Synthesis of the Northern Hemisphere of Amphidinolide H2

Florian P. Liesener, Ulrike Jannsen, Markus Kalesse*

Universität Hannover, Institut für Organische Chemie, Schneiderberg 1B, 30167 Hannover, Germany
Fax +49(511)7623011; E-mail: Markus.Kalesse@oci.uni-hannover.de

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Abstract: The stereoselective synthesis of the fully functionalized northern hemisphere of the marine natural product amphidinolide H2 is described. A vinylogous Mukaiyama aldol reaction and enzymatic desymmetrization of a *meso* compound are the key steps in the fragment synthesis. A stereoselective acetate aldol coupling and a 1,3-*anti*-reduction of the resulting β-hydroxy ketone complete the synthesis of the C14–C26 fragment.

Key words: natural products, aldol reaction, stereoselectivity, amphidinolides, macrolides

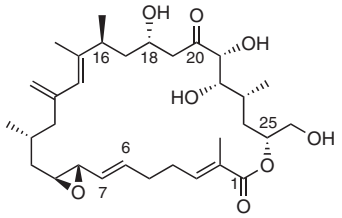
The amphidinolides are a group of cytotoxic macrolides isolated from marine dinoflagellate *Amphidinium* sp., which is symbiotic with the Okinawan flatworm *Amphiscolops* sp. Since 1986, when Kobayashi et al. first reported the isolation of a cytotoxic macrolide from laboratory cultured *Amphidinium* sp.,[1] 37 macrolides have been found by investigation of different strains to date.[2] Two further amphidinolides were isolated by Shimizu et al. from a free swimming dinoflagellate collected at Brewers Beach, St. Thomas, Virgin Islands, USA.[3] The ring sizes of the macrolactones range from 12 to 29 and all of them show significant biological activity.

Amphidinolide H (**1**) was first isolated in 1991 from extracts of cultured cells of the Y-25 strain separated from flatworm *Amphiscolops breviviridis*.[4] The absolute configuration of **1** was elucidated by X-ray diffraction analysis and by the synthesis of a degradation product.[5] Investigations of the strain Y-42 of the genus *Amphidinium* sp. led to the isolation of amphidinolide H2 (**2**) along with three other H-type amphidinolides (Figure 1).[6]

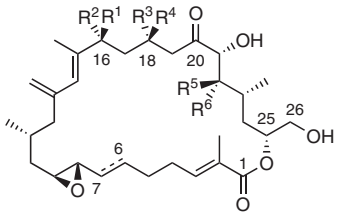
The structure of **2** was determined by comparison of the $J_{H,H}$ and $J_{C,H}$ coupling constants and NOESY correlations with those of amphidinolide H (**1**). Its cytotoxicity was tested against murine lymphoma L1210 and human epidermoid KB cell lines and an IC_{50} value of 0.06 mg/mL has been found for both.[6]

Within these investigations, first SAR studies indicated that an allyl epoxide unit, the *S-cis*-diene moiety, and the C20 ketone are relevant for the cytotoxicity of amphidinolides of the H-group.[6]

Biological studies on amphidinolide H (**1**) revealed that it acts as a specific and highly selective actin binder for which the C8,C9-epoxide seems to be crucial.[7,8]



amphidinolide H (**1**)



amphidinolide H2 (**2**) R^2 = Me, R^4, R^6 = OH, R^1, R^3, R^5 = H, $\Delta^{6,7}$
amphidinolide H3 (**3**) R^1 = Me, R^3, R^5 = OH, R^2, R^4, R^6 = H, $\Delta^{6,7}$
amphidinolide H4 (**4**) R^1 = Me, R^3, R^6 = OH, R^2, R^4, R^5 = H, 6,7-dihydro
amphidinolide H5 (**5**) R^2 = Me, R^4, R^6 = OH, R^1, R^3, R^5 = H, 6,7-dihydro

Figure 1 The amphidinolides of the H-group

Amphidinolide H (**1**) induces polyploid cell formation, which is believed to be a result of cytokinesis inhibition. It could be demonstrated that on treatment with amphidinolide H the actin cytoskeleton was modified whereas the microtubules remained unchanged.[8]

The remarkable biological activity and the interesting structural features have initiated considerable synthetic efforts, but although several syntheses of fragments of H-type amphidinolides and the structurally related amphidinolides B and L have been published,[9–15] to our knowledge no total synthesis of these amphidinolides has been accomplished so far.

Retrosynthetic Analysis

Our retrosynthetic analysis dissects amphidinolide H2 (**2**) into three fragments, allowing a convergent assembly of the molecule (Scheme 1).

The coupling of these fragments was planned to be achieved by a stereoselective acetate aldol coupling between C18 and C19, lactonization, and an enyne metathesis between C13 and C14. Alternatively, a palladium-catalyzed cross-coupling could also lead to the desired

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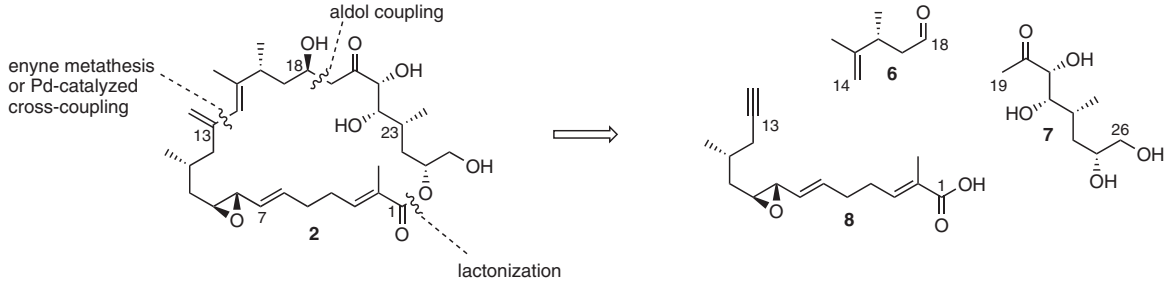


Scheme 1 Retrosynthetic disconnection of amphidinolide H2 (**2**)

1,3-diene system. This has been shown by Chakraborty et al.[14] and Nelson et al.,[12] who used a Stille and a Suzuki coupling, respectively in their partial syntheses of amphidinolide B.

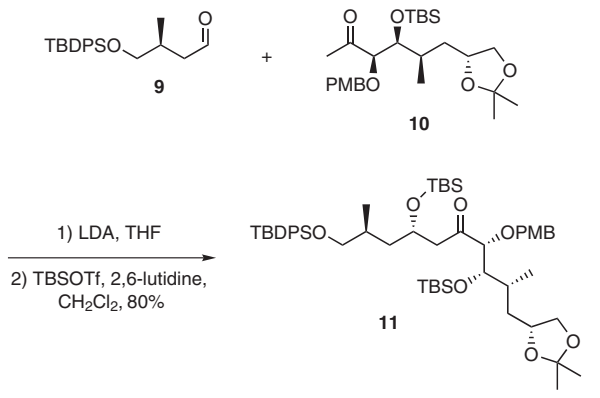
Synthetic Considerations

The enyne metathesis has attracted considerable attention during the past decade, which has led to a number of publications.[16]

Lee et al. have investigated the factors governing the regioisomeric outcome of the enyne metathesis, proposing that first the double bond would react with the catalyst.[17] Depending on the ring size to be formed the *exo* or the *endo* product can be obtained. For ring sizes between n = 5–11 atoms the *exo* product is favored. Rings with more than 11 atoms will preferably generate the *exo*-methylene unit (*endo* product).

Therefore, the desired *endo*-selective enyne ring closing metathesis will in principal be applicable to amphidinolide H2 (**2**) as a large 26-membered macrolactone.[18] Alternatively, a cross alkyne–alkene metathesis which is known to be *endo*-selective could also be employed.

For the selectivities in the aldol step Chakraborty et al. reported the aldol coupling between aldehyde **9** and methyl ketone **10** in the synthesis of amphidinolide H (**1**), which produced the desired product **11** selectively in 80% yield (Scheme 2).[10]

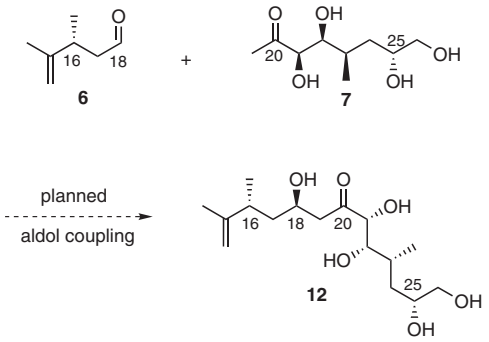


Scheme 2 Acetate aldol reaction in the synthesis of amphidinolide H (**1**) as employed by Chakraborty et al.

They proposed the substituent at C16 to be responsible for the observed selectivity, while in the relevant literature 1,3-induction by a methyl group is indicated as only moderate.[19]

We planned to investigate the stereochemical outcome of this aldol step with the aid of aldehyde **6**, which could be used for the subsequent enyne metathesis (Scheme 3).

In case the methyl ketone fragment induces the reported stereochemistry of aldol product **11**, it would produce the undesired diastereomer in our case. In order to overrule the potentially inherent induction chiral enolates or Lewis acids could be employed.

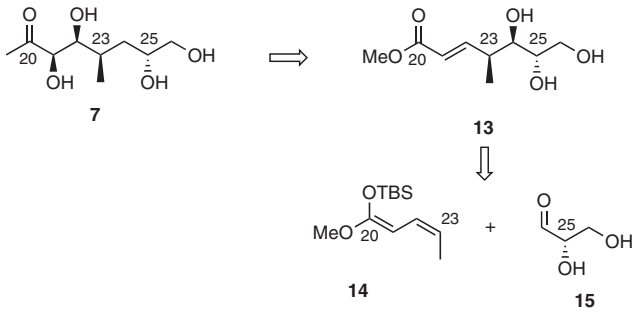


Scheme 3 Planned diastereoselective aldol reaction between aldehyde **6** and methyl ketone **7**

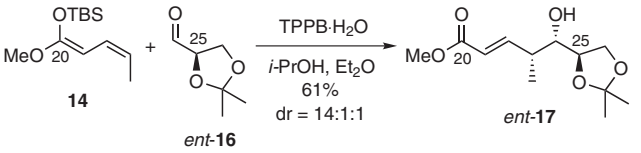
Synthesis of a C19–C26 Methyl Ketone

Our synthesis of the C19–C26 fragment **7** makes use of a diastereoselective vinylogous Mukaiyama aldol reaction (VMAR).[20] A Sharpless asymmetric dihydroxylation should be used in order to install the remaining hydroxy groups (Scheme 4).

