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Synthesis of the aglycon of the antibiotic disciformycin

Michael Wolling and Andreas Kirschning*[a]

Abstract: The synthesis of the aglycon of disciformycin, a new secondary metabolite from *Pyxidicoccus fallax*, is reported. The disciformycins are highly potent antibiotics including inhibitory activity towards methicillin- and vancomycin-resistant *Staphylococcus aureus*. The stereocontrolled installation of the olefinic double bonds at C2-C3/C3-C4 and C12-C13, respectively, as well the orthogonal differentiation of the oxy functionalities turned out to be key challenges of our approach.

Introduction

Recently, a group of macrocyclic polyketides was independently reported by the groups of Müller and Nett.[1,2] Disciformycins A (**1**) and B (**2**) were isolated *from Pyxidicoccus fallax AndGT8*. Both disciformycins inhibit growth of methicillin- and vancomycin-resistant *Staphylococcus aureus*, with disciformycin B (**2**) bearing stronger inhibiting activity.

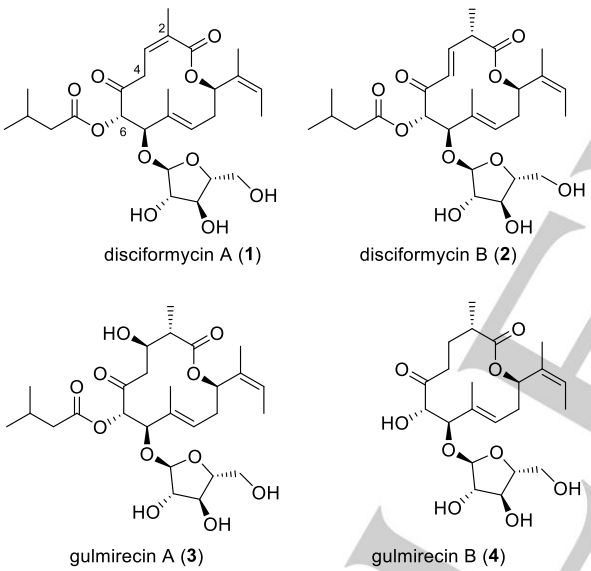
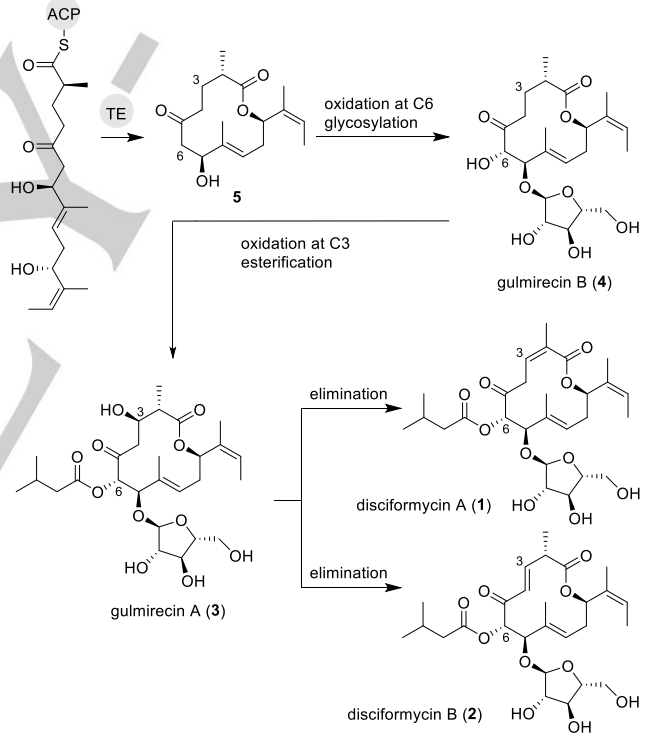


Figure 1. Structures of the disciformycins A (**1**) and B (**2**) and the gulmirecins A (**3**) and B (**4**).

Nett and coworkers disclosed the structures of gulmirecins A (**3**) and B (**4**), that were isolated from the predatory bacterium *Pyxidicoccus fallax* HKI 727. The gulmirecins also exhibit strong activity against staphylococci, including methicillin-resistant *Staphylococcus aureus*, with gulmirecin B (**4**) showing significantly less activity than A (**3**). No cytotoxic effects on human cells were encountered for all four natural products.

Structurally, these four polyketides only differ in the region at C2-C4 and the missing isovaleric ester on C6 in gulmirecin B (**4**). Due to their novel scaffold they provide a starting point for a total synthesis program, which will provide further insight into their structure–activity relationship.

We suggest that the four polyketides are biosynthetically linked to each other as depicted in Scheme 1. The last ACP-bound polyketide synthase intermediate cyclizes under the catalytic influence of the thioesterase to furnish macrolactone **5**. Then, two tailoring steps (Cyp450-based oxidation at C6 and glycosylation at C7 leads to gulmirecin B (**4**). Next, oxidation at C3 and esterification at C6 provides gulmirecin A (**3**). Elimination of the hydroxyl group at C3 can either lead to disciformycin A (**1**) and B (**2**), respectively. At this stage it is not clear whether both disciformycins are interconvertible, either enzymatically or chemically.



Scheme 1. Proposed biosynthetic relationship between gulmirecins and diciformycins starting from the last ACP-bound polyketide synthase intermediate (ACP= acyl carrier protein, TE= thioesterase).

Synthetically, the disciformycins bear several challenges, which are: a) A well-orchestrated protecting group strategy has to be developed for differentiating differently functionalized oxygen-bearing functionalities, b) stereo- and position control of the double bond at C3-C4 in disciformycin A (**1**) and C2-C3 in disciformycin B (**2**) has to be achieved, c) stereocontrol of the trisubstituted alkene at C12-C13 has to be achieved.

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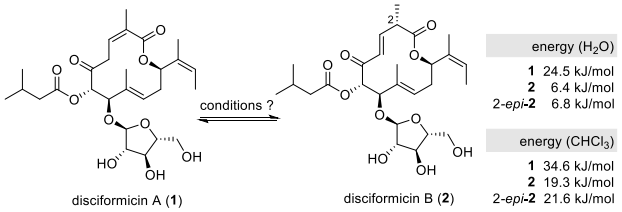
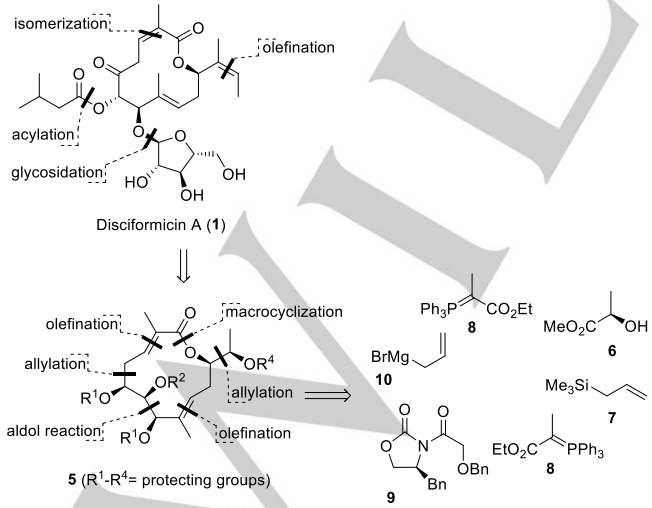
Results and Discussion

Disciformycin A (**1**) was chosen as the synthetic target, since computer modeling of the ground state energy of the disciformycins A (**1**), B (**2**) and 2-*epi*-disciformycin B (2-*epi*-**2**) (in H_2O as well as $CHCl_3$) suggests, that it might be possible to convert disciformycin A (**1**) to disciformycin B (**2**) under thermodynamically controlled reaction conditions, allowing direct access to the respective other natural product. The structurally closely related disciformycins B (**2**) and 2-*epi*-B (2-*epi*-**2**) might lead to a mixture of both compounds during this isomerization process.



Scheme 2. Interconversion of discifomrycins A (**1**) and B (**2**) and calculated ground state energies of the disciformycins A, B, and 2-*epi*-B (for details see SI).

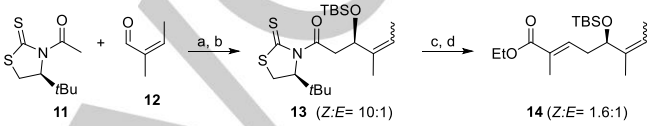
The retrosynthetic plan depicted in Scheme 3 is the result of several synthetic efforts to synthetically access the aglycons of the disciformycins (**1/2**).[4] Basically, the macrolactone is stripped off all elements attached to hydroxyl groups (isobutyric acid, D-arabinose) and the alkene unit at C11. We were aware of the fact, that isomerization of *Z*-configured-*α*,*β*-unsaturated acids can occur during macrolactonization.[4] Therefore, we chose the *E*-configured macrocycle **5** as synthetic target and isomerization was planned to be initiated towards the end of the the total synthesis. The macrolactone **5** is planned to be formed by macrolactonization and the precursor *seco*-acid is dissected into building blocks **6**-**10**. Several aldol reactions and allylations as well as olefinations were chosen to create the carbon backbone.



