2.01 (m, 3H), 2.12 (s, 3H), 1.76 (dd, J=12.9, 5.1 Hz, 1H), 1.68–1.53 (m, 2H), 1.61 (s, 3H), 1.32 (s, 3H), 1.24 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=206.1, 172.1 (2C), 149.4, 139.2, 122.2, 119.1, 84.9, 80.6, 77.4, 71.0, 47.9, 47.7, 36.4, 33.3, 33.0, 33.0, 30.8, 30.5, 29.1, 28.0, 16.6 ppm; IR (film): $\tilde{\nu}$=3413, 2972, 2930, 1716, 1655, 1159 cm^{-1}; MS (EI): m/z (%): 410 (<0.4) [M^+], 266 (11), 248 (3), 205 (5), 181 (7), 163 (8), 115 (6), 145 (8), 137 (8), 128 (100); HRMS (ESI): m/z: calcd for $C_{22}H_{34}O_7Na$ [M^++Na]: 433.2197, found: 433.2197.

Compound 53: Prepared analogously from ester **52** (59 mg, 94 μmol) as a colorless oil (29 mg, 54% over two steps). $[\alpha]_D^{20}$=−33.3 (c=1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=7.25 (d, J=8.7 Hz, 2H), 6.94 (dd, J= 15.7, 7.4 Hz, 1H), 6.87 (d, J=8.7 Hz, 2H), 5.73 (dd, J=15.7, 1.3 Hz, 1H), 5.25–5.19 (m, 1H), 5.12–5.09 (m, 1H), 4.44 (d, J=11.3 Hz, 1H), 4.36 (d, J=11.3 Hz, 1H), 3.91–3.85 (m, 1H), 3.79 (s, 3H), 3.76–3.72 (m, 1H), 2.86–2.79 (m, 1H), 2.69 (dd, J=16.7, 7.7 Hz, 1H), 2.58 (dd, J=16.7, 5.1 Hz, 1H), 2.34–2.24 (m, 3H), 2.13–2.01 (m, 3H), 2.10 (s, 3H), 1.99 (dd, J=13.1, 7.3 Hz, 1H), 1.79 (dd, J=13.1, 4.0 Hz, 1H), 1.65–1.25 (m, 6H), 1.60 (s, 3H), 1.28 (s, 3H), 1.11 (d, J=6.8 Hz, 3H), 0.91 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=206.0, 171.5, 170.0, 159.9, 154.3, 139.3, 131.2, 129.8, 120.5, 118.9, 114.3, 84.4, 83.6, 82.5, 71.7, 70.9, 55.8, 47.5, 45.8, 43.0, 41.2, 36.3, 34.0, 33.5, 32.9, 30.7, 26.6, 19.4, 18.5, 16.6, 15.0 ppm; IR (film): $\tilde{\nu}$=3150, 2959, 2931, 1718, 1698, 1656, 1613, 1513, 1455, 1247 cm^{-1}; MS (EI): m/z (%): 414 (3), 190 (2), 140 (17), 121 (100); HRMS (ESI): m/z: calcd for $C_{33}H_{48}O_8Na$ [M^++Na]: 595.3241, found: 595.3238.