The acetonide of L-glyceraldehyde (**15**) can be synthesized from L-ascorbic acid in three steps.[21] In order to optimize the vinylogous Mukaiyama aldol reaction as the first step, various reaction conditions were employed using the acetonide of D-glyceraldehyde *ent*-**16**, which is readily available from D-mannitol (Scheme 5). Interestingly it turned out that in contrast to other aliphatic aldehydes, substrates with protected α-hydroxy groups could be transformed into the desired aldol products with cata-



Scheme 4 Retrosynthesis of methyl ketone **7**

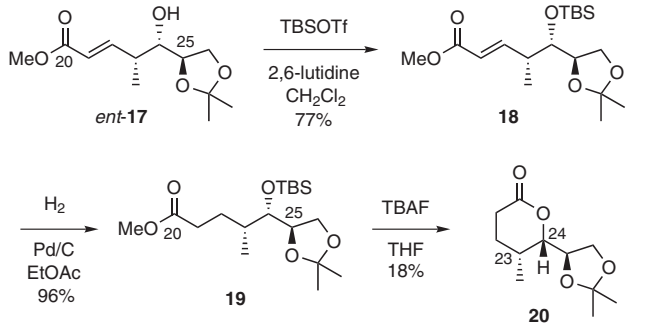


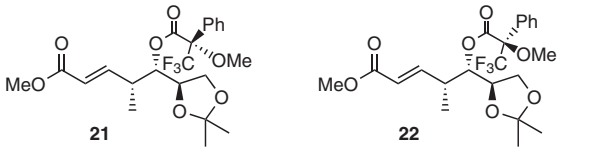
Scheme 5 Diastereoselective vinylogous Mukaiyama aldol reaction (VMAR)

lytic concentrations of tris(pentafluorophenyl)borane monohydrate (TPPB) as the Lewis acid.

No TBS catalysis was observed here even with only 1% of the Lewis acid present (Table 1, entry 9). With these optimized conditions the VMAR could be performed on gram-scale quantities.[9]

In order to determine the stereochemistry of VMAR product *ent*-**17**, lactone **20** was synthesized (Scheme 6). Subsequent analysis of the coupling constants in the ^{1}H NMR spectrum revealed a C23–C24 *syn* configuration. Felkin–Anh selectivity was proven unambiguously by transformation of *ent*-**17** to the corresponding Mosher esters **21** and **22**.[33]





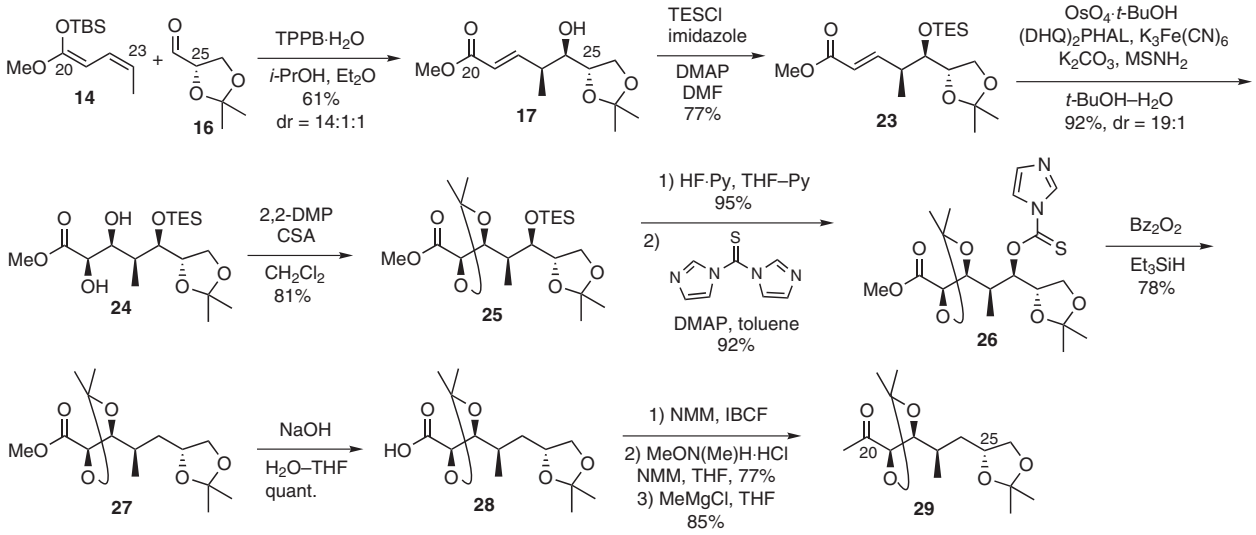
Scheme 6 Synthesis of lactone **20** for determination of the relative stereochemistry of *ent*-**17**

The optimized conditions were then applied to the reaction with protected L-glyceraldehyde **16** (Scheme 7). After TES-protection of the newly generated alcohol **17**, dihydroxylation of the double bond was achieved with a variation of AD-mix α[22] providing the desired diol **24**, which was subsequently protected as the acetonide. Removal of the TES group liberated the secondary alcohol for transformation into the thiocarbonyl imidazolide derivative **26**.[23] A tin-mediated free-radical deoxygenation[24] followed by saponification provided acid **28**. Subsequently, a sequence of acid activation by isobutyl chloroformate, transformation into the Weinreb amide[25] and addition of methyl magnesium chloride[26] furnished methyl ketone **29** in 11 steps and 16% overall yield (Scheme 7).[9]

Table 1 Vinylogous Mukaiyama Aldol Reaction (VMAR) with Protected D-Glyceraldehyde *ent*-**16**

Entry	**14** (equiv)	*i*-PrOH (equiv)	Time (min)	TPPB·H_2O/eq	Temp (°C)	Yield (%)	dr[a]
1	2	1.1	180	0.1	–78	34	10:1:1
2	2	1.1	60	0.1	–50	75	14:1:1
3	2	1.1	30	0.1	–50	45	13:1:2
4	2	1.1	60	0.05	–50	65	15:1:1
5	2	1.1	60	0.02	–50	67	10:1:1
6	1.2	0.7	40	0.02	–50	62	14:1:2
7	1.2	0.7	40	0.01	–50	63	12:1:1
8	1.2	0.7	40	0.01	–50 → r.t.	75[b]	13:1:1
9	1.2	0.7	40	0.01	–50 → r.t.	63[c]	14:1:1

[a] The diastereomeric ratio was determined from the ^{1}H NMR spectra by integration of the vinylic proton at C22.
[b] Scale: 2.51 mmol.
[c] Scale: 12.5 mmol.



Scheme 7 Synthesis of methyl ketone **29**:[9] $(DHQ)_2PHAL$ = bis(dihydroquinine)phthalazine; 2,2-DMP = 2,2-dimethoxypropane; IBCF = isobutyl chloroformate

Synthesis of the Northern Hemisphere

Next, the stereochemical outcome of the aldol coupling had to be investigated. For our initial orientating experiments, the aldol reaction between methyl ketone *ent*-**29** and *n*-hexanal (**30**) was studied. Surprisingly, it turned out that the expected aldol reaction took place only in moderate yields and aldol dimer **32** was produced in significant quantities (Scheme 8; 28%). Furthermore, the diastereomeric mixture of the aldol product **31** was in favor of the undesired isomer.[27]

Even extensive variation of the reaction conditions, such as changing the base (Table 2, entries 1–6) did not lead to better results. With boron aldol reaction chemistry[29] no product formation was observed, while DIP-Cl®[30] led to decomposition. Under Mukaiyama aldol reaction conditions, only a mixture of TMS-enolate and starting material could be isolated.

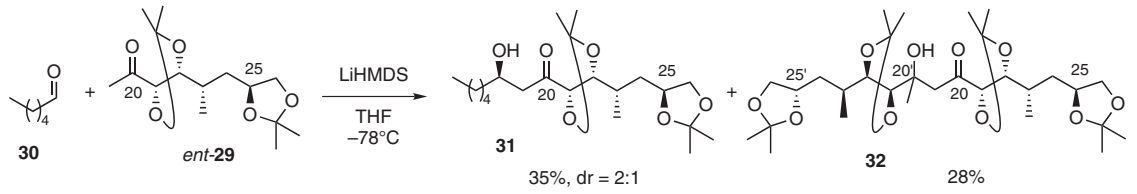
At this point we decided to change our initial synthetic plan since the yields and selectivities for the envisioned aldol reaction were by no means satisfactory for the future elaboration of amphidinolide H2 (**2**).

Therefore, exchanging the functionalities in the aldol reaction was considered; we modified our retrosynthetic analysis so that the C14–C19 fragment **33** would react with the C20–C26 aldehyde **34** (Scheme 9).