Scheme 3. Retrosynthetic considerations and planning.

Initially the introduction of the correctly (*Z*)-configured olefinic double bond at C12-C13 was planned to occur at the beginning of the synthesis. (*Z*)-2-Methyl-but-2-enal (**12**) was coupled with the Nagao building block **11** to yield the aldol product[5] which was silyl-protected (Scheme 4). The resulting silyl ether **13** was collected in good diastereomeric ratio. Nevertheless, we had to abandon this approach, because reductive removal of the auxiliary and Wittig olefination[6] led to almost complete loss of a defined stereochemistry on the trisubstituted double bond in ester **14**.

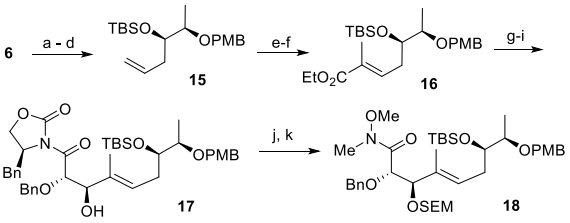
Scheme 4. Isomerization of the (*Z*)-olefine motif at C12-C13 (disciformycin numbering) (DIPEA= di*iso*propylethyl amine; Dibal-H= di*iso*butylaluminium hydride; *t*Bu= *tert*-butyl; TBS= *tert*-butyldimethylsilyl).



Reagents and conditions: a. $TiCl_4$, DIPEA, CH_2Cl_2, -95°C, 50 min; b. TBSOTf, 2,6 lutidine, CH_2Cl_2, (78% for 2 steps); c. Dibal-H, toluene, -78 °C, 1 h; d. $Ph_3PC(Me)CO_2Et$ **8**, CH_2Cl_2, 50°C, 60 h.

Consequently, we had to alter the synthesis and decided to introduce the alkene at a late stage of the total synthesis. The synthesis towards the linear precursor started from methyl (*R*)-lactate (**6**) (Scheme 5). This was converted into alkene **15** after *O*-protection[7], reduction to the aldehyde followed by a chelation controlled Hosomi-Sakurai allylation[8-9], and *O*-silylation. Next, ozonolysis provided the aldehyde[9] which was subjected to Wittig olefination conditions[6] to yield ethyl ester **16** with excellent stereocontrol (>10:1).

Scheme 5. Preparation of linear precursor **18** (PMB= p-methoxybenzyl; CSA= camphorsulfonic acid; TF= trifluoromethylsulfonyl; SEM= trimethylsilylethoxymethyl; DMAP= p-dimethylamino pyridine).



Reagents and conditions: a) $(CCl_3)CNH(OPMB)$, CSA, CH_2Cl_2, rt, 18 h (95 %); b) Dibal-H, CH_2Cl_2, -78 °C, 1 h; c) $SnCl_4$, **7**, CH_2Cl_2, -78 °C, 100 min; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 40 min (69 % for 3 steps), d.r.= 7:1; e) O_3, PPh_3, CH_2Cl_2/MeOH, -78 °C, 5 min; f) **8**, CH_2Cl_2, 40 °C, 18 h (87 % for 2 steps); g) $LiAlH_4$, THF, 0 °C, 20 min; h) MnO_2, CH_2Cl_2, rt, 5 h; i) **9**, Bu_2BOTf, NEt_3, PhMe, -78 °C, 16 h (61 % for 3 steps, d.r.= >10:1); j) Dibal-H in cyclohexane, Me(MeO)NH·HCl, -30 °C, 2 h (90%); k) SEMCl, DIPEA, DMAP, 40 °C, 18 h, 100 %.

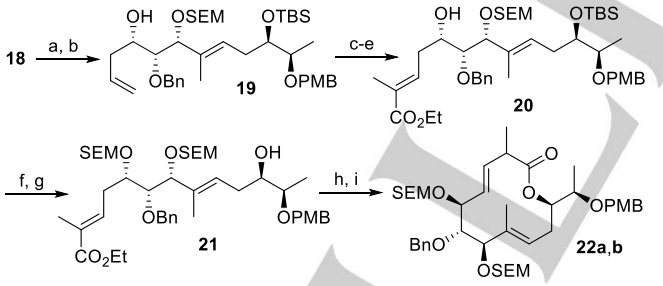
The ester was transformed into the corresponding aldehyde, which was subjected to an Evans aldol protocol using functionalized Evans auxiliary **9**.[10] The aldol product **17** was obtained with good diastereocontrol (>10:1) and could straightforwardly be transformed into Weinreb amide **18** by

direct transamidation[11] followed by protection of the free alcohol with the SEM-group.[12] With respect to yields, this sequence turned out to be superior to the one with reversed timing of protection and amide formation. Weinreb amide **18** was further elaborated towards macrolactone formation by first nucleophilic allylation[13] followed by diastereocontrolled reduction of the intermediate ketone using the CBS-reagent and $BH_3{\cdot}SMe_2$ (Scheme 6).[14] The resulting (*S*)-configured alcohol **19** was obtained with excellent stereocontrol. The configuration of the newly formed stereogenic center was determined using the Mosher-ester method.[15] It is worth mentioning that this reaction proceeds with strong substrate control, furnishing the same product with both CBS-enantiomers. Surprisingly, reduction using $Zn(BH_4)_2$ gave the other epimer in 63 % yield. Reduction with $NaBH_4$ led to a 1:1 mixture of diastereoisomers.

The alternative sequence, reduction to the aldehyde followed by diastereoselective allylation failed to deliver satisfying results.

Next, the allyl alcohol **19** was transformed into the ester **21** bearing the complete carbon backbone required for macrocyclization. The synthetic sequence consisted of dihydroxylation and periodate cleavage[16], Wittig olefination[6] and provided α,β-unsaturated ester **20** which was followed by protection of the free alcohol as SEM-acetal[12] and final removal of the TBS group at C11.[17] This set the stage for lactone formation. First ester hydrolysis provided the *seco* acid derivative which was smoothly cyclized under Yamaguchi conditions[18] to yield the macrolactones **22**, surprisingly deconjugated with respect to the olefinic double bond (C2-C3→C3-C4). As a consequence a new stereogenic center is formed at C2 so that macrolactone **22** was isolated as an unseparable mixture (4:1) of diastereomers.

Scheme 6. Synthesis of macrolacton **22**.

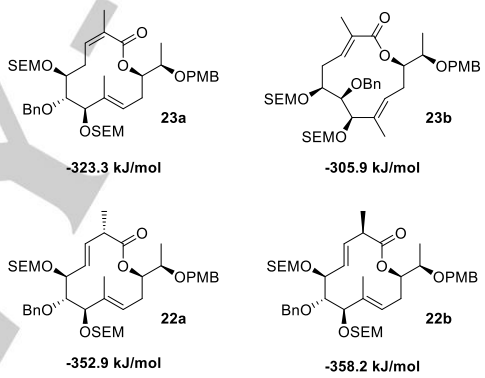


Reagents and conditions: a) Allyl-MgBr, THF, -78 °C, 15 min; b) (*R*)-CBS, $BH_3{\cdot}SMe_2$, THF, -78 °C, 1 h, -50 °C, 15 h (95 % for 2 steps), d.r.> 10:1; c) AD-mix-*β*, *t*BuOH/H_2O (1:1), rt, 21 h; d) $NaIO_4$, THF/H_2O (1:1), rt, 2 h; e) **8**, CH_2Cl_2, 0 °C, 4 h, then rt, 16 h (56 % over 3 steps); f) SEMCl, DIPEA, DMF, 40 °C, 18 h (80 %); g) HF·pyr, pyr, THF (1:3:5) (0.04 M) rt, 3 d (74 %); h) LiOH (1 M), THF, MeOH (1:1:1), 40 °C, 25 h; i) 2,4,6-trichlorobenzoyl chloride, DIPEA, 90 min, then slow addition over a period of 17 h to DMAP, PhMe (0.01 M), 80 °C (69% over 2 steps) d.r.= 4:1.

Several additional aspects of this synthetic sequence are worth discussing. An alternative approach based on cross metathesis for introducing the ester[19] was not successful, whereas dihydroxylation using OsO_4[20] instead of the AD-mix mixture turned out to lack chemoselectivity with respect to the olefinic double bond. For achieving best yields on a multigram scale, it was also important to carry out the Wittig olefination under mild conditions.