Compound 54: Prepared analogously from compound **53** (25 mg, 44 μmol) as a colorless oil (14 mg, 71 %). $[\alpha]_D^{20} = -31.6$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 6.91$ (dd, $J = 15.7$, 7.7 Hz, 1H), 5.79 (dd, $J = 15.7$, 1.2 Hz, 1H), 5.28–5.22 (m, 1H), 5.14–5.10 (m, 1H), 4.01 (dt, $J = 7.4$, 5.1 Hz, 1H), 3.74 (dt, $J = 7.7$, 4.9 Hz, 1H), 2.87–2.80 (m, 1H), 2.71 (dd, $J = 16.7$, 7.5 Hz, 1H), 2.58 (dd, $J = 16.7$, 5.4 Hz, 1H), 2.40–2.27 (m, 4H), 2.15–2.06 (m, 3H), 2.11 (s, 3H), 1.69 (dd, $J = 13.1$, 5.0 Hz, 1H), 1.66–1.42 (m, 4H), 1.60 (s, 3H), 1.37–1.27 (m, 3H), 1.30 (s, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.91 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 206.2$, 171.8 (2C), 154.2, 139.1, 120.9, 119.4, 84.5, 83.6, 77.4, 71.0, 47.8, 46.4, 46.2, 41.6, 36.5, 34.3, 33.1, 32.9, 30.9, 27.3, 19.8, 18.6, 16.7, 15.2 ppm; IR (film): $\tilde{\nu} = 3439$, 2964, 2930, 1717, 1654, 1264 cm^{-1}; MS (EI): *m/z* (%): 452 (0.7) [M^+], 294 (16), 233 (6), 181 (8), 163 (10), 156 (89), 122 (30), 95 (53), 84 (56), 71 (52), 55 (30), 43 (100); HRMS (ESI): *m/z:* calcd for $C_{25}H_{40}O_7Na$ [M^++Na]: 475.2666, found: 475.2664.

Compound 56: Prepared analogously from ester **55** (35 mg, 55 μmol) as a colorless oil (25 mg, 52% over two steps). $[\alpha]_D^{20} = -28.3$ ($c = 0.95$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.25$ (d, $J = 8.6$ Hz, 2H), 7.02 (dt, $J = 15.7$, 6.4 Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.83 (dt, $J = 15.7$, 1.5 Hz, 1H), 5.22–5.18 (m, 1H), 5.01 (dd, $J = 9.4$, 0.8 Hz, 1H), 4.44 (d, $J = 11.2$ Hz, 1H), 4.36 (d, $J = 11.2$ Hz, 1H), 3.93–3.83 (m, 1H), 3.79 (s, 3H), 3.77–3.72 (m, 1H), 3.69 (s, 3H), 2.70–2.41 (m, 6H), 2.12–1.96 (m, 2H), 2.08 (s, 3H), 1.78 (dd, $J = 13.0$, 4.0 Hz, 1H), 1.61 (d, $J = 1.2$ Hz, 3H), 1.66–1.44 (m, 4H), 1.38–1.26 (m, 2H), 1.27 (s, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.92 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 206.3$, 172.1, 170.2, 159.9, 149.9, 137.9, 131.2, 129.8, 125.4, 122.0, 114.3, 84.5, 83.4, 82.5, 74.0, 71.8, 55.8, 45.9, 45.8, 43.0, 36.5, 36.3, 33.7, 33.2, 30.7, 28.1, 26.5, 18.5, 17.2, 16.7, 15.0 ppm; IR (film): $\tilde{\nu} = 2959$, 2933, 1720, 1654, 1514, 1248, 1267, 1172 cm^{-1}; MS (EI): *m/z* (%): 428 (3), 140 (24), 121 (100); HRMS (ESI): *m/z*: calcd for $C_{33}H_{48}O_8Na$ [M^++Na]: 595.3241, found: 595.3238.

Compound 57: Prepared analogously from compound **56** (22 mg, 38 μmol) as a colorless oil (14 mg, 81 %). $[\alpha]_D^{20} = -28.2$ ($c = 0.9$, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.02$ (dt, $J = 15.7$, 6.4 Hz, 1H), 5.84 (dt, $J = 15.7$, 1.3 Hz, 1H), 5.22–5.18 (m, 1H), 5.02 (dd, $J = 9.7$, 1.0 Hz, 1H), 4.04–3.96 (m, 1H), 3.72–3.68 (m, 1H), 2.69–2.42 (m, 7H), 2.17–2.01 (m, 3H), 2.10 (s, 3H), 1.69–1.55 (m, 4H), 1.62 (d, $J = 1.1$ Hz, 3H), 1.48–1.27 (m, 5H), 1.28 (s, 3H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.91 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 206.4$, 172.2, 169.9, 149.8, 137.7, 125.6, 122.2, 84.2, 82.9, 77.2, 74.2, 46.2, 46.2, 45.9, 36.5, 36.4, 33.3, 32.9, 30.7, 28.0, 27.1, 18.4, 17.4, 16.7, 15.0 ppm; IR (film): $\tilde{\nu} = 2961$, 2932, 1715, 1656, 1256, 1154 cm^{-1}; MS (EI): *m/z* (%): 452 (<0.9) [M^+], 308 (20), 247 (6), 211 (7), 177 (9), 156 (100); HRMS (ESI): *m/z*: calcd for $C_{25}H_{40}O_7Na$ [M^++Na]: 475.2666, found: 475.2672.