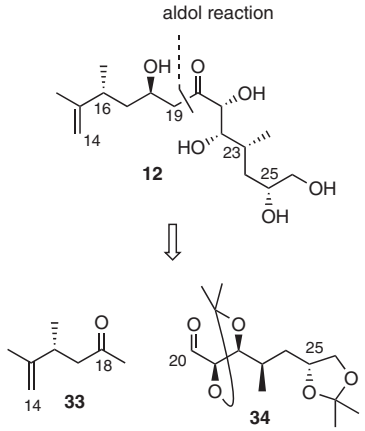
Table 2 Variation of Conditions in the Aldol Reaction

Entry	Base, solvent	Yield (%)	
		31	**32**
1	LiHMDS, THF	35	28
2	KHMDS, THF	13	16
3	NaHMDS, THF	19	13
4	LDA, THF	35	28
5	LDA, HMPA, THF	35	28
6	Schwesinger base, THF[28]	35	28

Methyl ketone **33** could be synthesized starting from *meso* compound dimethyl-3-methyl-glutarate (**35**). A known literature sequence of enzymatic desymmetrization using *porcine* liver esterase (PLE), selective reduction of the free acid with borane dimethylsulfide complex, and TBS protection delivered ester **37**.[31] This was methylated α to the ester group, producing **38** as a mixture of diastereomers. Subsequent DIBAL-H reduction and tosylation of the alcohol led to compound **39**. Deprotection of the silyl ether, Swern oxidation, addition of methyl magnesium chloride, and another Swern oxidation provided ketone **41**. In situ conversion to the corresponding iodide and



Scheme 8 Aldol reaction between methyl ketone *ent*-**29** and *n*-hexanal (**30**)



Scheme 9 Modified retrosynthetic analysis of the northern half of **2**

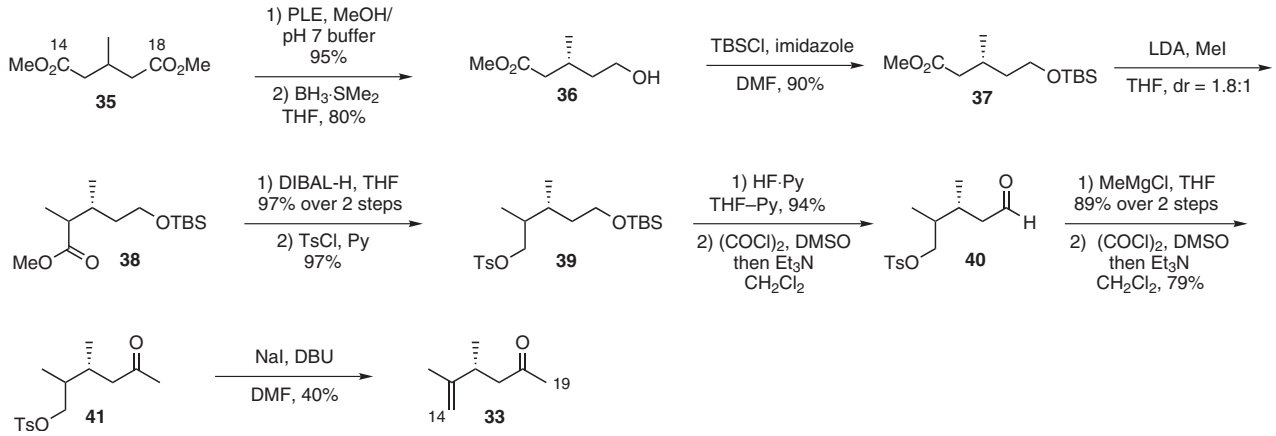
elimination with DBU as base,[32] afforded the desired C14–C19 fragment **33** in 11 steps with an overall yield of 17% (Scheme 10).

Aldehyde **34** was obtained in one step by DIBAL-H reduction of ester **27**. Now the aldol reaction was performed using LiHMDS at –78 °C. The coupling product **42** was obtained in 50% yield and 15:1 dr in favor of the Felkin product (Scheme 11). The configuration at C20 was assigned by synthesizing (*S*)-Mosher ester **43** and (*R*)-Mosher ester **44**.[33]

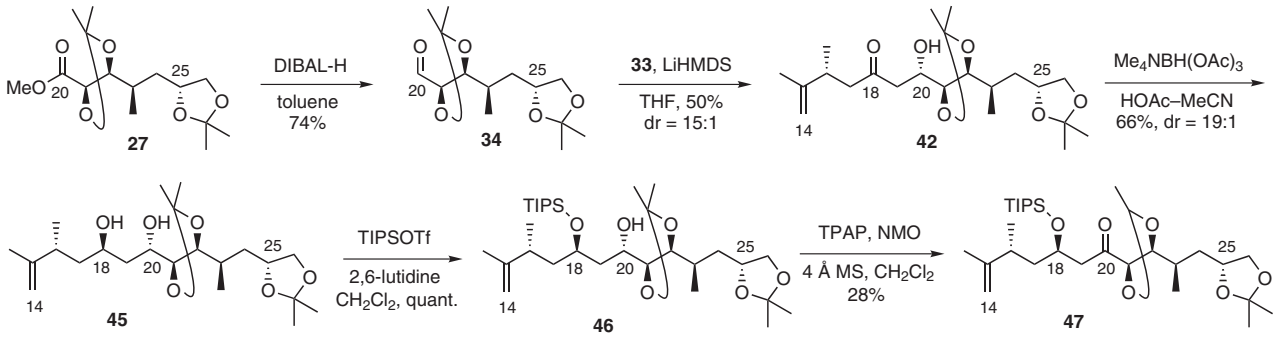
In order to elaborate the C18-stereocenter, a 1,3-*anti*-reduction with tetramethylammonium trisacetoxyborohydride using a method developed by Evans, was employed.[34] The selectivity of this reaction is derived from an intramolecular hydride transfer in the borate formed from reagent and substrate. Protection of the less sterically hindered alcohol was obtained using TIPSOTf. Finally, reoxidation at C20 provided the fully functionalized northern hemisphere **47** of amphidinolide H2 (**2**).

In summary, the C14–C26 fragment of amphidinolide H2 (**2**) has been synthesized, making use of a diastereoselective acetate aldol reaction and a subsequent selective 1,3-*anti*-reduction. The fragment contains the necessary functional groups for further synthesis of the natural product. Esterification with a C1–C13 acid could be realized after selective cleavage of the terminal acetonide and protection of the primary alcohol. The terminal double bond at C14 can be used in an enyne metathesis with a suitable alkyne. Investigations towards those couplings are currently underway and should provide a convergent access to amphidinolide H2 (**2**) in due course.

All reactions were carried out in dried glassware under a positive pressure of argon, using Schlenk techniques when air-sensitive compounds were employed. Commercially available materials were obtained from Aldrich, Fluka, Merck or Acros, and were used without further purification unless otherwise noted. TPPB was pur-



Scheme 10 Synthesis of methyl ketone **33**



Scheme 11 Synthesis of the protected northern hemisphere of amphidinolide H2 (**2**); TPAP = tetrapropylammonium perruthenate

chased from Acros and was handled under argon in a glovebox. THF and Et_2O were distilled from Na/benzophenone, CH_2Cl_2 and Et_3N were distilled from CaH_2 prior to use. Flash chromatography was performed using Merck silica gel 230–400 mesh. ^1H and ^{13}C NMR spectra were recorded with a Bruker DRX 500, DPX 400, AVANCE 400, or Jeol ECP 500 spectrometers. The residual undeuterated solvent peak ($CDCl_3$ at 7.26 ppm) was used as the internal standard. HRMS-EI measurements were performed using a VG Autospec and ESI with a Waters Micromass LCT. Optical rotations were determined with a Perkin Elmer 341 polarimeter at 23 °C at 589.3 nm (Na lamp) using a 1 mL quartz cell.

Tris(pentafluorophenyl)borane Monohydrate[35]

To a solution of tris(pentafluorophenyl)borane (998 mg, 1.95 mmol) in pentane (60 mL) was added H_2O (35 mL, 1.95 mmol) at r.t. After 2 h the solution and the precipitate were separated; the precipitate was dried in vacuo overnight. TPPB·H_2O was obtained as a colorless solid (999 mg, 1.89 mmol, 97%) and was stored under argon at –18 °C.

^{19}F NMR (500 MHz, C_6D_6): δ = –134.5 (m, *ortho*), –153.3 (m, *para*), 162.4 (m, *meta*).

α,β-Unsaturated Ester *ent*-17

A solution of freshly distilled aldehyde *ent*-**16** (3.13 g, 24.0 mmol) in Et_2O (75 mL) was stirred at –50 °C. TPPB·H_2O (318 mg, 601 mmol) was added and the resulting mixture was stirred for 5 min. Then a solution of ketene acetal **14** (6.59 g, 28.8 mmol) and *i*-PrOH (1.27 mL, 16.6 mmol) in Et_2O (total solution volume, 30 mL) was added over 40 min. The solution was allowed to warm to r.t. overnight. After stirring for 48 h the solution was concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 3:1 → 1:1) to provide ester *ent*-**17** as a colorless oil (3.51 g, 14.4 mmol, 61%, dr 14:1:1).

$[\alpha]_D^{23}$ –51.5 (*c* 0.94, $CHCl_3$); R_f 0.53 (hexane–EtOAc, 1:2).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.92 (dd, *J* = 15.7, 8.2 Hz, 1 H), 5.85 (dd, *J* = 15.7, 1.0 Hz, 1 H), 4.02 (app q, *J* = 5.7 Hz, 1 H), 3.96 (dd, *J* = 8.0, 6.3 Hz, 1 H), 3.89 (dd, *J* = 7.9, 6.5 Hz, 1 H), 3.72 (s, 3 H), 3.71–3.68 (m, 1 H), 2.51–2.43 (m, 1 H), 2.24 (br s, 1 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 150.3, 121.4, 109.0, 76.4, 73.5, 64.9, 51.6, 39.2, 26.6, 25.2, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{21}O_5$ $[M + H]^+$: 245.1389; found: 245.1396.

Silyl Ether 18

A solution of alcohol *ent*-**17** (93.3 mg, 383 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C and 2,6-lutidine (0.11 mL, 0.96 mmol) and TBSOTf (0.15 mL, 0.65 mmol) were added. The reaction mixture was stirred for 3.5 h at r.t. and subsequently quenched with a sat. aq solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with MTBE (30 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 19:1) to provide silyl ether **18** as a colorless oil (105 mg, 292 mmol, 77%).

$[\alpha]_D^{23}$ +44.3 (*c* 2.61, $CHCl_3$); R_f 0.31 (hexane–EtOAc, 9:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.83 (dd, *J* = 15.8, 1.4 Hz, 1 H), 3.97 (app q, *J* = 6.2 Hz, 1 H), 3.93 (dd, *J* = 7.6, 6.3 Hz, 1 H), 3.79–3.74 (m, 2 H), 3.72 (s, 3 H), 3.64–2.57 (m, 1 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 151.7, 120.8, 108.7, 76.5, 75.8, 66.6, 51.4, 40.3, 26.6, 25.9 (3 C), 25.3, 18.2, 14.1, –4.1, –4.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{31}O_5Si$ $[M - CH_3]^+$: 343.19409; found: 343.19522.

Ester 19

A solution of α,β-unsaturated ester **18** (94.1 mg, 262 mmol) in EtOAc (5 mL) was stirred at r.t. Pd/C (cat.) was added and the mixture was stirred under a hydrogen atmosphere (balloon pressure) for 1.5 h. The mixture was filtered through a pad of silica gel, which was washed with EtOAc. The filtrate was concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 19:1) to provide ester **19** as a colorless oil (90.3 mg, 251 mmol, 96%).