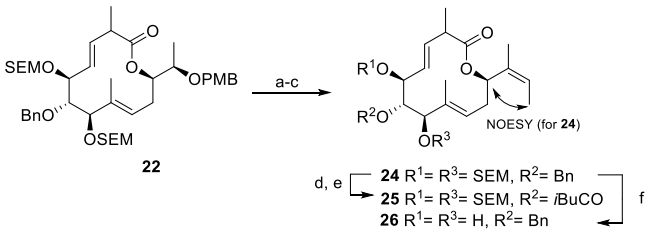
As pointed out, migration of the olefinic double bond occurred during macrocyclization. Several efforts to isomerize the double bond in **22a**,**b** back to the conjugated system were pursued, however, different acidic as well as basic conditions did not affect this isomerization. To understand these unexpected results, the ground state energies of the possible isomers were calculated by molecular modeling (figure 2). With these data in hand, one can conclude that compared to macrocycles **22a,b** the *E*-configured macrocycle **23b** is less stable and hence its formation is not observed. These results explain the observation that macrolactone **22** was formed under the macrolactonization conditions as mixture of diastereoisomers. It also provides a rationale of why the *Z*-configured macrocycle **23a** was not formed through an isomerization process under thermodynamic conditions.

Figure 2. Calculated ground state energies of isomers **22a**,**b** and **23a**,**b**.



Next, the installation of the *Z*-configured alkene was pursued and finally achieved by first removing the PMB-protection in macrolactones **22**,[21] oxidation of the resulting alcohol[22] and Wittig olefination.[23] A reaction temperature of -50°C was the key to successfully obtain the desired *Z*-alkene **24**. Furthermore, it was important to add the ketone to an excess of the Wittig ylide and conduct the olefination in a mixture of DME and HMPA.

Scheme 7. Final steps of the synthesis.



Reagents and conditions: a) DDQ, CH_2Cl_2:pH7-buffer 10:1, 0 °C, 3 h; b) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 75 min, (55 % over 2 steps, d.r.= 6:1); c) $EtPPh_3{\cdot}Br$, KHMDS, DME:HMPA 10:1, -50 °C, 20 min, (70 %, d.r.= 6:1); d) DDQ, CH_2Cl_2/pH7-buffer 10:1, 35 °C, 20 h; e) isovaleric anhydride, DIPEA, DMAP, CH_2Cl_2, rt, 3 d, (68 % over 2 steps, d.r.= 10:1); f) $ZnCl_2{\cdot}OEt_2$, Et_2O, EtSH, 0 °C, 1 h, (69 %, d.r.= 10:1).

The configuration of the olefinic double bond was confirmed by a ^{1}H-NMR NOESY experiment. Conditions for the manipulation of the three hydroxyl groups were tested. Introduction of the ester side chain at C6 was possible using DDQ at elevated temperatures for removal of the benzyl group. [24] However, it was not possible to remove the SEM groups from the resulting ester **25** without substantial decomposition or acyl migration, but it is possible to cleave both SEM groups in benzyl ether **24** furnishing diol **26**.[25]

Conclusions

In essence, we developed the first total synthesis of the aglycon of disciformycin B. It unravels the principal synthetic challenges of these macrolactones. Key issues to be solved are associated with the stereochemistry and position of the two olefinic double bonds at C2-C3/C3-C4 and C12-C13 and with the orthogonal differentiation of the oxy-functionalities. This work allows to successfully access the disciformycins and the structurally related gulmirecins and subsequently paves the way to develop a medicinal chemistry programme for these highly active antibacterial polyketides.

Experimental Section

General information: ^{1}H-NMR spectra were recorded at 400 MHz or 500 MHz, respectively, and ^{13}C-NMR spectra were recorded at 100 MHz or 125 MHz, respectively, with a Bruker Avance 400, DPX 400 or DRX 500. Chemical shift values of NMR data are reported as values in ppm relative to (residual undeuterated) solvent signal as internal standard. Multiplicities for ^{1}H-NMR signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; where appropriate with the addition of b = broad. The residual undeuterated solvent signals were used as an internal standard for the ^{1}H-NMR spectra; the carbon signal was used for the ^{13}C spectra.[26] Chemical shifts δ are given in ppm, coupling constants J in Hertz (Hz). Multiplicities for ^{1}H-NMR signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The multiplicity of the ^{13}C-NMR signals is given as: p = primary, s = secondary, t = tertiary, q = quaternary. Assignment of the benzyl and PMB protecting groups is presented: for aromatic rings= Ar, for benzylic positions= Bn and for methoxy groups in PMB= ArOMe. Mass spectra were obtained with a type LCT (ESI) (Micromass) equipped with a lockspray dual ion source in combination with a Waters Alliance 2695 LC system, or with a type QTOF premier (Micromass) spectrometer (ESI mode) in combination with a WATERS Acquity UPLC system equipped with a Waters BEH C18 1.7 µm (SN 01473711315545) column (solvent A: water + 0.1%(v/v) formic acid, solvent B: MeOH + 0.1 % (v/v) formic acid; flow rate = 0.4 mL/min; gradient (t [min]/solvent B [%]): (0:5) (2.5:95) (6.5:95) (6.6:5) (8:5)). Ion mass signals (m/z) are reported as values in atomic mass units. Melting points were measured using a SRS OptiMelt apparatus.Optical rotations were measured on a Perkin-Elmer polarimeter type 341 or 241 in a quartz glass cuvette at l = 589 nm (Na D-line). The optical rotation is given in [° ml·g^{-1}·dm^{-1}] with c= 1 corresponding to 10 mg ml^{-1}. Flash chromatography was performed using silica gel with a particle size of 40 to 63 µm as the stationary phase (Machery-Nagel); mixtures of petroleum ether (PE) and ethyl acetate (EA) as mobile phase. High resolution mass spectra were obtained with a Micromass LCT via loop-mode injection from a Waters (Alliance 2695) HPLC system or via a Micromass Q-TOF in combination with a Waters Aquity Ultraperformance LC system. Ionization is achieved by ESI. All reactions were performed under an argon atmosphere unless otherwise stated. Glassware was dried by heating under vacuum followed by flushing with argon gas prior to use. Dry solvents were obtained after filtration through drying columns on a M. BRAUN solvent purification system or purchased from commercial providers. Wittig reagent **8** was was prepared according to reference [27]. Evans building block **9** was prepared according to reference [28].

Synthesis of homoallyl alcohol 15 from methyl lactate 6: To a solution of methyl (*R*)-2-[(4-methoxybenzyl)oxy]propanoate (8.71 g, 38.9 mmol, 1.0 eq.; obtained according to reference [7]) in CH_2Cl_2 (390 ml) at -78 °C was added a solution of DiBAl-H (1M in PhMe, 42.8 ml, 42.8 mmol, 1.1 eq.) dropwise over 15 min. The solution was stirred for 1 h at -78 °C, before an aqueous saturated solution of potassium sodium tartrate was added. It was stirred for 3 h at rt and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The aldehyde was added dropwise to a solution of $SnCl_4$ (4.53 ml, 38.9 mmol, 1 eq.) in CH_2Cl_2 (180 ml) at -78 °C and the red solution was stirred for 15 min. Allyltrimethylsilane (6.78 ml, 42.8 mmol, 1.1 eq.) was added and it was stirred for 100 min at -78 °C. The reaction was terminated by addition of H_2O (90 ml). The aqueous phase was extracted with CH_2Cl_2 (3x) the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to a volume of about 100 ml. The resulting solution was cooled to -78 °C and 2,6-lutidine (18.1 ml, 155 mmol, 4.0 eq.) and TBSOTf (14.1 ml, 77.7 mmol, 2 eq.) were added sequentially. After stirring at room temperature for 40 min, the reaction was terminated by addition of a saturated NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash chromatography (10:1) afforded the title compound **15** (9.39 g, 26.8 mmol, 69 % over 3 steps) as a colorless oil. ^{1}H-NMR-spectroscopic data and the optical rotation are in accordance with those published in the literature.[9]
$[\alpha]_D^{24}$= +0.42° (c= 2.16, $CHCl_3$; ref.: +0.40° [c= 2.4, $CHCl_3$]); ^{1}H-NMR (400 MHz, $CDCl_3$) □: 7.28-7.24 (2H, m, H_{Ar}), 6.89-6.85 (2H, m, H_{Ar}), 5.88-5.77 (1H, ddt, J= 17.1, 10.3, 7.2 Hz, H-2), 5.07-5.00 (2H, m, H-1), 4.52 (1H, d, J= 11.6, H_{Bn}), 4.44 (1H, d, J= 11.6 Hz, H_{Bn}), 3.80 (3H, s, H_{ArOMe}), 3.72 (1H, ddd, J= 8.0, 4.7, 3.6 Hz, H-4), 3.47 (1H, dq, J= 4.7, 6.4 Hz, H-5), 2.41-2.33 (1H, m, H-3), 2.15-2.08 (1H, m, H-3), 1.12 (3H, d, J= 6.4 Hz, H-6), 0.87 (9H, s, H_{TBS}), 0.01 (3H, s, H_{TBS}), -0.02 (3H, s, H_{TBS}) ppm.