Compound 59: Prepared analogously from ester **58** (37 mg, 57 μmol) as a colorless oil (23 mg, 68% over 2 steps). $[\alpha]_D^{20} = -29.5$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.24$ (d, $J = 8.7$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 5.46–5.42 (m, 1H), 5.21 (dd, $J = 9.6$, 1.1 Hz, 1H), 4.36 (d, $J = 11.5$ Hz, 1H), 4.26 (d, $J = 11.5$ Hz, 1H), 4.17–4.13 (m, 1H), 3.70–3.65 (m, 1H), 3.34 (s, 3H), 2.76 (ddd, $J = 9.6$, 6.9, 4.3 Hz, 1H), 2.49 (dd, $J = 16.3$, 7.7 Hz, 1H), 2.31 (dd, $J = 16.3$, 5.4 Hz, 1H), 2.26–1.87 (m, 7H), 1.82–1.48 (m, 7H), 1.74 (s, 3H), 1.60 (d, $J = 1.2$ Hz, 3H), 1.40–1.31 (m, 4H), 1.37 (s, 3H), 0.96 (d, $J = 6.9$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H), 0.80 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 204.3$, 177.7, 171.7, 159.9, 137.3, 131.0, 129.5, 125.8, 114.2, 84.2, 83.0, 82.2, 73.5, 71.5, 54.9, 45.7, 45.5, 43.0, 41.6, 36.3, 36.1, 33.5, 31.7, 31.6, 30.0, 29.8, 26.3, 19.4, 18.2, 17.2, 16.7, 14.9 ppm; IR (film): $\tilde{\nu} = 3114$, 2961, 2932, 1731, 1711, 1514, 1456, 1248, 1172 cm^{-1}; MS (EI): *m/z* (%): 428 (3), 331 (2), 190 (3), 140 (23), 121 (100); HRMS (ESI): *m/z:* calcd for $C_{34}H_{52}O_8Na$ [M^++Na]: 611.3554, found: 611.3560.

Compound 60: Prepared analogously from compound **59** (22 mg, 37 μmol) as a colorless oil (12.5 mg, 71 %). $[\alpha]_D^{20} = -28.2$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 5.43$ (dt, $J = 7.2$, 5.2 Hz, 1H), 5.29 (br s, 2H), 5.23 (dd, $J = 9.6$, 1.0 Hz, 1H), 3.91–3.85 (m, 2H), 2.75–2.64 (m, 1H), 2.49 (dd, $J = 16.3$, 7.5 Hz, 1H), 2.31 (dd, $J = 16.3$, 5.4 Hz, 1H), 2.25–2.08 (m, 5H), 2.02–1.88 (m, 3H), 1.81–1.57 (m, 4H), 1.75 (s, 3H), 1.59 (d, $J = 1.0$ Hz, 3H), 1.49–1.25 (m, 5H), 1.35 (s, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.87 (t, $J = 7.1$ Hz, 3H), 0.80 ppm (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 204.8$, 177.4, 172.1, 137.4, 125.8, 84.0, 82.6, 77.2, 73.9, 46.4, 46.2, 45.8, 41.9, 36.6, 36.4, 32.9, 32.1, 31.8, 30.1, 30.1, 27.2, 19.7, 18.4, 17.8, 17.1, 15.1 ppm; IR (film): $\tilde{\nu} = 3421$, 2961, 2932, 1723, 1713, 1154 cm^{-1}; MS (EI): *m/z* (%): 308 (17), 247 (5), 211 (5), 177 (7), 156 (87), 137 (13), 107 (35), 101 (27), 84 (59), 71 (37), 55 (47), 43 (100); HRMS (ESI): *m/z:* calcd for $C_{26}H_{44}O_7Na$ [M^++Na]: 491.2979, found: 491.2981.