$[\alpha]_D^{23}$ +26.1 (*c* 1.05, $CHCl_3$); R_f 0.20 (hexane–EtOAc, 9:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 4.01 (app q, *J* = 6.2 Hz, 1 H), 3.97 (dd, *J* = 7.6, 6.2 Hz, 1 H), 3.80 (dd, *J* = 7.5, 6.7 Hz, 1 H), 3.67 (dd, *J* = 6.0, 2.7 Hz, 1 H), 3.66 (s, 3 H), 2.38 (ddd, *J* = 15.7, 9.6, 5.8 Hz, 1 H), 2.28 (ddd, *J* = 15.7, 9.3, 6.5 Hz, 1 H), 1.79 (dddd, *J* = 13.3, 9.6, 6.5, 4.9 Hz, 1 H), 1.69 (dddq, *J* = 9.3, 7.0, 4.7, 2.3 Hz, 1 H), 1.45 (app ddt, *J* = 13.3, 9.4, 5.8 Hz, 1 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 108.4, 76.7, 76.2, 67.0, 51.5, 36.4, 32.4, 28.3, 26.6, 25.9 (3 C), 25.3, 18.2, 14.0, –4.0, –4.1.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{33}O_5Si$ $[M - CH_3]^+$: 345.20972; found: 345.20855.

Lactone 20

To a stirred solution of silyl ether **19** (28.0 mg, 77.7 mmol) in THF (1 mL) was added TBAF (1 M in THF; 0.09 mL, 0.09 mmol) at r.t. The reaction mixture was stirred for 4 h at r.t. and subsequently quenched with a sat. aq solution of $NaHCO_3$ (2 mL). The aqueous layer was extracted with MTBE (25 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 4:1) to provide lactone **20** as a colorless oil (3.0 mg, 14 mmol, 18%).

$[\alpha]_D^{23}$ +42.5 (*c* 0.08, $CHCl_3$); R_f 0.22 (hexane–EtOAc, 2:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 4.16 (dd, *J* = 9.3, 2.8 Hz, 1 H), 4.16 (dd, *J* = 8.8, 5.8 Hz, 1 H), 4.10 (ddd, *J* = 9.4, 5.7, 4.0 Hz, 1 H), 4.01 (dd, *J* = 8.7, 4.1 Hz, 1 H), 2.56 (dd, *J* = 8.8, 6.1 Hz, 2 H), 2.34 (dddq, *J* = 7.2, 5.4, 3.3, 2.8 Hz, 1 H), 2.08 (ddt, *J* = 13.9, 8.7, 5.3 Hz, 1 H), 1.74 (ddt, *J* = 13.8, 6.0, 3.4 Hz, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.06 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 109.7, 82.9, 73.8, 67.7, 27.0, 26.4 (2 C), 26.2, 25.1, 11.8.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{15}O_4$ $[M - CH_3]^+$: 199.09703; found: 199.09716.

(*S*)-Mosher Ester 21

Et_3N (32 mL, 24 mg, 0.24 mmol), DMAP (3.2 mg, 26 mmol), and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (7.4 mL, 40 mmol) were added to a stirred solution of alcohol *ent*-**17** (6.5 mg, 26 mmol) in CH_2Cl_2 (0.5 mL) at r.t. After 14 h EtOAc (20 mL) was added. The organic layer was washed with a solution of $NaHSO_4$ (1 M; 30 mL), NaOH (2 M; 10 mL), a sat. aq solution of $NaHCO_3$ (20 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the crude (*S*)-Mosher ester **21** as a colorless liquid (11.0 mg, 23.9 mmol, 90%).

R_f 0.36 (hexane–EtOAc, 2:1).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 2 H), 7.42–7.39 (m, 3 H), 6.84 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.76 (dd, *J* = 15.8, 1.5 Hz, 1 H), 5.27 (dd, *J* = 6.7, 4.1 Hz, 1 H), 4.18 (q, *J* = 6.5 Hz, 1 H), 3.94

(dd, J = 8.4, 6.2 Hz, 1 H), 3.73 (dd, J = 8.4, 6.3 Hz, 1 H), 3.73 (s, 3 H), 3.50 (app q, $^5J_{H\text{-}F}$ = 1.2 Hz, 3 H), 2.80 (ddquin, J = 7.0, 4.1, 1.5 Hz, 1 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.08 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 165.8, 148.4, 131.7, 129.8, 128.5 (2 C), 127.4 (2 C), 123.3 (app d, $^1J_{C\text{-}F}$ = 288.9 Hz), 122.1, 109.6, 84.7 (app d, $^2J_{C\text{-}F}$ = 27.8 Hz), 77.5, 74.1, 66.3, 55.4 (app d, $^3J_{C\text{-}F}$ = 1.4 Hz), 51.6, 37.8, 26.5, 25.1, 13.3.

HRMS (EI): m/z calcd for $C_{22}H_{27}F_3O_7$ $[M]^+$: 460.17090; found: 460.17147.

(*R*)-Mosher Ester 22

To a mixture of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (10.1 mg, 43.0 mmol), DCC (17.7 mg, 86.0 mmol), and DMAP (3.5 mg, 29 mmol) in THF (0.8 mL) was added alcohol *ent*-**17** (7.0 mg, 29 mmol) in THF (0.5 mL) at r.t. The reaction was diluted with CH_2Cl_2 (2 mL) after 4 d and a sat. aq solution of $NaHCO_3$ (1 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (6 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the crude (*R*)-Mosher ester **22** as a colorless liquid (7.0 mg, 15 mmol, 53%).

R_f 0.37 (hexane–EtOAc, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 2 H), 7.42–7.39 (m, 3 H), 6.92 (dd, J = 15.8, 6.8 Hz, 1 H), 5.83 (dd, J = 15.8, 1.6 Hz, 1 H), 5.24 (dd, J = 7.5, 3.7 Hz, 1 H), 4.11 (dt, J = 7.5, 6.1 Hz, 1 H), 3.87 (dd, J = 8.5, 6.2 Hz, 1 H), 3.75 (s, 3 H), 3.68 (dd, J = 8.5, 6.2 Hz, 1 H), 3.48 (app q, $^5J_{H\text{-}F}$ = 1.2 Hz, 3 H), 2.86 (ddquin, J = 6.8, 3.7, 1.7 Hz, 1 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.12 (d, J = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 165.9, 148.9, 131.5, 129.8, 128.5 (2 C), 127.6 (2 C), 123.3 (app d, $^1J_{C\text{-}F}$ = 288.9 Hz), 122.1, 109.7, 84.7 (app d, $^2J_{C\text{-}F}$ = 28.3 Hz), 77.7, 74.0, 66.6, 55.4 (app d, $^3J_{C\text{-}F}$ = 1.4 Hz), 51.4, 37.7, 26.5, 25.3, 13.0.

HRMS (EI): m/z calcd for $C_{22}H_{27}F_3O_7$ $[M]^+$: 460.17090; found: 460.17155.

Triethylsilyl Ether 23

Alcohol *ent*-**17** (50.0 mg, 0.204 mmol) was dissolved in DMF (2 mL). Imidazole (31 mg, 0.45 mmol), DMAP (cat., 0.5 mg, 0.4 mmol), and TESCl (52 mL, 0.31 mmol) were added at 0 °C. After stirring for 6 h, the reaction mixture was quenched with H_2O (5 mL), and the aqueous layer was extracted with MTBE (15 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 19:1) to provide **23** as a colorless oil (57 mg, 0.16 mmol, 77%).

$[\alpha]_D^{23}$ –43.3 (*c* 1.04, $CHCl_3$); R_f 0.30 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (dd, J = 15.6, 7.2 Hz, 1 H), 5.82 (dd, J = 15.8, 1.5 Hz, 1 H), 3.98–3.91 (m, 2 H), 3.81–3.74 (m, 2 H), 3.72 (s, 3 H), 2.58 (app ddquin, J = 7.9, 3.7, 1.5 Hz, 1 H), 1.37 (s, 3 H), 1.30 (s, 3 H) 1.07 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 7.8 Hz, 9 H), 0.58 (q, J = 8.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 151.7, 120.8, 108.8, 76.5, 75.9, 66.5, 51.4, 40.3, 26.6, 25.3, 13.1, 6.8 (3 C), 5.2 (3 C).

HRMS (ESI): m/z calcd for $C_{18}H_{35}O_5Si$ $[M + H]^+$: 359.2254; found: 359.2242.

Diol 24

To a stirred solution of $(DHQ)_2PHAL$ (622 mg, 799 mmol), $K_3Fe(CN)_6$ (7.89 g, 24.0 mmol), and K_2CO_3 (3.31 g, 24.0 mmol) in *t*-BuOH–H_2O (70 mL, 1:1) was added OsO_4 (0.08 M in *t*-BuOH; 2.0 mL, 0.16 mmol) and $MsNH_2$ (2.28 g, 24.0 mmol) at r.t. The mixture was stirred for 5 min at ambient temperature, cooled to 0 °C, and α,β-unsaturated ester **23** (2.86 g, 7.99 mmol) was added. After 20 h, the reaction was quenched by the addition of Na_2SO_3 (12.1 g, 98.8 mmol), warmed to r.t., and stirred for 1 h. Brine (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (175 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 2:1) to provide diol **24** (2.89 g, 7.37 mmol, 92%, dr 19:1) as a colorless liquid.

$[\alpha]_D^{23}$ –24.2 (*c* 1.19, $CHCl_3$); R_f 0.18 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (d, J = 2.1 Hz, 1 H), 4.08 (t, J = 6.1 Hz, 1 H), 4.03 (dd, J = 7.7, 6.4 Hz, 1 H), 3.84–3.78 (m, 3 H), 3.81 (s, 3 H), 3.16 (br s, 1 H), 2.43 (br s, 1 H), 2.03 (app dquin, J = 6.9, 2.5 Hz, 1 H), 1.39 (s, 3 H), 1.31 (s, 3 H), 1.05 (d, J = 7.2 Hz, 3 H), 0.96 (t, J = 8.0 Hz, 9 H), 0.61 (q, J = 7.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 108.7, 77.0, 74.9, 72.6, 72.2, 66.9, 52.7, 40.5, 26.5, 25.1, 10.5, 6.8 (3 C), 5.2 (3 C).

HRMS (ESI): m/z calcd for $C_{18}H_{37}O_7Si$ $[M + H]^+$: 393.2309; found: 393.2296.

Acetonide 25

To a stirred solution of diol **24** (2.84 g, 7.23 mmol) in CH_2Cl_2 (45 mL) was added 2,2-DMP (13.3 mL, 108 mmol) and CSA (168 mg, 723 mmol) at r.t. The mixture was stirred for 3 h at ambient temperature and the reaction was quenched by the addition of a sat. aq solution of $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was extracted with MTBE (60 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 9:1) to provide acetonide **25** as a colorless liquid (2.52 g, 5.82 mmol, 81%).