Synthesis of ethyl hept-2-enoate 16: A solution of homoallyl alcohol **15** (9.39 g, 26.8 mmol, 1.0 eq.) in a 5:1 mixture of CH_2Cl_2/MeOH (54 ml) was cooled to -78 °C. Ozone was passed through the solution until the blue color persisted. Then oxygen gas was lead through the solution until the blue color had disappeared and PPh_3 (21.1 g, 80.5 mmol, 3.0 eq.) was added. The solution was warmed to room temperature and stirred for an additional hour and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 ml) and Wittig reagent **8** (5.15 g, 14.2 mmol, 3.0 eq.) was added. The solution was stirred for 18 h at 40 °C. Silica gel was added and the solvent was removed under reduced pressure. Flash chromatography of the loaded silica gel sample (20:1) afforded the title compound **16** (10.2 g, 23.3 mmol, 87 %) as a colorless oil.
$[\alpha]_D^{26}$= +2.70° (c= 1.11, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26-7.22 (2H, m, H_{Ar}), 6.89-6.85 (2H, m, H_{Ar}), 6.85-6.81 (1H, m, H-3), 4.53 (1H, d, J= 11.6 Hz, H_{Bn}), 4.43 (1H, d, J= 11.6 Hz, H_{Bn}), 4.18 (1H, q, J= 7.2 Hz, H_{Et}), 3.84-3.81 (1H, m, H-5), 3.80 (3H, s, H_{ArOMe}), 3.50 (1H, dq, J= 4.8, 6.5 Hz, H-6), 2.46 (1H, m, H-4), 2.31-2.23 (1H, m, H-4), 1-84 (3H, d, J= 1.2 Hz, H-8), 1.28 (3H, t, J= 7.2 Hz, H_{Et}), 1.14 (3H, d, J= 6.5 Hz), 0.85 (9H, s, H_{TBS}), 0.00 (3H, s, H_{TBS}), -0.03 (3H, s, H_{TBS}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.2 (q, C-1), 159.3 (q, C_{Ar}), 140.1 (t, C-3), 131.0 (q, C_{Ar}), 129.2 (t, C_{Ar}), 128.8 (q, C-2), 113,9 (t, C_{Ar}), 77.0 (t, C-6), 73.0 (t, C-5), 70.8 (s, C_{Bn}), 60.4 (s, C_{Et}), 55.4 (p, C_{ArOMe}), 30.8 (s, C-4), 25.9 (p, C_{TBS}), 18.1 (q, C_{TBS}), 14.4 (p, C_{Et}), 13.8 (p, C-7), 12.7 (p, C-8), -4.5 (p, C_{TBS}), -4.6 (p, C_{TBS}) ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{40}O_5SiNa$ $[M + Na]^+$: 459.2543, found: 459.2546.

Synthesis of amide 17: Ester **16** (9.49 g, 21.7 mmol, 1.0 eq.) was dissolved in Et_2O (200 ml) at 0 °C. After addition of lithium aluminium hydride (2.48 g, 65.1 mmol, 3.0 eq.) the suspension was stirred for 20 min at 0 °C. The reaction was terminated by cautious addition of H_2O (2.50 ml), an aqueous 15 % NaOH solution (2.50 ml) und a second portion of H_2O (7.50 ml). After 15 minutes $MgSO_4$ was added and stirring was continued for additional 15 min. The mixture was filtered and the filter cake was washed with CH_2Cl_2. The combined extracts were removed under reduced pressure. The resulting alcohol (8.34 g, 21.1 mmol, 97 %) was obtained as a colorless oil and was directly used in the next step without further purification. This alcohol (8.07 g, 20.4 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (50 ml) and the solution was stirred for 4.5 h after addition of MnO_2 (53.3 g, 613 mmol, 30 eq.). After filtration through a pad of Celite™, the solvent was removed under reduced pressure. The resulting aldehyde was used in the following step without further purification. To a solution of Evans building block **9** (8.36 g, 25.7 mmol, 1.2 eq.) and NEt_3 (4.77 ml, 34.3 mmol, 1.6 eq.) in PhMe (64 ml) at -78 °C was added Bu_2BOTf (1 M solution in CH_2Cl_2, 30.0 ml, 30.0 mmol, 1.4 eq.). The mixture was stirred for 2 h at 0 °C, the solution was cooled to -78 °C and the aldehyde (7.64 g, 19.4 mmol, 1.0 eq.) dissolved in toluene (15 ml) was added dropwise. The mixture was stirred for 16 h at -78 °C and then warmed up to 0 °C and stirred for further 30 minutes The reaction was quenched by addition of aqueous pH 7-buffer (20 ml). A mixture of aqueous 30 % H_2O_2 solution (20 ml) and MeOH (60 ml) was added dropwise over 30 minutes and stirring was continued for 1 h at room temperature. The aqueous phase was extracted five times with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The title compound **17** (9.62 g, 13.4 mmol, 66 % over 2 steps) was obtained by purification using flash chromatography (4:1) as a 1.5:1 mixture along with the Evans building block **9**.
HRMS (ESI): *m/z* calcd for $C_{41}H_{55}NO_8SiNa$ [M + Na]$^+$: 740.3589, found 740.3467.

Synthesis of Weinreb amide 18: To a suspension of *N,O*-dimethylhydroxylamine·HCl (20.0 g, 206 mmol, 15 eq.) in THF (70 ml) at 0 °C DiBAl-H (1 M in hexane, 206 ml, 206 mmol, 15 eq.) was slowly added. The reaction mixture was stirred at room temperature until a clear solution was obtained (30 min). The solution was cooled to -30 °C, amide **17** (9.86 g, 13.8 mmol, 1.0 eq.) in THF (40 ml) was added and stirring was continued for 3 h. The solution was added to a mixture of an aqueous saturated solution of potassium sodium tartrate (120 ml) and CH_2Cl_2 (120 ml) at 0 °C. The reaction mixture was stirred for 18 h at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA= 1:1) to afford the aldol product (7.46 g, 12.4 mmol, 90 %) as an oil.
$[\alpha]_D^{22}$= -15.9° (*c*= 0.97, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (7H, m, H_{Ar}), 6.90-6.87 (2H, m, H_{Ar}), 5.56 (1H, t, *J*= 7.5 Hz, H-5), 4.75 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.52 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.48 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.46 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.38 (1H, d, *J*= 4.6 Hz, H-2), 4.31 (1H, t, *J*= 4.6 Hz, H-3), 3.79 (3H, s, H_{ArOMe}), 3.74-3.70 (1H, m, H-7), 3.52 (3H, s, $H_{N\text{-}OMe}$), 3.51-3.45 (1H, m, H-8), 3.16 (3H, s, H_{NMe}), 2.87 (1H, d, *J*= 4.6 Hz, H_{OH}), 2.46-2.40 (1H, m, H-6), 2.11-2-04 (1H, m, H-6), 1.62 (3H, s, H-10), 1.13 (3H, d, *J*= 6.5 Hz, H-9), 0.88 (9H, s, H_{TBS}) , 0.03 (3H, s, H_{TBS}), 0.00 (3H, s, H_{TBS}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.2 (q, C_{Ar}), 137.3 (q, C_{Ar}), 133.9 (q, C-4), 131.2 (q, C_{Ar}), 129.2 (t, C_{Ar}), 128.6 (t, C_{Ar}), 128.3 (t, C_{Ar}), 128.1 (t, C_{Ar}), 125.3 (t, C-5), 113.8 (t, C_{Ar}), 77.0 (C-8), 76.9 (s, C-2,3), 73.8 (t, C-7), 72.2 (s, C_{Bn}), 70.79 (s, C_{Bn}), 61.2 (p, $C_{N\text{-}OMe}$), 55.4 (p, C_{ArOMe}), 32.6 (p, C_{NMe}), 30.0 (s, C-6), 26.0 (p, C_{TBS}), 18.1 (q, C_{TBS}), 14.2 (p, C-9), 12.8 (p, C-10), -4.4 (p, C_{TBS}), -4.4 (p, C_{TBS}) ppm; The signal for C-1 could not be detected; HRMS (ESI): *m/z* calcd for $C_{33}H_{51}NO_7SiNa$ [M + Na]$^+$: 624.3333, found 624.3329.
To a solution of this aldol product (7.95 g, 13.2 mmol, 1.0 eq.) in DMF (130 ml) were added DIPEA (13.3 ml, 78.5 mmol, 6.0 eq.), SEMCl (4.65 ml, 26.2 mmol, 2.0 eq.) and DMAP (cat.). The mixture was stirred for 18 h at 40 °C. The red solution was terminated by addition of H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA= 4:1) to afford the title compound **18** (9.65 g, 13.2 mmol, 100 %) as a colorless oil.
$[\alpha]_D^{23}$= -36.2° (*c*= 0.81, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.23 (7H, m, H_{Ar}), 6.87-6.84 (2H, m, H_{Ar}), 5.58 (1H, t, *J*= 6.8 Hz, H-5), 4.73 (1H, d, *J*= 11.7 Hz, H_{Bn}), 4.66 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.59 (d, *J*= 6.8 Hz, H_{SEM}), 4.51 (1H, d, *J*= 11.7 Hz, H_{Bn}), 4.50 (1H, d, *J*= 11.5, H_{Bn}), 4.44-4.38 (2H, m, H-2,3), 4.42 (1H, d, *J*= 11.5 Hz, H_{Bn}), 3.79 (3H, s, H_{ArOMe}), 3.77-3.67 (2H, m, H-7, H_{SEM}), 3.53-3.41 (5H, m, H-8, H_{SEM}, $H_{N\text{-}OMe}$), 3.12 (3H, s, H_{NMe}), 2.46-2.39 (1H, m, H-6), 2.08-2.01 (1H, m, H-6), 1.60 (3H, s, H-10), 1.09 (3H, d, *J*= 6.5 Hz, H-9), 0.92-0.86 (2H, m, H_{SEM}), 0.86 (9H, s, H_{TBS}), 0.03 (3H, s, H_{TBS}), -0.01 (3H, s, H_{TBS}), -0.02 (9H, s, H_{SEM}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.1 (q, C_{Ar}), 138.0 (q, C_{Ar}), 132.5 (q, C-4), 131.22 (q, C_{Ar}), 129.2 (t, C_{Ar}), 128.4 (t, C_{Ar}), 128.0 (t, C_{Ar}), 127.7 (t, C-5), 127.2 (t, C_{Ar}), 113.8 (t, C_{Ar}), 92.4 (s, C_{SEM}), 81.0 (t, C-2/C-3), 79.2 (t, C-2/C-3), 76.9 (t, C-8), 74.1 (t, C-7), 72.4 (s, C_{Bn}), 70.8 (s, C_{Bn}), 65.3 (s, C_{SEM}), 61.2 (p, $C_{N\text{-}OMe}$), 55.4 (p, C_{ArOMe}), 35.5 (p, C_{NMe}), 30.4 (s, C-6), 26.0 (p, C_{TBS}), 18.2 (q, C_{TBS}), 18.1 (q, C_{SEM}), 14.4 (p, C-9), 13.1 (p, C-10), -1.3 (p, C_{SEM}), -4.4 (p, C_{TBS}), -4.5 (p, C_{TBS}) ppm; HRMS (ESI): *m/z* calcd for $C_{39}H_{66}NO_8Si_2$ [M + H]$^+$: 732.4327, found 732.4330.