Yamaguchi lactonizations and elaboration of the analogues

Compound 4: Et_3N (8.6 μL, 62 μmol) and 2,4,6-trichlorobenzoyl chloride (4.8 μL, 31 μmol) were successively added to a solution of acid **46** (9.0 mg, 21 μmol) in THF (600 μL). The mixture was stirred for 1 h at ambient temperature before most of the THF was removed under a flow of Ar. The residue was dissolved in toluene (8.0 mL) and added via syringe pump over 2 h to a solution of DMAP (50 mg, 0.41 mmol) in toluene (30 mL) at ambient temperature. Once the addition was complete, the mixture was stirred for 2 h before the reaction was quenched with aq. sat. NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 7:1) to afford compound **4** as a colorless oil (4.8 mg, 56 %). $[\alpha]_D^{20} = -32.4$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.12$ (dd, $J = 15.8$, 7.2 Hz, 1H), 5.78 (d, $J = 15.8$ Hz, 1H), 5.26–5.19 (m, 2H), 4.96 (d, $J = 10.3$ Hz, 1H), 3.97 (dt, $J = 11.0$, 3.7 Hz, 1H), 2.81–2.66 (m, 2H), 2.69 (dd, $J = 16.1$, 6.0 Hz, 1H), 2.61–2.55 (m, 2H), 2.41 (dd, $J = 13.3$, 6.4 Hz, 1H), 2.20–2.08 (m, 3H), 2.14 (s, 3H), 2.00–1.92 (m, 1H), 1.85 (dd, $J = 13.8$, 1.4 Hz, 1H), 1.55 (s, 3H), 1.60–1.52 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.15 (d, $J = 6.9$ Hz, 3H), 0.92 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.3$, 170.6, 165.7, 153.1, 135.4, 126.1, 120.2, 81.0, 80.4, 78.7, 74.3, 47.2, 45.5, 41.5, 35.6, 35.3, 33.1, 30.6, 30.3, 28.8, 26.4, 18.1, 17.5, 15.4 ppm; IR (film): $\tilde{\nu} = 2966$, 2928, 1735, 1365 cm^{-1}; MS (EI): *m/z* (%): 420 (29) [M^+], 255 (31), 141 (14), 110 (51), 95 (32), 59 (38), 43 (100); HRMS (ESI): *m/z*: calcd for $C_{24}H_{36}O_6Na$ [M^++Na]: 443.2404, found: 443.2407.

Compound 5: Prepared analogously from *seco*-acid **57** (10 mg, 23 μmol) as a colorless oil (5.8 mg, 58 %). $[\alpha]_D^{20} = -29.4$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.12$–7.05 (m, 1H), 5.85 (d, $J = 15.6$ Hz, 1H), 5.23–5.19 (m, 1H), 5.16–5.13 (m, 1H), 4.97 (d, $J = 10.3$ Hz, 1H), 3.94 (dt, $J = 11.0$, 3.7 Hz, 1H), 2.76 (dd, $J = 16.4$, 6.0 Hz, 1H), 2.74–2.66 (m, 1H), 2.58 (dd, $J = 16.4$, 7.2 Hz, 1H), 2.54–2.38 (m, 3H), 2.22–2.08 (m, 3H), 2.14 (s, 3H), 1.95 (tt, $J = 13.1$, 3.3 Hz, 1H), 1.74 (dd, $J = 13.9$, 2.5 Hz, 1H), 1.57–1.30 (m, 6H), 1.55 (s, 3H), 1.28 (s, 3H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.93 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.6$, 172.2, 165.6, 148.1, 135.7, 126.1, 123.0, 83.0, 80.7, 78.5, 74.7, 47.0, 44.4, 43.7, 35.7, 35.5, 34.5, 30.6, 30.5, 28.5, 24.7, 18.2, 17.9, 15.4, 14.7 ppm; IR (film): $\tilde{\nu} = 2960$, 2931, 1719, 1659 cm^{-1}; MS (EI): *m/z* (%): 434 (83) [M^+], 308 (14), 290 (13), 269 (36), 247 (13), 193 (16), 153 (25), 138 (66), 125 (30), 107 (29), 95 (66), 82 (16), 67 (19), 55 (35), 43 (100); HRMS (ESI): *m/z*: calcd for $C_{25}H_{38}O_6Na$ [M^++Na]: 457.2561, found: 457.2557.