$[\alpha]_D^{23}$ –43.4 (*c* 1.04, $CHCl_3$); R_f 0.24 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (dd, J = 7.7, 2.5 Hz, 1 H), 4.23 (d, J = 7.7 Hz, 1 H), 4.15 (app dt, J = 6.7, 4.0 Hz, 1 H), 3.98 (dd, J = 7.9, 6.4 Hz, 1 H), 3.88 (t, J = 4.0 Hz, 1 H), 3.87 (dd, J = 7.8, 6.9 Hz, 1 H), 3.76 (s, 3 H), 2.07 (ddq, J = 7.1, 3.8, 2.7 Hz, 1 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.32 (s, 3 H), 1.00 (d, J = 7.2 Hz, 3 H), 0.95 (t, J = 7.8 Hz, 9 H), 0.61 (q, J = 7.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 111.1, 108.0, 78.0, 77.0, 76.4, 74.7, 65.4, 52.2, 39.1, 26.9, 26.5, 25.5, 25.0, 9.1, 6.9 (3 C), 5.1 (3 C).

HRMS (ESI): m/z calcd for $C_{21}H_{41}O_7Si$ $[M + H]^+$: 433.2622; found: 433.2624.

Thiocarbonyl Imidazolide 26

To a solution of triethyl silyl ether **25** (2.27 g, 5.26 mmol) in py (15 mL) and THF (15 mL) was added HF·py (ca. 7:3, 2.73 mL, 105 mmol). After stirring for 14 h at r.t., the mixture was quenched with a sat. aq solution of $NaHCO_3$ (40 mL), and $NaHCO_3$ (17 g) was added until the solution was pH 8. The aqueous layer was extracted with MTBE (100 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 3:1 → 1:1) to provide the desired secondary alcohol as a colorless liquid (1.58 g, 4.97 mmol, 95%).

$[\alpha]_D^{23}$ –27.6 (*c* 1.03, $CHCl_3$); R_f 0.21 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (d, J = 7.5 Hz, 1 H), 4.25 (dd, J = 7.5, 4.1 Hz, 1 H), 4.08 (dd, J = 7.7, 6.3 Hz, 1 H), 4.02 (ddd, J = 7.6, 5.6, 5.4 Hz, 1 H), 3.94 (dd, J = 7.7, 4.7 Hz, 1 H), 3.78 (s, 3 H), 3.75–3.71 (m, 1 H), 2.56 (br s, 1 H), 2.21–2.14 (m, 1 H), 1.45 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.03 (d, J = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 111.1, 109.0, 82.0, 76.5, 75.5, 74.9, 67.3, 52.6, 36.3, 26.8, 26.5, 25.3, 25.2, 6.7.

HRMS (ESI): *m/z* calcd for $C_{15}H_{27}O_7$ [M + H]$^+$: 319.1757; found: 319.1765.

A stirred solution of the secondary alcohol (1.5 g, 4.7 mmol), 1,1-thiocarbonyldiimidazole (1.51 g, 8.47 mmol), and DMAP (172 mg, 1.41 mmol) in toluene (40 mL) was heated to 120 °C. After 21 h the solvent was removed in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 1:1) to provide **26** as a colorless liquid (1.85 g, 4.32 mmol, 92%).

$[\alpha]_D^{23}$ –4.6 (*c* 0.96, $CHCl_3$); R_f 0.21 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1 H), 7.61 (s, 1 H), 7.02 (s, 1 H), 5.91 (dd, *J* = 6.7, 3.1 Hz, 1 H), 4.42–4.38 (m, 1 H), 4.26–4.24 (m, 1 H), 4.21 (d, *J* = 8.0 Hz, 1 H), 4.07 (dd, *J* = 8.8, 6.4 Hz, 1 H), 4.00 (dd, *J* = 8.8, 4.8 Hz, 1 H), 3.73 (s, 3 H), 2.64–2.58 (m, 1 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.21 (s, 3 H) 1.16 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.3, 170.9, 136.8, 130.4, 118.2, 111.2, 109.9, 85.2, 79.6, 76.3, 74.0, 66.3, 52.4, 35.4, 26.6, 26.4, 24.9 (2 C), 7.4.

HRMS (ESI): *m/z* calcd for $C_{19}H_{29}N_2O_7S$ [M + H]$^+$: 429.1695; found: 429.1692.

Ester 27

A stirred solution of thiocarbonylimidazolide **26** (1.72 g, 4.02 mmol) in Et_3SiH (19.3 mL, 14.0 g, 121 mmol) was heated to reflux. Bz_2O_2 (5 × 195 mg, 4.02 mmol) was added in five portions at 40 min intervals. The reaction was quenched with a sat. aq solution of NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (50 mL). The combined organic layers were washed with $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 4:1) to provide ester **27** as a colorless liquid (943 mg, 3.12 mmol, 78%).

$[\alpha]_D^{23}$ –20.4 (*c* 0.855, $CHCl_3$); R_f 0.29 (hexane–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (d, *J* = 7.2 Hz, 1 H), 4.19 (dddd, *J* = 8.9, 6.9, 5.9, 4.1 Hz, 1 H), 4.13 (dd, *J* = 7.0, 4.4 Hz, 1 H), 4.05 (dd, *J* = 7.8, 5.9 Hz, 1 H), 3.78 (s, 3 H), 3.51 (dd, *J* = 7.8, 7.2 Hz, 1 H), 2.11–2.01 (m, 1 H), 1.76 (ddd, *J* = 13.5, 9.1, 4.2 Hz, 1 H), 1.45 (s, 3 H), 1.44–1.38 (m, 1 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 110.9, 108.8, 82.7, 76.6, 73.8, 69.8, 52.4, 37.5, 32.3, 27.0, 26.8, 25.8, 25.6, 13.7.

HRMS (ESI): *m/z* calcd for $C_{15}H_{27}O_6$ [M + H]$^+$: 303.1808; found: 303.1813.

Acid 28

A solution of methyl ester **27** (37.0 mg, 126 mmol) in H_2O–THF (1:1, 1.5 mL) was stirred with NaOH (12.6 mg, 314 mmol) for 2.5 h at r.t. The reaction was quenched with H_2O (5 mL), CH_2Cl_2 (5 mL), and citric acid monohydrate (91.8 mg, 478 mmol). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to provide acid **28** as a colorless liquid (35.9 mg, 125 mmol, 99%).

$[\alpha]_D^{23}$ –16.2 (*c* 1.02, $CHCl_3$); R_f 0.02 (EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.1 (br s, 1 H), 4.30 (d, *J* = 7.0 Hz, 1 H), 4.23–4.18 (m, 1 H), 4.15 (dd, *J* = 6.9, 4.5 Hz, 1 H), 4.06 (dd, *J* = 7.9, 6.0 Hz, 1 H), 3.52 (app t, *J* = 7.5 Hz, 1 H), 2.12–2.05 (m, 1 H), 1.78 (ddd, *J* = 13.6, 9.2, 4.3 Hz, 1 H), 1.46 (s, 3 H), 1.43–1.40 (m, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8, 111.2, 108.9, 82.7, 76.1, 73.7, 69.7, 37.4, 32.4, 27.0, 26.8, 25.7, 25.5, 13.5.

HRMS (ESI): *m/z* calcd for $C_{14}H_{24}O_6$ [M + H]$^+$: 289.1651; found: 289.1645.

Methyl Ketone 29

To a stirred solution of acid **28** (86.3 mg, 299 mmol) in THF (2 mL) was added NMM (36 mL, 0.33 mmol) and isobutyl chloroformate (43 mL, 0.33 mmol) at –20 °C. After 20 min NMM (43 mL, 0.39 mmol) and *N*,*O*-dimethylhydroxylamine (32.1 mg, 329 mmol) were added. The reaction was stirred for 2 h at 0 °C then quenched with a sat. aq solution of $NaHCO_3$ (5 mL) and MTBE (5 mL). The layers were separated and the aqueous layer was extracted with MTBE (20 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 2:1) to provide the desired Weinreb amide as a colorless liquid (76.6 mg, 231 mmol, 77%).

$[\alpha]_D^{23}$ –9.1 (*c* 1.00, $CHCl_3$); R_f 0.16 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59–4.51 (m, 1 H), 4.40–4.32 (m, 1 H), 4.21–4.15 (m, 1 H), 4.03 (dd, *J* = 7.8, 6.0 Hz, 1 H), 3.74 (s, 3 H), 3.47 (app t, *J* = 7.5 Hz, 1 H), 3.22 (br s, 3 H), 2.03–1.94 (m, 1 H), 1.63 (ddd, *J* = 13.5, 9.0, 4.0 Hz, 1 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.40–1.35 (m, 1 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 110.3, 108.7, 81.9, 77.2, 74.3, 73.6, 69.8, 61.7, 37.3, 32.1, 30.9, 27.0, 26.0, 25.7, 14.4.

HRMS (ESI): *m/z* calcd for $C_{16}H_{30}NO_6$ [M + H]$^+$: 332.2073; found: 332.2082.

MeMgCl (3 M in THF; 0.24 mL, 0.73 mmol) was added dropwise to a stirred solution of the Weinreb amide (48.3 mg, 146 mmol) in THF (3 mL) at 0 °C. After 1 h the reaction was quenched with a sat. aq solution of NH_4Cl (4 mL) and MTBE (5 mL). The layers were separated and the aqueous layer was extracted with MTBE (20 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and carefully concentrated in vacuo (bath temperature 35 °C). The crude material was purified by flash column chromatography (hexane–EtOAc, 9:1) to provide methyl ketone **29** as a colorless liquid (35.4 mg, 124 mmol, 85%).

$[\alpha]_D^{23}$ +19.3 (*c* 1.01, $CHCl_3$); R_f 0.33 (hexane–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (dddd, *J* = 8.9, 7.0, 5.9, 4.1 Hz, 1 H), 4.07 (d, *J* = 7.3 Hz, 1 H), 4.04 (dd, *J* = 8.0, 6.1 Hz, 1 H), 4.01 (dd, *J* = 7.3, 4.4 Hz, 1 H), 3.49 (app dd, *J* = 7.7, 7.3 Hz, 1 H), 2.27 (s, 3 H), 2.04–1.95 (m, 1 H), 1.72 (ddd, *J* = 13.7, 9.1, 4.4 Hz, 1 H), 1.44 (s, 3 H), 1.42–1.35 (m, 1 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 110.2, 108.7, 83.0, 81.3, 73.8, 69.8, 37.6, 32.5, 27.0, 26.8, 26.5, 26.1, 25.8, 13.8.