Synthesis of allyl alcohol 19: To a solution of Weinreb amide **18** (9.65 g, 13.2 mmol, 1.0 eq.) in THF (100 ml) at -78 °C was slowly added AllylMgBr (1 M in Et_2O, 40.0 ml, 40.0 mmol, 3.0 eq.). The mixture was stirred for 15 min at -78 °C, then warmed up to 0 °C and stirring was continued for 15 min until the reaction was terminated by addition of an aqueous saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification. To a solution of the resulting ketone (9.65 g, 13.2 mmol, 1.0 eq.) in THF (130 ml) at -78 °C was added (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1 M solution in PhMe, 40 ml, 40.0 mmol, 3.0 eq.) and the reaction mixture was stirred for 90 min. After addition of BH_3·SMe_2 (12.5 ml, 132 mmol, 10 eq.) the solution was stirred for 1 h at -78 °C and then for additional 15 h at -50 °C. The reaction was terminated by careful addition of MeOH (20 ml) and the resulting mixture was slowly warmed up to room temperature and H_2O was added. The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA= 10:1) to afford the title compound **19** (8.98 g, 12.6 mmol, 95 % over 2 steps) as a colorless oil.
$[\alpha]_D^{25}$= -31.4° (*c*= 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.24 (7H, m, H_{Ar}), 6.87-6.85 (2H, m, H_{Ar}), 5.73 (1H, dddd, *J*= 17.1, 8.7, 7.0, 5.1 Hz, H-2), 5.64 (1H, t, *J*= 6.8 Hz, H-8), 5.05-4.99 (2H, m, H-1), 4.96 (1H, d, *J*= 11.2 Hz, H_{Bn}), 4.61 (2H, s, H_{SEM}), 4.60 (1H, d, *J*= 11.2 Hz, H_{Bn}), 4.51 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.42 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.26 (1H, d, *J*= 7.5 Hz, H-6), 3.80 (3H, s, H_{ArOMe}), 3.76-3.70 (2H, m, H-10, H_{SEM}), 3.57-3.43 (4H, m, H-4,5,11, H_{SEM}), 2.46-2.40 (1H, m, H-9), 2.33-2.10 (3H, m, H-3,9), 1.60 (3H, s, H-13), 1.11 (3H, d, *J*= 6.5 Hz, H-12), 0.92-0.88 (2H, m, H_{SEM}), 0.87 (9H, s, H_{TBS}), 0.04 (3H, s, H_{TBS}), -0.01 (3H, s, H_{TBS}), -0.04 (9H, s, H_{SEM}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.2 (q, C_{Ar}), 138.7 (q, C_{Ar}), 135.0 (t, C-2), 132.6 (q, C-7), 131.2 (q, C_{Ar}), 129.3 (t, C_{Ar}), 128.5 (t, C_{Ar}), 128.3 (t, C_{Ar}), 128.2 (t, C-8), 127.8 (t, C_{Ar}), 117.5 (s, C-1), 113.9 (t, C_{Ar}), 92.2 (s, C_{SEM}), 83.2 (t, C-6), 81.0 (t, C-5), 76.9 (t, C-11), 75.4 (s, C_{Bn}), 74.1 (t, C-10), 70.8 (s, C_{Bn}), 70.4 (t, C-4), 65.5 (s, C_{SEM}), 55.4 (p, C_{PMB}), 39.2 (s, C-3), 30.6 (s, C-9), 26.0 (p, C_{TBS}), 18.2 (q, C_{TBS}), 18.2 (s, C_{SEM}), 14.3 (p, C-12), 12.7 (p, C-13), -1.3 (p, C_{SEM}), -4.4 (p, C_{TBS}), -4.4 (p, C_{TBS}) ppm; HRMS (ESI): *m/z* calcd for $C_{40}H_{66}O_7Si_2Na$ [M + Na]$^+$: 737.4245, found 737.4243.

Preparation of diastereomeric Mosher esters derived from alcohol 19: To a solution of the alcohol **19** (1.0 eq.) in CH_2Cl_2 (0.1 M) were added DMAP (cat.), DIPEA (3.0 eq.) and either of the two enantiomers of Mosher acid chloride (1.0 eq.). After stirring for 18 h at room temperature the reaction was terminated by addition of H_2O. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA= 10:1) to afford the corresponding esters.

	δ (*S*)-ester (ppm)	δ (*R*)-ester (ppm)	$\Delta\ \delta^{SR} = \delta(S) - \delta(R)$ (ppm)
1a	5.0688	5.1042	-0.0354
1b	5.0346	5.0705	-0.0359
2	5.6566	5.7060	-0.0494
3a	2.5981	2.6268	-0.0287
3b	2.4377	2.5115	-0.0738
6	4.1871	4.1384	0.0487
8	5.5440	5.5346	0.0094
9a	2.4493	2.4284	0.0209
9b	2.0799	2.0649	0.0150
12	1.0842	1.1004	-0.0162
13	1.5410	1.5027	0.0383

Missing signals could not be assigned with sufficient accuracy.