Compound 6: Prepared analogously from acid **54** (15 mg, 34 μmol) as a colorless oil (4.8 mg, 32 %). Because of the sensitivity of the product, the flash chromatography should be carried out as fast as possible. $[\alpha]_D^{20} = -35.4$ ($c = 0.8$, C_6H_6); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.00$ (dd, $J = 15.8$, 7.3 Hz, 1H), 5.92 (dd, $J = 15.8$, 1.1 Hz, 1H), 5.47–5.41 (m, 1H), 5.27–5.19 (m, 2H), 4.14 (ddd, $J = 10.4$, 5.3, 3.1 Hz, 1H), 2.50–2.37 (m, 1H), 2.44 (dd, $J = 16.1$, 6.9 Hz, 1H), 2.22–2.19 (m, 2H), 2.14–1.99 (m, 7H), 1.69 (s, 3H), 1.65 (dd, $J = 13.6$, 3.9 Hz, 1H), 1.53–1.25 (m, 5H), 1.38 (s, 3H), 1.23 (s, 3H), 0.85 (t, $J = 7.1$ Hz, 3H), 0.70 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 203.6$, 170.7, 165.2, 151.8, 136.3, 121.3, 121.0, 82.2, 80.3, 78.8, 70.3, 47.5, 44.8, 44.4, 41.0, 35.5, 33.9, 32.5, 31.2, 29.7, 25.4, 19.1, 18.0, 15.5, 14.8 ppm; IR: $\tilde{\nu} = 2961$, 2932, 1717, 1654, 1268 cm^{-1}; MS (EI): *m/z* (%): 434 (62) [M^+], 309 (7), 294 (36), 283 (17), 233 (9), 181 (8), 151 (16), 138 (100), 123 (25), 113 (25), 95 (82), 81 (24), 55 (25), 43 (93); HRMS (ESI): *m/z:* calcd for $C_{25}H_{38}O_6Na$ [M^++Na]: 457.2561, found: 457.2560.

Compound 7: Prepared analogously from *seco*-acid **49** (6.0 mg, 15 μmol) as a colorless oil (0.9 mg, 16 %). Because of the sensitivity of the product, the flash chromatography should be carried out as fast as possible. $[\alpha]_D^{20} = -24$ ($c = 0.3$, C_6H_6); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.96$ (dt, $J = 15.8$, 6.5 Hz, 1H), 5.86 (d, $J = 15.8$ Hz, 1H), 5.37 (dq, $J = 6.4$, 4.2 Hz, 1H), 5.27

(ddd, $J=8.6$, 5.1, 3.7 Hz, 1H), 5.17 (t, $J=6.6$ Hz, 1H), 4.09 (ddd, $J=8.2$, 5.1, 3.1 Hz, 1H), 2.45 (dd, $J=16.2$, 6.6 Hz, 1H), 2.23–2.20 (m, 2H), 2.14–1.92 (m, 9H), 1.72–1.64 (m, 1H), 1.68 (s, 3H), 1.50–1.42 (m, 1H), 1.37 (s, 3H), 1.24 (s, 3H), 1.17 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=$ 203.6, 171.2, 165.0, 147.2, 136.2, 123.1, 121.0, 80.6, 79.9, 78.8, 70.6, 47.3, 45.9, 35.4, 33.4, 32.3, 31.3, 29.7, 29.2, 27.7, 27.1, 15.2 ppm; HRMS (ESI): *m/z:* calcd for $C_{22}H_{32}O_6Na$ [M^++Na]: 415.2091, found: 415.2091.