HRMS (ESI): *m/z* calcd for $C_{15}H_{27}O_5$ [M + H]$^+$: 287.1858; found: 287.1857.

Ester 38

A solution of *i*-Pr_2NH (4.6 mL, 32.7 mmol) in THF (40 mL) was treated with *n*-BuLi (2.5 M solution in hexane; 13.1 mL, 32.7 mmol) at 0 °C. After stirring at this temperature for 45 min, the mixture was cooled to –78 °C, and ester **37**[31] (7.09 g, 27.2 mmol) dissolved in THF (20 mL) was added. The resulting solution was stirred for 2 h at –78 °C, before MeI (2.0 mL, 32.7 mmol) was added. The cooling bath was removed after 20 min and stirring continued at r.t. for 1 h. The mixture was diluted with MTBE (50 mL), washed with a solution of HCl (2 M; 40 mL), a sat. aq solution of $Na_2S_2O_3$ (40 mL), H_2O (40 mL), brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo to provide the product **38** as a colorless

oil, which could be used in the next reaction without further purification (dr 1.8:1).

R_f 0.65 (hexane–EtOAc, 3:1)

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3 H), 3.64–3.57 (m, 2 H), 2.41 (ddd, *J* = 14.0, 7.0, 5.7 Hz, 1 H), 2.03–1.96 (m, 1 H), 1.56 (dtd, *J* = 13.6, 7.2, 5.0 Hz, 1 H), 1.35 (dddd, *J* = 13.6, 8.7, 6.7, 5.6 Hz, 1 H), 1.06 (d, *J* = 7.2 Hz, 3 H), 0.88 (s, 9 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 61.3, 51.3, 44.1, 37.5, 32.2, 25.9, 18.3, 15.8, 12.2, –5.3.

Minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69–3.62 (m, 2 H), 3.65 (s, 3 H), 2.38 (ddd, *J* = 13.9, 7.0, 5.8 Hz, 1 H), 1.93–1.85 (m, 1 H), 1.64 (dtd, *J* = 13.5, 7.3, 4.2 Hz, 1 H), 1.31 (dddd, *J* = 13.5, 9.2, 6.6, 5.5 Hz, 1 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 61.1, 51.2, 44.5, 36.4, 32.8, 25.9, 18.3, 17.0, 13.9, –5.4 (2C).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{27}O_3Si$ $[M - CH_3]^+$: 259.1729; found: 259.1727.

Tosylate 39

A solution of ester **38** (7.21 g, 26.3 mmol) in THF (70 mL) was treated at –78 °C with DIBAL-H (1.5 M solution in toluene; 44 mL, 65.7 mmol). After stirring at –78 °C for 2.5 h, a sat. aq solution of NH_4Cl (10 mL), a sat. aq solution of Rochelle salt (100 mL), and EtOAc (50 mL) were added. The mixture was extracted with EtOAc (180 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 5:1) to provide the desired alcohol as a colorless oil (6.31 g, 25.6 mmol, 97% over two steps).

R_f 0.43 (hexane–EtOAc, 3:1)

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67–3.58 (m, 2 H), 3.57–3.42 (m, 2 H), 1.89 (br s, 1 H), 1.78–1.69 (m, 1 H), 1.66–1.54 (m, 2 H), 1.38 (dddd, *J* = 13.5, 8.0, 7.0, 5.6 Hz, 1 H), 0.88 (s, 9 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.7, 61.7, 39.8, 37.8, 30.1, 25.9, 18.3, 14.7, 11.8, –5.3 (2 C).

Minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72–3.66 (m, 2 H), 3.57–3.42 (m, 2 H), 1.89 (br s, 1 H), 1.78–1.69 (m, 1 H), 1.66–1.54 (m, 2 H), 1.22 (dddd, *J* = 13.7, 8.9, 6.1, 4.8 Hz, 1 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.0, 62.0, 40.3, 34.9, 30.4, 25.9, 18.3, 17.5, 12.7, –5.4 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{31}O_2Si$ $[M + H]^+$: 247.2093; found: 247.2101.

A solution of the primary alcohol (6.31 g, 25.6 mmol) in py (50 mL) was treated at 0 °C with TsCl (14.6 g, 76.8 mmol) dissolved in py (20 mL). The mixture was slowly warmed to r.t. with stirring for 16 h, then H_2O (40 mL) was added. The mixture was extracted with MTBE (150 mL). The combined organic layers were washed with a sat. aq solution of $NaHCO_3$ (60 mL), HCl (2 M; 60 mL), brine (60 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 8:1), to provide tosylate **39** as a colorless oil (9.95 g, 24.8 mmol, 97%).

R_f 0.64 (hexane–EtOAc, 3:1)

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.5 Hz, 2 H), 7.35–7.32 (m, 2 H), 3.98–3.81 (m, 2 H), 3.64–3.49 (m, 2 H), 2.44 (s, 3 H), 1.86–1.80 (m, 1 H), 1.78–1.61 (m, 1 H), 1.52–1.44 (m, 1 H), 1.30 (dddd, *J* = 13.2, 8.6, 7.0, 5.9 Hz, 1 H), 0.87 (s, 9 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.71 (d, *J* = 6.8 Hz, 3 H), 0.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 133.1, 129.8, 127.9, 73.7, 61.2, 37.3, 36.5, 29.9, 25.9, 21.6, 18.2, 14.2, 11.3, –5.4 (2 C).

Minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.5 Hz, 2 H), 7.35–7.32 (m, 2 H), 3.98–3.81 (m, 2 H), 3.64–3.49 (m, 2 H), 2.44 (s, 3 H), 1.86–1.80 (m, 1 H), 1.78–1.61 (m, 1 H), 1.52–1.44 (m, 1 H), 1.21 (dddd, *J* = 13.1, 9.6, 7.1, 5.7 Hz, 1 H), 0.87 (s, 9 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 133.1, 129.8, 127.8, 73.4, 61.3, 37.5, 35.7, 31.0, 25.9, 21.6, 18.3, 16.6, 13.5, –5.4 (2 C).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{37}O_4SSi$ $[M + H]^+$: 401.2182; found: 401.2181.

Aldehyde 40

A solution of silyl ether **39** (8.00 g, 20.0 mmol) in THF (40 mL) and py (11.4 mL) was treated with a solution of HF·py (ca. 7:3, 5.2 mL, 200 mmol) at r.t. and the resulting solution was stirred for 14 h. A sat. aq solution of $NaHCO_3$ (100 mL) was carefully added until the solution was pH 7 and the mixture was extracted with MTBE (210 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 1:1) to provide the desired alcohol as a colorless oil (5.40 g, 18.9 mmol, 94%).

R_f 0.28 (hexane–EtOAc, 1:1)

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 3.90 (dd, *J* = 9.6, 7.2 Hz, 1 H), 3.85 (dd, *J* = 9.6, 6.8 Hz, 1 H), 3.68–3.51 m, 2 H), 2.43 (s, 3 H), 1.87–1.80 (m, 1 H), 1.69–1.63 (m, 2 H), 1.57–1.48 (m, 1 H), 1.36 (dddd, *J* = 13.5, 8.7, 7.2, 6.0 Hz, 1 H), 0.78 (d, *J* = 7.5 Hz, 3 H), 0.72 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 132.9, 129.8, 127.8, 73.6, 60.8, 37.2, 36.5, 29.6, 21.6, 14.0, 11.2.

Minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 3.96 (dd, *J* = 9.6, 6.1 Hz, 1 H), 3.83 (dd, *J* = 9.6, 6.8 Hz, 1 H), 3.68–3.51 (m, 2 H), 2.43 (s, 3 H), 1.79–1.71 (m, 1 H), 1.69–1.63 (m, 2 H), 1.57–1.48 (m, 1 H), 1.26 (dddd, *J* = 13.5, 9.9, 7.0, 5.1 Hz, 1 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 132.9, 129.8, 127.8, 73.1, 60.9, 37.4, 35.3, 30.7, 21.6, 16.5, 13.1.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{23}O_4S$ $[M + H]^+$: 287.1317; found: 287.1314.

A solution of $(COCl)_2$ (2.3 mL, 26.4 mmol) in CH_2Cl_2 (50 mL) was treated at –78 °C with DMSO (2.5 mL, 35.3 mmol). After stirring for 45 min, the primary alcohol (5.05 g, 17.6 mmol) dissolved in CH_2Cl_2 (40 mL) was added. The mixture was stirred at –78 °C for 1.5 h, before it was treated with Et_3N (12.3 mL, 88.2 mmol). The solution was slowly warmed to r.t. with stirring over 1 h, then diluted with H_2O (100 mL), and the mixture was extracted with MTBE (210 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to provide aldehyde **40** as a slightly yellow oil, which could be used in the next reaction without further purification.

R_f 0.22 (hexane–EtOAc, 3:1)

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (t, *J* = 1.6 Hz, 1 H), 7.78 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 3.90–3.87 (m, 2 H), 2.44 (s, 3 H), 2.39–2.12 (m, 3 H), 1.88–1.79 (m, 1 H), 0.81 (d, *J* = 6.5 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7, 144.8, 132.8, 129.8, 127.8, 72.8, 48.6, 36.5, 28.1, 21.6, 14.6, 11.5.

Minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (t, *J* = 1.6 Hz, 1 H), 7.77 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 3.93–3.84 (m, 2 H), 2.44 (s, 3 H), 2.39–2.12 (m, 3 H), 1.88–1.79 (m, 1 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 144.9, 132.8, 129.9, 127.8, 72.5, 47.1, 37.1, 29.0, 21.6, 17.2, 13.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{23}NO_4SNa$ [M + Na + MeCN]$^+$: 348.1245; found: 348.1248.

Methyl Ketone 41

To a solution of MeMgCl (22% in THF; 30.8 mL, 88.0 mmol) in THF (50 mL) was added a solution of aldehyde **40** (5.0 g, 17.6 mmol) in THF (40 mL) at –78 °C. The mixture was slowly warmed to –50 °C with stirring for 3.5 h. A sat. aq solution of NH_4Cl (60 mL) was added and the reaction mixture was extracted with MTBE (150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 4:1) to provide the desired secondary alcohol as a slightly yellow oil (4.69 g, 15.6 mmol, 89% over two steps).