Synthesis of α,β-unsaturated ester 20: To a solution of allyl alcohol **19** (4.20 g, 5.87 mmol, 1.0 eq.) in a mixture of *t*-BuOH (30 ml) and H_2O (30 ml) at 0 °C was added AD-mix-α (8.80 g, 1.5 g/mmol) and it was stirred for 21 h at room temperature. The product was collected after direct flash chromatography (PE:EA= 1:1) of the solution as a colorless oil. The resulting triol was dissolved in THF (30 ml) and H_2O (30 ml) and $NaIO_4$ (1.88 g, 8.80 mmol, 1.5 eq.) was added. The reaction mixture was stirred for 2 h. The product was obtained after direct flash chromatography (PE:EA= 1:1) of the solution as a colorless oil after removal of the eluent. Then, a solution of the resulting aldehyde in CH_2Cl_2 (60 ml) at 0 °C was added Wittig ylid **8** (5.31 g, 14.7 mmol, 2.5 eq.). The mixture was stirred for 72 h at room temperature. Silica gel was added and the solvent was removed under reduced pressure. Flash chromatography of the loaded silica gel (4:1) afforded the Horner-Wadsworth-Emmons product (2.63 g, 3.29 mmol, 56 % over 3 steps) as a colorless oil.
$[\alpha]_D^{22}$= -33.0° (*c*= 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.23 (7H, m, H_{Ar}), 6.87-6.85 (2H, m, H_{Ar}), 6.72 (1H, t, *J*= 6.7 Hz, H-3), 5.65 (1H, t, *J*= 6.8 Hz, H-9), 4.98 (1H, d, *J*= 11.3 Hz, H_{Bn}), 4.61 (2H, s, H_{SEM}), 4.58 (1H, d, *J*= 11.3 Hz, H_{Bn}), 4.51 (1H, d, *J*= 11.7 Hz, H_{Bn}), 4.41 (1H, d, *J*= 11.7 Hz, H_{Bn}), 4.27 (1H, d, *J*= 7.5 Hz, H-7), 4.15 (2H, q, *J*= 7.0 Hz, H_{Et}), 3.79 (3H, s, H_{ArOMe}), 3.79-3.70 (2H, m, H-11, H_{SEM}), 3.64-3.61 (1H, m, H-5), 3.54-3.40 (3H, m, H-6,12, H_{SEM}), 2.47-2.33 (2H, m, H-4,10), 2.26-2.11 (2H, m, H-4,10), 1.77 (3H, s, H-14), 1.60 (3H, s, H-15), 1.26 (3H, t, *J*= 7.0 Hz, H_{Et}), 1.11 (3H, d, *J*= 6.3 Hz, H-13), 0.92-0.86 (2H, m, H_{SEM}), 0.86 (9H, s, H_{TBS}), 0.03 (3H, s, H_{TBS}), -0.02 (3H, s, H_{TBS}), 0.03 (9H, s, H_{SEM}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.9 (q, C-1), 159.2 (q, C_{Ar}), 138.5 (q, C_{Ar}), 138.1 (t, C-3), 132.4 (t, C-9), 131.2 (t, C_{Ar}), 129.7 (q, C-2), 129.3 (q, C_{Ar}), 128.7 (q, C-8), 128.6 (t, C_{Ar}), 128.2 (t, C_{Ar}), 127.9 (t, C_{Ar}), 113.8 (t, C_{Ar}), 92.2 (s, C_{SEM}), 83.3 (t, C-7), 81.4 (t, C-6), 76.9 (t, C-12), 75.4 (s, C_{Bn}), 74.0 (t, C-11), 70.8 (s, C_{Bn}), 70.1 (t, C-5), 65.5 (s, C_{SEM}), 60.6 (s, C_{Et}), 55.4 (p, C_{ArOMe}), 34.2 (s, C-4), 30.6 (s, C-10), 26.0 (p, C_{TBS}), 18.2 (s, C_{SEM}), 18.2 (q, C_{TBS}), 14.4 (p, C_{Et}), 14.2 (p, C-13), 12.8 (p, C-14), 12.5 (p, C-15), -1.3 (p, C_{SEM}), -4.4 (p, C_{TBS}), -4.4 (p, C_{TBS}) ppm; HRMS (ESI): *m/z* calcd for $C_{44}H_{72}O_9Si_2Na$ [M + Na]$^+$: 823.4613, found 823.4614.

Synthesis of alcohol 21: To a solution of Horner-Wadsworth-Emmons product **20** (2.63 g, 3.29 mmol, 1.0 eq.) in DMF (33 ml) were added DIPEA (3.35 ml, 19.7 mmol, 6.0 eq.), DMAP (cat.) and SEMCl (1.17 ml, 6.58 mmol, 2.0 eq.). The reaction mixture was stirred for 18 h at 40 °C and terminated by addition of H_2O. After stirring for 10 min at room temperature the aqueous phase was extracted with EtOAc (3x), the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE:EA= 20:1) to afford the SEM-ether (2.45 g, 2.64 mmol, 80 %) as a colorless oil.
$[\alpha]_D^{22}$= -41.9° (*c*= 0.87, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.22 (7H, m, H_{Ar}), 6.87-6.85 (2H, m, H_{Ar}), 6.72 (1H, tq, *J*= 7.1, 1.3 Hz, H-3), 5.57 (1H, t, *J*= 7.2 Hz, H-9), 4.78 (1H, d, *J*= 11.4 Hz, H_{Bn}), 4.70 (1H, d, *J*= 7.0 Hz, H_{SEM}), 4.67 (1H, d, *J*= 7.0 Hz, H_{SEM}), 4.62 (1H, d, *J*= 11.4 Hz, H_{Bn}), 4.61 (1H, d, *J*= 6.7 Hz, H_{SEM}), 4.58 (1H, d, *J*= 6.7 Hz, H_{SEM}), 4.50 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.41 (1H, d, *J*= 11.6 Hz, H_{Bn}), 4.20-4.14 (3H, m, H-7, H_{Et}), 3.80 (3H, s, H_{ArOMe}), 3.78-3.67 (4H, m, H-5,11, H_{SEM}), 3.54-3.42 (4H, m, H-6,12, H_{SEM}), 2.55 (2H, t, *J*= 6.6 Hz, H-4), 2.47-2.41 (1H, m, H-10), 2.10-2.03 (1H, m, H-10), 1.80 (3H, d, *J*= 1.3 Hz, H-14), 1.55 (3H, s, H-15), 1.28 (3H, t, *J*= 7.2 Hz, H_{Et}), 1.10 (3H, d, *J*= 6.4 Hz, H-13), 0.92-0.85 (4H, m, H_{SEM}), 0.86 (9H, s, H_{TBS}), 0.03 (3H, s, H_{TBS}), -0.02 (12H, s, H_{SEM}, H_{TBS}), -0.02 (9H, s, H_{SEM}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.9 (q, C-1), 159.2 (q, C_{Ar}), 138.7 (q, C_{Ar}), 138.2 (t, C-3), 132.8 (q, C-8), 131.2 (q, C_{Ar}), 129.5 (q, C-2), 129.2 (t, C_{Ar}), 128.4 (t, C_{Ar}), 128.4 (t, C_{Ar}), 127.6 (t, C-9), 113.8 (t, C_{Ar}), 96.3 (s, C_{SEM}), 92.4 (s, C_{SEM}), 82.2 (t, C-7), 81.4 (t, C-6), 78.3 (t, C-5), 76.9 (t, C-12), 75.2 (s, C_{Bn}), 74.1 (t, C-11), 70.8 (s, C_{Bn}), 65.8 (s, C_{SEM}), 65.5 (s, C_{SEM}), 60.5 (s, C_{Et}), 55.4 (p, C_{ArOMe}), 31.6 (t, C-4), 30.5 (t, 10), 26.0 (p, C_{TBS}), 18.2 (q, C_{SEM}), 18.1 (s, C_{TBS}), 18.1 (s, C_{SEM}), 14.5 (p, C_{Et}), 14.3 (p, C-13), 12.9 (p, C-14), 12.9 (p, C-15), -1.3 (p, C_{SEM}), -1.3 (p, C_{SEM}), -4.4 (p, C_{TBS}), -4.4 (p, C_{TBS}) ppm; HRMS (ESI): *m/z* calcd for $C_{50}H_{86}O_{10}Si_3Na$ [M + Na]$^+$: 953.5427, found 953.5424.

The SEM-ether described above (2.45 g, 2.64 mmol, 1.0 eq.) was divided and inserted into two plastic vessels at 0 °C. A solution of HF·Py (6.6 ml HF·Py, 19.2 ml pyridine) in THF (33.6 ml) was added to both vessels. The mixture was stirred for 72 h and the reaction was terminated by addition of an aqueous saturated solution of $NaHCO_3$. Then, also solid $NaHCO_3$ was carefully added, until gas evolution stopped. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield the title compound **21** (1.59 g, 1.95 mmol, 74 %) as a colorless oil which was directly employed in the next reaction.