Compound 8: Prepared analogously from *seco*-acid **60** (10 mg, 21 μmol) as a colorless oil (5.7 mg, 59%). $[\alpha]_D^{20}=-25.2$ ($c=0.8$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.18$ (ddd, $J=7.6$, 5.6, 2.3 Hz, 1H), 5.05 (ddd, $J=$ 7.3, 6.5, 2.9 Hz, 1H), 5.00 (dd, $J=10.2$, 0.7 Hz, 1H), 4.05 (ddd, $J=8.9$, 5.7, 3.9 Hz, 1H), 2.72 (dd, $J=16.7$, 5.5 Hz, 1H), 2.75–2.66 (m, 1H), 2.61 (dd, $J=16.7$, 7.5 Hz, 1H), 2.51–2.43 (m, 1H), 2.40–2.33 (m, 1H), 2.28–1.99 (m, 5H), 2.25 (dd, $J=6.3$, 3.5 Hz, 1H), 2.14 (s, 3H), 1.83–1.61 (m, 4H), 1.71 (dd, $J=13.8$, 2.5 Hz, 1H), 1.57 (s, 3H), 1.54–1.44 (m, 2H), 1.39–1.29 (m, 2H), 1.27 (s, 3H), 1.02 (d, $J=6.7$ Hz, 3H), 0.98 (d, $J=$ 6.9 Hz, 3H), 0.93 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=205.6$, 172.6, 171.7, 135.0, 125.7, 82.9, 80.3, 79.1, 74.4, 46.8, 45.0, 43.0, 41.2, 35.5, 34.7, 32.5, 31.5, 31.1, 30.4, 29.6, 25.7, 20.1, 18.4, 17.9, 16.6, 14.6 ppm; IR (film): $\tilde{\nu}=2960$, 2929, 1731, 1256 cm^{-1}; MS (EI): *m/z* (%): 450 (61) [M^+], 392 (10), 311 (11), 308 (11), 290 (22), 285 (90), 247 (17), 198 (22), 138 (100), 125 (70), 107 (48), 95 (54), 82 (26), 69 (25), 43 (88); HRMS (ESI): *m/z:* calcd for $C_{26}H_{42}O_6Na$ [M^++Na]: 473.2874, found: 473.2876.

Compound 9: A solution of LiOH (11 mg, 44 μmol) in MeOH (400 μL) was added to a solution of ester **40** (8.0 mg, 15 μmol) in THF/H_2O 1:1 (200 μL). The mixture was stirred for 15 h at ambient temperature, cooled to 0°C and diluted with *tert*-butyl methyl ether (2 mL) before the reaction was quenched with aq. sat. NH_4Cl (300 μL). The aqueous phase was rapidly extracted with *tert*-butyl methyl ether and the combined organic layers were dried over Na_2SO_4 and filtered. Et_3N (10 μL, 74 μmol) was added before the filtrate was evaporated and the triethylammonium salt **41** was immediately used in the next step without further purification.

2,4,6-Trichlorobenzoyl chloride (3.5 μL, 22 μmol) was added to a solution of this compound and Et_3N (10 μL, 74 μmol) in THF (550 μL). The mixture was stirred for 1 h at ambient temperature before it was filtered under Argon through a pad of Celite which had been treated with dry THF. The Celite was carefully rinsed with dry THF before most of the solvent was removed under a flow of argon. The residue was diluted with toluene (4.5 mL) and the resulting solution was added dropwise over 2 h via syringe pump to a solution of DMAP (36 mg, 300 μmol) in toluene (20 mL). Once the addition was complete, stirring was continued for 2 h, before the mixture was neutralized with aq. sat. $NaHCO_3$ (3.0 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated, and the residue filtered through a pad of silica (hexanes/ethyl acetate 10:1 + 1% Et_3N) to remove the DMAP. Evaporation of the filtrate afforded **42**, which was used in the next step without further purification.