R_f 0.40 (hexane–EtOAc, 1:1)

Mixture of four diastereomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.77 (m, 2 H), 7.35–7.33 (m, 2 H), 4.01–3.77 (m, 3 H), 2.44 (s, 3 H), 1.93–1.59 (m, 3 H), 1.39–1.07 (m, 5 H), 0.86–0.71 (m, 6 H).

Major diastereomer

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 133.0, 129.8, 127.9, 73.6, 65.6, 44.0, 37.0, 29.7, 24.4, 21.6, 14.0, 11.4.

Minor diastereomer 1

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 133.0, 129.8, 127.8, 73.7, 66.0, 43.9, 35.9, 29.8, 23.6, 21.6, 14.4, 10.9.

Minor diastereomer 2

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 133.0, 129.8, 127.8, 72.9, 66.6, 42.1, 37.2, 31.5, 23.3, 21.6, 16.9, 13.4.

Minor diastereomer 3

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 133.0, 129.8, 127.9, 73.1, 65.5, 42.0, 37.7, 30.4, 24.6, 21.6, 16.4, 13.0.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{25}O_4S$ [M + H]$^+$: 301.1474; found: 301.1471.

A solution of $(COCl)_2$ (1.9 mL, 22.22 mmol) in CH_2Cl_2 (40 mL) was treated at –78 °C with DMSO (2.1 mL, 29.63 mmol). After stirring for 1.5 h, the secondary alcohol (4.45 g, 14.81 mmol), dissolved in CH_2Cl_2 (35 mL), was added. The mixture was stirred at –78 °C for 1.5 h, then treated with Et_3N (10.3 mL, 74.07 mmol). The solution was slowly warmed to r.t. with stirring over 45 min, then diluted with H_2O (50 mL), and the reaction mixture was extracted with MTBE (150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane–EtOAc, 3:1) afforded methyl ketone **41** as a slightly yellow oil (3.48 g, 11.66 mmol, 79%).

R_f 0.50 (hexane–EtOAc, 1:1)

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.75 (m, 2 H), 7.34–7.32 (m, 2 H), 3.87 (dd, *J* = 9.7, 6.5 Hz, 1 H), 3.83 (dd, *J* = 9.7, 7.2 Hz, 1 H), 2.43 (s, 3 H), 2.41–2.20 (m, 2 H), 2.18–2.07 (m, 1 H), 2.09 (s, 3 H), 1.84–1.74 (m, 1 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 144.7, 132.9, 129.8, 127.8, 73.2, 48.4, 36.4, 30.3, 29.5, 21.6, 14.7, 11.7.

Minor diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.75 (m, 2 H), 7.34–7.32 (m, 2 H), 3.91 (dd, *J* = 9.7, 6.3 Hz, 1 H), 3.82 (dd, *J* = 9.7, 7.3 Hz, 1 H), 2.43 (s, 3 H), 2.41–2.20 (m, 2 H), 2.18–2.07 (m, 1 H), 2.08 (s, 3 H), 1.84–1.74 (m, 1 H), 0.84 (d, *J* = 7.2 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.1, 144.8, 132.8, 129.8, 127.8, 72.7, 47.0, 36.9, 30.3, 30.2, 21.6, 16.7, 13.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}O_4S$ [M + H]$^+$: 299.1317; found: 299.1312.

Olefin 33

A solution of tosylate **41** (2.14 g, 7.17 mmol) in DMF (70 mL) was treated at r.t. with NaI (2.69 g, 17.9 mmol) and DBU (5.4 mL, 35.9 mmol), and the resulting solution was heated to 100 °C with stirring for 2.5 h. After cooling to r.t., the mixture was diluted with Et_2O (25 mL) and H_2O (10 mL), and extracted with Et_2O (90 mL), the combined organic phases were washed with a sat. aq solution of $NaHCO_3$ (40 mL), HCl (2 M; 20 mL), brine (60 mL), dried over $MgSO_4$, and concentrated in vacuo (>550 mbar, bath temperature 30 °C). The crude material was purified by flash column chromatography (pentane–Et_2O, 10:1) to provide olefin **33** as a colorless liquid (430 mg, 3.4 mmol, 40%).

$[\alpha]_D^{23}$ +13.7 (*c* 0.68, $CHCl_3$); R_f 0.54 (hexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65 (s, 2 H), 2.64 (sext, *J* = 7.0 Hz, 1 H), 2.52 (dd, *J* = 15.9, 6.3 Hz, 1 H), 2.33 (dd, *J* = 15.9, 8.0 Hz, 1 H), 2.08 (s, 3 H), 1.66 (s, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 148.8, 109.4, 49.3, 36.5, 30.1, 19.8, 19.4.

HRMS (EI): *m*/*z* calcd for $C_8H_{14}O$ [M]$^+$: 126.1045; found: 126.1045.

Aldehyde 34

DIBAL-H (1 M in hexane; 0.19 mL, 0.28 mmol) was added to a stirred solution of ester **27** (70.0 mg, 232 mmol) in toluene (5 mL) at –78 °C over 15 min. The reaction was stirred for 30 min at –78 °C and then quenched with MeOH (0.40 mL) and an aq solution of Rochelle salt (1 M; 5 mL). The layers were separated and the aqueous layer was extracted with MTBE (25 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 9:1→3:1) to provide aldehyde **34** as a colorless liquid (46.4 mg, 170 mmol, 74%).

$[\alpha]_D^{23}$ +13.8 (*c* 0.98, $CHCl_3$); R_f 0.28 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (d, *J* = 2.0 Hz, 1 H), 4.18 (dddd, *J* = 9.2, 7.0, 5.8, 3.8 Hz, 1 H), 4.09 (dd, *J* = 7.0, 2.1 Hz, 1 H), 4.05 (dd, *J* = 7.9, 5.9 Hz, 1 H), 3.99 (dd, *J* = 6.9, 5.3 Hz, 1 H), 3.50 (dd, *J* = 7.8, 7.0 Hz, 1 H), 2.07–1.97 (m, 1 H), 1.73 (ddd, *J* = 13.6, 9.3, 4.0 Hz, 1 H), 1.48 (s, 3 H), 1.39 (s, 3 H), 1.38–1.32 (m, 1 H), 1.38 (s, 3 H), 1.34 (s, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 110.9, 108.8, 82.6, 80.9, 73.6, 69.8, 37.0, 32.9, 27.0, 26.7, 25.9, 25.7, 14.4.

HRMS (ESI): *m/z* calcd for: $C_{16}H_{27}NO_5Na$ [M + Na + MeCN]$^+$: 336.1785; found: 336.1787.

β-Hydroxy Ketone 42

LiHMDS (1 M in hexane; 0.21 mL, 0.21 mmol) was added dropwise to a solution of ketone **33** (22.9 mg, 182 mmol) in THF (3 mL) at –78 °C. The mixture was stirred for 1 h and then aldehyde **34** (41.8 mg, 154 mmol) dissolved in THF (0.7 mL) was added. The reaction was stopped after 40 min by the addition of a buffer solution at pH 7 (5 mL) and allowed to warm to r.t. The aqueous layer was extracted with MTBE (25 mL). The organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 4:1) to provide aldol product **42** as a colorless liquid (30.3 mg, 76.0 mmol, 50%, dr 15:1).

$[\alpha]_D^{23}$ –31.5 (*c* 1.24, $CHCl_3$); R_f 0.33 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72–4.70 (m, 2 H), 4.19 (dddd, *J* = 8.5, 7.2, 5.9, 4.5 Hz, 1 H), 4.05 (dd, *J* = 7.8, 5.9 Hz, 1 H), 4.01–3.96 (m, 1 H), 3.91 (dd, *J* = 6.8, 4.0 Hz, 1 H), 3.68 (dd, *J* = 7.7, 6.9 Hz, 1 H), 3.50 (app t, *J* = 7.5 Hz, 1 H), 3.27 (d, *J* = 4.0 Hz, 1 H), 2.84 (dd, *J* = 17.9, 2.5 Hz, 1 H), 2.71 (app sext, *J* = 6.9 Hz, 1 H), 2.60 (dd, *J* = 17.7, 8.8 Hz, 1 H), 2.60 (dd, *J* = 15.9, 6.8 Hz, 1 H), 2.41 (dd, *J* = 15.8, 7.5 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.77 (ddd, *J* = 13.6, 8.7, 4.8 Hz, 1 H), 1.71 (dd, *J* = 1.3, 1.0 Hz, 3 H), 1.45–1.37 (m, 1 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 148.7, 109.8, 108.9, 108.7, 83.7, 79.7, 74.1, 69.9 (2 C), 49.3, 46.0, 38.4, 36.5, 32.4, 27.4, 27.3, 27.1, 25.8, 19.9, 19.6, 13.5.

HRMS (ESI): *m/z* calcd for $C_{22}H_{38}O_6Na$ [M + Na]$^+$: 421.2566; found: 421.2578.

(*S*)-Mosher Ester 43

Et_3N (18 mL, 0.13 mmol), DMAP (2.0 mg, 16 mmol), and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (12 mL, 64 mmol) were added to a stirred solution of alcohol **42** (6.4 mg, 16 mmol) in CH_2Cl_2 (1 mL) at r.t. The reaction was quenched with EtOAc (10 mL) after 3.5 h and the organic layer was washed with a solution of $NaHSO_4$ (1 M; 15 mL), NaOH (2 M; 5 mL), a sat. aq solution of $NaHCO_3$(10 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the crude (*S*)-Mosher ester **43** as a colorless liquid (12.0 mg).