Synthesis of macrolactone 22: To the α,β-unsaturated ester **21** (1.59 g, 1.95 mmol, 1.0 eq.) in THF/MeOH (10 ml each) was added an aqueous 1 M LiOH solution (19.5 ml, 19.5 mmol, 10 eq.). The reaction mixture was stirred for 25 h at 40 °C and the reaction was terminated by addition of an aqueous saturated solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3x), the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the seco acid. It was dissolved in THF (20 ml) and DIPEA (2.08 ml, 11.7 mmol, 6.0 eq.) and 2,4,6-trichloro benzoylchloride (0.91 ml, 5.84 mmol, 3.0 eq.) were added. After stirring for 2 h, the mixture was filtered through a pad of Celite™ and the solvent was removed under reduced pressure. The residue was dissolved in toluene (1.25 l). The solution was divided into three portions, each of which was added over a period of 5.5 h to a solution of DMAP (each 793 mg, 6.50 mmol, 10 eq.) in toluene (each 70 ml volume) at 80 °C. After cooling to room temperature, the reaction was terminated by addition of an aqueous saturated solution of $NaHCO_3$. The aqueous phase was extracted with Et_2O (3x), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduces pressure. The residue was purified by flash chromatography (PE:EA= 4:1) to afford the macrolactone **22** (1.03 g, 1.34 mmol, 69 % over 2 steps, d.r.= 4:1), as a yellowish oil.
$[\alpha]_D^{24}$= -13.9° (*c*= 0.64, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.22 (7H, m, H_{Ar}), 6.89-6.86 (2H, m, H_{Ar}), 5.54 (1H, dd, *J*= 15.5, 7.3 Hz, H-3), 5.38 (1H, ddd, *J*= 15.5, 8.0, 0.8 Hz, H-4), 5.22-5.19 (1H, m, H-9), 5.02 (1H, ddd, *J*= 11.9, 4.3, 2.9 Hz, H-11), 4.88 (1H, d, *J*= 10.8 Hz, H_{Bn}), 4.72 (1H, d, *J*= 10.8 Hz, H_{Bn}), 4.67 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.65 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.60 (1H, d, *J*= 6.6 Hz, H_{SEM}), 4.59 (1H, d, *J*= 11.5 Hz, H_{Bn}), 4.58 (1H, d, *J*= 6.6 Hz, H_{SEM}), 4.45 (1H, d, *J*= 11.5 Hz, H_{Bn}), 4.00 (1H, dd, *J*= 8.0, 8.0 Hz, H-5), 3.86 (1H, d, *J*= 9.8 Hz, H-7), 3.80 (3H, s, H_{ArOMe}), 3.67-3.37 (6H, m, H-6,12, H_{SEM}), 3.16 (1H, qd, *J*= 7.3, 6.6 Hz, H-2), 2.79-2.70 (1H, m, H-10), 2.07-2.03 (1H, m, H-10), 1.62 (3H, s, H-15), 1.19 (3H, d, *J*= 6.6 Hz, H-14), 1.16 (3H, d, *J*= 6.4 Hz, H-13), 0.88-0.81 (4H, m, H_{SEM}), -0.08 (18H, s, H_{SEM}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 174.5 (q, C-1), 159.4 (q, C_{Ar}), 139.5 (q, C_{Ar}), 134.7 (q, C-8), 134.0 (t, C-3), 130.6 (q, C_{Ar}), 129.5 (t, C_{Ar}), 128.5 (t, C-9), 128.4 (t, C-4), 128.3 (t, C_{Ar}), 127.7 (t, C_{Ar}), 127.3 (t, C_{Ar}), 113.9 (t, C_{Ar}), 92.9 (s, C_{SEM}), 91.6 (s, C_{SEM}), 82.7 (t, C-7), 82.5 (t, C-6), 79.5 (t, C-5), 75.7 (s, C_{Bn}), 74.7 (t, C-12), 73.6 (t, C-11), 70.9 (s, C_{Bn}), 65.4 (s, C_{SEM}), 65.1 (s, C_{SEM}), 55.4 (p, C_{ArOMe}), 42.9 (t, C-2), 29.1 (s, C-10), 18.1 (s, C_{SEM}), 18.1 (s, C_{SEM}), 16.2 (p, C-14), 15.6 (p, C-13), 12.6 (p, C-15),-1.3 (p, C_{SEM}, p, C_{SEM}) ppm; HRMS (ESI): *m/z* calcd for $C_{42}H_{66}O_9Si_2Na$ [M + Na]$^+$: 793.4143; found 793.4144.

Synthesis of alkene 24: To a solution of macrolactone **21** (285 mg, 0.37 mmol, 1.0 eq.) in a mixture composed of CH_2Cl_2 and a pH 7-buffer (10:1, 4.0 ml) at 0 °C was slowly added DDQ (252 mg, 1.11 mmol, 3.0 eq.). After stirring for 2 h at 0 °C the alcohol was collected as a colorless oil after flash chromatography (PE:EA= 1:1, traces of NEt_3). The resulting alcohol was dissolved in CH_2Cl_2 (4.0 ml) and the solution was stirred after addition of $NaHCO_3$ (621 mg, 7.40 mmol, 20 eq.) and Dess-Martin periodinane (785 mg, 1.85 mmol, 5.0 eq.) for 90 min at room temperature. The reaction was terminated by addition of an aqueous, saturated solution of $NaHCO_3$ followed by a $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x), the combined organic

phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA= 10:1 to 4:1) to afford the ketone (131 mg, 0.20 mmol, 55 % over 2 steps) as a mixture of diastereoisomers (6:1), as a colorless oil.
$[\alpha]_D^{25}$= +21.3° (*c*= 0.30, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.37-7.21 (5H, m, H_{Ar}), 5.55 (1H, dd, *J*= 15.6, 7.9 Hz, H-3), 5.41 (1H, ddd, *J*= 15.6, 7.9, 0.7 Hz, H-4), 5.25-5.21 (1H, m, H-9), 5.15 (1H, dd, *J*= 12.0, 3.4 Hz, H-11), 4.87 (1H, d, *J*= 11.1 Hz, H_{Bn}), 4.74 (1H, d, *J*= 11.1 Hz, H_{Bn}), 4.68 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.66 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.60 (2H, s, H_{SEM}), 4.01 (1H, dd, *J*= 8.1, 7.9 Hz, H-5), 3.89 (1H, d, *J*= 9.8 Hz, H-7), 3.66-3.38 (4H, m, H_{SEM}), 3.64 (1H, dd, *J*= 9.9, 7.9 Hz, H-6), 3.27 (1H, dq, *J*= 7.2, 7.0 Hz, H-2), 2.70-2.61 (1H, m, H-10), 2.52-2.47 (1H, m, H-10), 2.19 (3H, s, H-13), 1.63 (3H, s, H-15), 1.23 (3H, d, *J*= 6.8 Hz, H-14), 0.87-0.81 (4H, m, H_{SEM}), -0.07 (9H, s, H_{SEM}), -0.07 (9H, s, H_{SEM}) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 205.3 (q, C-12), 173.8 (q, C-1), 139.3 (q, C_{Ar}), 136.4 (q, C-8), 133.4 (t, C-3), 128.8 (t, C-4), 128.3 (t, C_{Ar}), 127.7 (t, C_{Ar}), 127.3 (t, C_{Ar}), 126.6 (t, C-9), 92.9 (s, C_{SEM}), 91.7 (s, C_{SEM}), 82.7 (t, C-7), 82.7 (t, C-6), 79.0 (t, C-5), 76.3 (t, C-11), 75.9 (s, C_{Bn}), 65.5 (s, C_{SEM}), 65.2 (s, C_{SEM}), 42.6 (t, C-2), 29.8 (s, C-10), 26.4 (p, C-13), 18.1 (s, C_{SEM}), 18.1 (s, C_{SEM}), 16.0 (p, C-14), 12.8 (p, C-15), -1.3 (p, C_{SEM}), -1.3 (p, C_{SEM}) ppm; HRMS (ESI): *m/z* for $C_{34}H_{56}O_8Si_2Na$ $[M + Na]^+$: 671.3411; found 671.3410.

Ethyltriphenylphosphonium bromide (453 mg, 1.22 mmol, 6.0 eq.) was dissolved in a mixture of 1,2-dimethoxyethane and HMPA (10:1, 2.0 ml) and KHDMS (0.5 m solution in toluene, 2.03 ml, 5.0 eq.) was slowly added. The dark red solution was stirred for 10 min at room temperature, then it was cooled to -50 °C and stirring was continued for additional 5 min. The ketone described above (131 mg, 0.20 mmol, 1.0 eq.) dissolved in 1,2-dimethoxyethane (0.4 ml) was slowly added to the solution. The reaction was terminated after 20 min at room temperature by addition of pH 7-buffer. The aqueous phase was extracted with Et_2O (3x), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA= 10:1 to 4:1) to afford the alkene **24** (93.6 mg, 0.14 mmol, 70 %) as a mixture of diastereoisomers (6:1) as a colorless oil.
$[\alpha]_D^{21}$ = -13.2° (*c*= 0.19, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.37-7.36 (2H, m, H_{Ar}), 7.30-7.21 (3H, m, H_{Ar}), 5.69 (1H, dd, *J*= 12.1, 2.9 Hz, H-11) 5.55 (1H, dd, *J*= 15.6, 7.8 Hz, H-3), 5.41 (1H, ddd, *J*= 15.6, 8.0, 0.7 Hz, H-4), 5.39-5.36 (1H, m, H-13), 5.32-5.28 (1H, m, H-9), 4.89 (1H, d, *J*= 10.9 Hz, H_{Bn}), 4.75 (1H, d, *J*= 10.9 Hz, H_{Bn}), 4.69 (1H, d, *J*= 6.7 Hz, H_{SEM}), 4.67 (1H, d, *J*= 6.7 Hz, H_{SEM}), 4.63 (1H, d, *J*= 6.7 Hz, H_{SEM}), 4.60 (1H, d, *J*= 6.7 Hz, H_{SEM}), 4.01 (1H, dd, *J*= 8.0, 8.0 Hz, H-5), 3.90 (1H, d, *J*= 9.9 Hz, H-7), 3.67-3.58 (2H, m, H-6, H_{SEM}), 3.66 (1H, d, *J*= 9.9, 8.0 Hz, H-6), 3.54-3.48 (1H, m, H_{SEM}), 3.44-3.39 (1H, m, H_{SEM}), 3.13 (1H, dq, *J*=7.8, 6.6 Hz, H-2), 2.81 (1H, dt, *J*= 14.3, 11.5 Hz, H-10), 1.96-1.93 (1H, m, H-10), 1.71 (3H, dq, *J*= 8.4, 1.4 Hz, H-14), 1.71 (3H, dq, *J*= 1.6, 1.4 Hz, H-17), 1.65 (3H, s, H-16), 1.17 (3H, d, *J*= 6.6 Hz, H-15), 0.87-0.82 (4H, m, H_{SEM}), -0.07 (18H, s, H_{SEM}) ppm; NOESY interactions between H-11 and H-14 can only be explained by a (*Z*)-configuration of the olefin double bond; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 173.9 (s, C-1), 139.5 (q, C_{Ar}), 134.8 (q, C-8), 133.9 (t, C-3), 133.7 (q, C-12), 128.7 (t, C-9), 128.3 (t, C_{Ar}), 128.2 (C-4), 127.7 (t, C_{Ar}), 127.3 (t, C_{Ar}), 123.3 (t, C-13), 93.0 (s, C_{SEM}), 91.5 (s, C_{SEM}), 82.9 (t, C-6), 82.9 (t, C-7), 79.3 (t, C-5), 75.9 (s, C_{Bn}), 70.8 (t, C-11), 65.5 (s, C_{SEM}), 65.1 (s, C_{SEM}), 42.9 (t, C-2), 31.9 (s, C-10), 18.3 (p, C-17), 18.2 (s, C_{SEM}), 18.1 (s, C_{SEM}), 16.1 (p, C-15), 13.1 (p, C-14), 12.6 (p, C-16), -1.3 (p, C_{SEM}), -1.3 (p, C_{SEM}) ppm; HRMS (ESI): *m/z* calcd for $C_{36}H_{60}O_7Si_2Na$ $[M + Na]^+$: 683.3775, found 683.3774.