The material thus obtained was dissolved in HOAc/THF/H_2O 4:1:1 (600 μL) and the resulting solution was stirred for 2.5 h at ambient temperature. The mixture was diluted with ethyl acetate (1.5 mL) and the reaction quenched with aq. sat. $NaHCO_3$. The aqueous layer was repeatedly extracted with ethyl acetate, the combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 4:1) to give compound **9** as a colorless oil (2.7 mg, 43% over three steps; ratio of the 6-ketone/6(9)-hemiacetal form in $CDCl_3$ = 4.8:1). $[\alpha]_D^{20}=-36.7$ ($c=0.56$, $CHCl_3$); ^{1}H NMR (ketone form, 400 MHz, $CDCl_3$): $\delta=6.60$ (dd, $J=15.7$, 9.4 Hz, 1H), 5.78 (d, $J=15.7$ Hz, 1H), 4.93–4.89 (m, 1H), 4.87 (d, $J=8.8$ Hz, 1H), 4.35 (s, 1H), 3.92 (dt, $J=6.9$, 3.9 Hz, 1H), 3.11 (dt, $J=9.1$, 1.3 Hz, 1H), 3.08–3.03 (m, 1H), 2.94 (dd, $J=17.6$, 11.4 Hz, 1H), 2.37 (dd, $J=17.6$, 2.4 Hz, 1H), 2.26 (dt, $J=9.3$, 6.7 Hz, 1H), 2.16–2.13 (m, 2H), 2.08 (dd, $J=14.0$, 7.4 Hz, 1H), 2.03–1.95 (m, 2H), 1.93–1.81 (m, 1H), 1.86 (dd, $J=14.0$, 2.6 Hz, 1H), 1.77 (dd, $J=14.7$, 9.0 Hz, 1H), 1.71 (d, $J=1.2$ Hz, 3H), 1.66–1.49 (m, 1H), 1.36 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.10 (d, $J=6.8$ Hz, 3H), 0.87 ppm (d, $J=6.7$ Hz, 3H); ^{13}C NMR (ketone form, 100 MHz, $CDCl_3$): $\delta=211.3$, 166.0, 153.8, 138.3, 128.8, 120.2, 80.7, 80.6, 79.1, 77.4, 71.2, 45.1, 44.8, 42.8, 39.4, 34.9, 34.3, 32.2, 29.8, 27.7, 26.8, 20.0, 17.7, 17.0 ppm; IR (film): $\tilde{\nu}=3491$, 2970, 2929, 1717 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{24}H_{38}O_6Na$ [M^++Na]: 445.2561, found: 445.2563.

Cytotoxicity assays: Six of the ten cell lines were established from patient-derived tumor xenografts passaged subcutaneously in nude mice; the origin of the donor xenografts has already been described.[46,47] The other four cell lines were obtained from American Type Culture Collection (22RV1), Rockville, MD, USA or the National Cancer Institute (HT29, OVCAR-3, PC3M), Bethesda, MD, USA. All cells were grown at 37°C in a humidified atmosphere (95% air, 5% CO_2) in RPMI 1640 medium (PAA, Cölbe, Germany) supplemented with 10% fetal calf serum (PAA) and 0.1 mg mL^{-1} gentamicin (PAA). A modified propidium iodide assay was used to assess the effects of the compounds.[48] Tumor derived cell lines were incubated in 96 multi-well plates. After one day, the compounds under test were added to the plates at five concentrations in the range from 0.001 μg up to 10 μg mL^{-1} and left for further four days. The inhibition of proliferation was determined by measuring the DNA content using an aqueous propidium iodide solution (7 μg mL^{-1}). Fluorescence was measured using the Cytofluor 4000. In each experiment, all data points were determined in triplicate.

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