R_f 0.49 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.51 (m, 2 H), 7.40–7.37 (m, 3 H), 5.58 (dt, *J* = 8.0, 3.8 Hz, 1 H), 4.68–4.64 (m, 2 H), 4.14 (dddd, *J* = 9.3, 7.2, 5.7, 3.7 Hz, 1 H), 4.08 (dd, *J* = 7.9, 3.8 Hz, 1 H), 4.03 (dd, *J* = 7.9, 5.8 Hz, 1 H), 3.63 (dd, *J* = 7.5, 4.8 Hz, 1 H), 3.54–3.53 (m, 3 H), 3.49 (t, *J* = 7.5 Hz, 1 H), 2.92 (dd, *J* = 17.8, 8.2 Hz, 1 H), 2.70 (dd, *J* = 17.8, 3.4 Hz, 1 H), 2.61 (app sext, *J* = 6.8 Hz, 1 H), 2.53 (dd, *J* = 16.2, 6.3 Hz, 1 H), 2.24 (dd, *J* = 16.2, 6.3 Hz, 1 H), 1.98–1.90 (m, 1 H), 1.75–1.69 (m, 1 H), 1.68–1.67 (m, 3 H), 1.44–1.37 (m, 1 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.5, 165.7, 148.9, 132.0, 129.6, 128.3 (2 C), 127.5 (2 C), 109.6, 109.3, 108.8, 82.0, 78.4, 73.6, 72.3, 69.9, 55.4 (app q, $^3J_{C\text{-}F}$ = 1.2 Hz), 49.0, 42.1, 37.7, 36.3, 32.3, 27.2, 27.1, 26.9, 25.8, 20.1, 19.4, 13.7.

HRMS (ESI): *m/z* calcd for $C_{32}H_{45}F_3O_8Na$ [M + Na]$^+$: 637.2964; found: 637.2957.

(*R*)-Mosher Ester 44

Et_3N (18 mL, 0.13 mmol), DMAP (2.0 mg, 16 mmol), and (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (12 mL, 64 mmol) were added to a stirred solution of alcohol **42** (6.4 mg, 16 mmol) in CH_2Cl_2 (1 mL) at r.t. The reaction was quenched with EtOAc (10 mL) after 4.5 h. The organic layer was washed with a solution of $NaHSO_4$ (1 M; 15 mL), NaOH (2 M; 5 mL), a sat. aq solution of $NaHCO_3$ (10 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the crude (*R*)-Mosher ester **44** as a colorless liquid (13.0 mg).

R_f 0.49 (hexane–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2 H), 7.41–7.38 (m, 3 H), 5.51 (ddd, *J* = 8.0, 4.6, 3.6 Hz, 1 H), 4.70–4.68 (m, 2 H), 4.09 (dddd, *J* = 9.3, 6.9, 6.1, 3.3 Hz, 1 H), 4.04–3.98 (m, 2 H), 3.54 (dd, *J* = 7.0, 5.3 Hz, 1 H), 3.52–3.51 (m, 3 H), 3.46 (t, *J* = 7.5 Hz, 1 H), 2.92 (dd, *J* = 17.8, 7.9 Hz, 1 H), 2.82 (dd, *J* = 17.8, 3.4 Hz, 1 H), 2.67 (app sext, *J* = 6.8 Hz, 1 H), 2.60 (dd, *J* = 16.2, 6.3 Hz, 1 H), 2.35 (dd, *J* = 15.9, 7.3 Hz, 1 H), 1.92–1.89 (m, 1 H), 1.70–1.69 (m, 3 H), 1.60 (ddd, *J* = 13.5, 9.2, 4.1 Hz, 1 H), 1.44–1.34 (m, 1 H), 1.39 (s, 3 H), 1.34 (s, 6 H), 1.32 (s, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 166.0, 148.8, 132.1, 129.6, 128.4 (2 C), 127.5 (2 C), 109.7, 109.5, 108.7, 82.4, 78.5, 73.6, 72.4, 69.9, 55.5 (app q, $^3J_{C\text{-}F}$ = 1.5 Hz), 49.0, 42.8, 37.7, 36.4, 32.4, 27.3, 27.2, 27.0, 25.8, 20.0, 19.5, 13.7.

HRMS (ESI): *m/z* calcd for $C_{32}H_{45}F_3O_8Na$ [M + Na]$^+$: 637.2964; found: 637.2957.

***anti*-Diol 45**

To a stirred suspension of $Me_4NBH(OAc)_3$ (106 mg, 402 mmol) in MeCN (1.5 mL) was added AcOH (100%, 1.5 mL) at r.t. After stirring for 40 min the reaction was cooled to –35 °C and a solution of hydroxy ketone **42** (20.0 mg, 50.2 mmol) in MeCN (1 mL) and AcOH (100%, 0.7 mL) was added. After 24 h an aq solution of Rochelle salt (0.5 M; 4 mL) was added and the reaction was allowed to warm to r.t. over 30 min. The reaction was quenched by the addition of CH_2Cl_2 (10 mL) and a sat. aq solution of $NaHCO_3$ (8 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with a sat. aq solution of $NaHCO_3$ (5 mL). The aqueous phases were re-extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 4:1) to provide *anti*-diol **45** as a colorless liquid (13.3 mg, 33.2 mmol, 66%, dr 19:1).

$[\alpha]_D^{23}$ –10.6 (*c* 0.83, $CHCl_3$); R_f 0.37 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84–4.81 (m, 1 H), 4.75–4.72 (m, 1 H), 4.20 (dddd, *J* = 8.5, 6.9, 6.1, 4.4 Hz, 1 H), 4.09–4.02 (m, 1 H), 4.06 (dd, *J* = 7.9, 5.8 Hz, 1 H), 3.97 (dd, *J* = 6.8, 3.8 Hz, 1 H), 3.95–3.90 (m, 1 H), 3.76 (t, *J* = 6.8 Hz, 1 H), 3.51 (t, *J* = 7.7 Hz, 1 H), 3.07 (br s, 1 H), 2.43 (br s, 1 H), 2.41–2.33 (m, 1 H), 2.04–1.93 (m, 1 H), 1.77 (ddd, *J* = 13.9, 9.0, 4.9 Hz, 1 H), 1.77–1.66 (m, 2 H), 1.72–1.71 (m, 3 H), 1.64–1.59 (m, 2 H), 1.44 (ddd, *J* = 13.7, 9.4, 4.3 Hz, 1 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8& nbsp;Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 110.3, 108.7 (2 C), 82.8, 80.4, 74.2, 70.6, 69.9, 69.1, 42.5, 39.4, 39.0, 37.8, 32.4, 27.5, 27.4, 27.1, 25.8, 20.0, 19.5, 13.4.

HRMS (ESI): *m/z* calcd for $C_{22}H_{40}O_6Na$ [M + Na]$^+$: 423.2723; found: 423.2739.

Silyl Ether 46

A solution of diol **45** (2.5 mg, 6.2 mmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C. 2,6-Lutidine (9.2 mL, 79 mmol) and TIPSOTf (12.2 mL, 45.4 mmol) were added. The reaction mixture was stirred for 3.5 h at r.t. and subsequently quenched with a sat. aq solution of $NaHCO_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic layers were washed with an aq so-

lution of $NaHSO_4$ (1 M; 10 mL), a sat. aq solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane–EtOAc, 9:1) to provide silyl ether **46** as a colorless oil in quantitative yield (3.5 mg, 6.2 mmol).

$[\alpha]_D^{23}$ –16.9 (*c* 0.35, $CHCl_3$); R_f 0.26 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72–4.70 (m, 1 H), 4.69–4.68 (m, 1 H), 4.21 (dddd, *J* = 8.5, 7.0, 6.1, 4.3 Hz, 1 H), 4.11–4.06 (m, 1 H), 4.06 (dd, *J* = 8.0, 6.0 Hz, 1 H), 4.00 (dd, *J* = 6.5, 4.4 Hz, 1 H), 3.98–3.93 (m, 2 H), 3.65 (app t, *J* = 6.7 Hz, 1 H), 3.50 (t, *J* = 7.7 Hz, 1 H), 2.23–2.13 (m, 1 H), 2.02–1.96 (m, 1 H), 1.96 (ddd, *J* = 14.8, 3.7, 1.8 Hz, 1 H), 1.82 (ddd, *J* = 13.7, 8.7, 4.6 Hz, 1 H), 1.81–1.68 (m, 3 H), 1.66–1.65 (m, 3 H), 1.42 (ddd, *J* = 14.0, 9.0, 4.9 Hz, 1 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.09–1.05 (m, 21 H), 1.03 (d, *J* = 7.2 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 110.8, 108.8, 108.6, 83.1, 81.7, 74.0, 70.8, 70.3, 70.0, 40.1, 38.5, 38.3, 36.3, 32.7, 27.6, 27.5, 27.1, 25.9, 20.9, 18.1 (7 C), 13.4, 12.3 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{60}O_6SiNa$ $[M + Na]^+$: 579.4057; found: 579.4075.

Ketone 47

A solution of silyl ether **46** (2.5 mg, 4.5 mmol) in CH_2Cl_2 (1 mL) was added to MS (4 Å) and cooled to 0 °C. To this suspension NMO (2.2 mg, 19 mmol) and after 10 min TPAP (0.2 mg, 0.6 mol) were added. The reaction was warmed to r.t. in 20 min. After stirring for an additional 30 min a second aliquot of NMO (2.2 mg, 19 mmol) and TPAP (1.0 mg, 2.8 mmol) were added. After stirring for 1 h the mixture was filtered through silica gel and washed with EtOAc (15 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to provide **47** as a colorless oil (0.7 mg, 1.3 mmol, 28%).

$[\alpha]_D^{23}$ +27.1 (*c* 0.07, $CHCl_3$); R_f 0.33 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68–4.67 (m, 2 H), 4.33 (app quin, *J* = 6.1 Hz, 1 H), 4.17 (dddd, *J* = 8.7, 7.2, 5.8, 4.3 Hz, 1 H), 4.06 (d, *J* = 7.2 Hz, 1 H), 4.05 (dd, *J* = 7.9, 5.8 Hz, 1 H), 4.01 (dd, *J* = 7.2, 4.1 Hz, 1 H), 3.49 (dd, *J* = 7.7, 7.3 Hz, 1 H), 3.00 (dd, *J* = 17.1, 6.1 Hz, 1 H), 2.75 (dd, *J* = 17.2, 5.3 Hz, 1 H), 2.31 (app sext, *J* = 6.9 Hz, 1 H), 2.04–1.95 (m, 1 H), 1.72 (ddd, *J* = 13.7, 9.1, 4.1 Hz, 1 H), 1.72–1.64 (m, 1 H), 1.67 (t, *J* = 1.2 Hz, 3 H), 1.48–1.37 (m, 1 H), 1.45–1.32 (m, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.19–1.05 (m, 21 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 149.8, 109.8, 108.7 (2 C), 83.0, 81.2, 73.8, 69.9, 66.9, 46.4, 43.1, 37.7, 37.3, 32.5, 27.1, 26.8, 26.1, 25.8, 20.1, 19.0, 18.2 (6 C), 13.7, 12.7 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{58}O_6SiNa$ $[M + Na]^+$: 577.3900; found: 577.3895.

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