To a solution of benzyl ether **24** (22.4 mg, 34 µmol, 1.0 eq.) in a mixture of CH_2Cl_2/pH 7-buffer (10:1, 0.33 ml) was added DDQ (38.5 mg, 0.17 mmol, 5.0 eq.) and the mixture was stirred for 20 h at 35 °C. The free alcohol was obtained by direct flash chromatography (4:1) of the solution and immediately used in the following step. To a solution of the alcohol in CH_2Cl_2 (0.4 ml) were added DIPEA (0.09 ml, 0.51 mmol, 15 eq.), DMAP (cat.) and isovaleric anhydride (0.03 ml, 0.17 mmol, 5.0 eq.). The mixture was stirred for 3 d at room temperature and was then terminated by addition of an aqueous, saturated $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1) to give product **25** (15.1 mg, 23 µmol, 68 % over 2 steps) as a mixture of diastereoisomers (10:1), in form of a colorless oil.
$[\alpha]_D^{24}$ = -29.2° (*c*= 0.12, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 5.68 (1H, dd, *J*= 11.7, 2.9 Hz, H-11), 5.58 (1H, dd, *J*= 15.5, 7.6 Hz, H-3), 5.40-5.30 (4H, m, H-4,6,9,13), 4.64 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.56 (1H, d, *J*= 1.7 Hz, H_{SEM}), 4.54 (1H, d, *J*= 1.7 Hz, H_{SEM}), 4.46 (1H, d, *J*= 6.8 Hz, H_{SEM}), 4.03 (1H, t, *J*= 8.7 Hz, H-5), 3.87 (1H, d, *J*= 10.2 Hz, H-7), 3.73-3.65 (2H, m, H_{SEM}), 3.46 (1H, dt, *J*= 7.4, 9.5 Hz, H_{SEM}), 3.39 (1H, dt, *J*= 6.7, 9.9 Hz, H_{SEM}), 3.15 (1H, dq, *J*= 7.6, 7.1 Hz, H-2), 2.82 (1H, dt, *J*= 14.3, 11.7 Hz, H-10), 2.22-2.14 (3H, m, H-2',3'), 1.98-1.94 (1H, m, H-10), 1.72-1.69 (6H, m, H-14,17), 1.68 (3H, s, H-16), 1.18 (3H, d, *J*= 7.1 Hz, H-15), 0.97 (6H, d, *J*= 6.1 Hz, H-4'), 0.94-0.83 (4H, m, H_{SEM}), 0.03 (9H, s, H_{SEM}), 0.02 (9H, s, H_{SEM}) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 173.7 (q, C-1), 172.5 (q, C-1'), 136.1 (t, C-3), 133.7 (q, C-8), 133.5 (q, C-12), 130.2 (t, C-9), 127.2 (t, C-4), 123.4 (t, C-13), 91.4 (s, C_{SEM}), 90.3 (s, C_{SEM}), 79.3 (t, C-7), 76.5 (t, C-5), 73.0 (t, C-6), 70.8 (t, C-11), 65.4 (s, C_{SEM}), 65.1 (s, C_{SEM}), 43.7 (s, C-2'), 43.2 (t, C-2), 31.9 (s, C-10), 25.5 (p, C-3'), 22.6 (p, C-4'), 22.6 (p, C-4'), 18.3 (C-17), 18.2 (s, C_{SEM}), 18.2 (s, C_{SEM}), 16.0 (p, C-15), 13.1 (p, C-14), 12.4 (p, C-16), -1.1 (p, C_{SEM}), -1.2 (p, C_{SEM}) ppm; HRMS (ESI): *m/z* calcd for $C_{34}H_{62}O_8Si_2Na$ $[M + Na]^+$: 677.3881, found 671.3876.

Thionylchloride (2.0 ml) was added to $ZnCl_2$ (29.3 mg, 0.22 mmol) and the mixture was heated under refluxing conditions for 2 h. After removal of thionylchloride under reduced pressure, the residue was dissolved in Et_2O (2.0 ml) and EtSH (0.3 ml). This solution was cooled to 0 °C and compound **24** in Et_2O (2x 0.5 ml) (71.1 mg, 108 µmol, 1.0 eq.) was added dropwise. The mixture was terminated after stirring for 35 min at 0 °C, by addition of an aqueous, saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc, the combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (4:1 to 1:1) to give product **26** (35.6 mg, 89 µmol, 83 %) as a mixture of diastereoisomers (10:1), in form of a colorless oil.
$[\alpha]_D^{24}$= -2.4° (*c*= 0.25, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.40-7.33 (5H, m, H_{Ar}), 5.72 (1H, dd, *J*= 12.0, 3.1 Hz, H-11), 5.61 (1H, dd, *J*= 15.6, 7.3 Hz, H-3), 5.50 (1H, dd, *J*= 15.6, 7.5 Hz, H-4), 5.40-5.33 (2H, m, H-9,13), 4.90 (1H, d, *J*= 10.9 Hz, H_{Bn}), 4.85 (1H, d, *J*= 10.9 Hz, H_{Bn}), 4.04 (1H, dd, *J*= 8.6, 7.5 Hz, H-5), 3.86 (1H, d, *J*= 9.5 Hz, H-7), 3.49 (1H, dd, *J*= 9.5, 8.6 Hz, H-6), 3.12 (1H, dq, *J*= 7.3, 6.9 Hz, H-2), 2.85-2.76 (1H, ddd, *J*= 14.5, 12.0, 11.1, H-10), 2.80 (1H, br, H_{OH}), 2.28 (1H, br, H_{OH}), 2.01-1.91 (1H, m, H-10), 1.73-1.69 (9H, m, H-14,16,17), 1.18 (3H, d, *J*= 6.9 Hz, H-15) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 173.8 (q, C-1), 137.6 (q, C_{Ar}), 136.4 (q, C-8), 133.9 (t, C-3), 133.4 (q, C-12), 129.9 (t, C-4), 128.8 (t, C_{Ar}), 128.5 (t, C_{Ar}), 128.3 (t, C-9), 128.1 (t, C_{Ar}), 123.3 (t, C-13), 84.0 (t, C-6), 78.1 (t, C-7), 76.1 (s, C_{Bn}), 75.3 (t, C-5), 70.8 (t, C-11), 43.0 (t, C-2), 31.9 (s, C-10), 18.2 (p, C-17), 15.8 (p, C-15), 13.0 (p, C-14), 12.0 (p, C-16) ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}O_5Na$ $[M + Na]^+$: 423.2147, found 423.2156.

Keywords: Antibiotics • Disciformycin • Natural product synthesis • Polyketides

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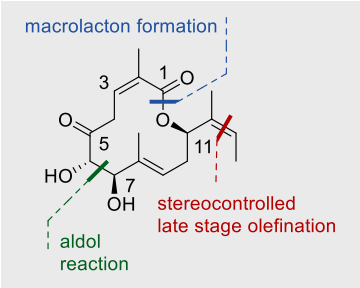
Entry for the Table of Contents

FULL PAPER

Challenging alkenes: The synthesis of the aglycon of disciformycin, a new secondary metabolite from *Pyxidicoccus fallax*, with high antibacterial potency is reported. The stereocontrolled installation of the olefinic double bonds at C2-C3/C3-C4 and C12-C13, respectively, as well the orthogonal differentiation of the oxy functionalities unexpectedly were found to be key challenges of the project.



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Synthesis of the aglycon of the antibiotic disciformycin