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Diastereoselective synthesis of the C14–C29 fragment of amphidinol 3†

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An efficient stereoselective synthesis of the C14–C29 fragment highlighting a coupling reaction between a 1,3-dithiane derivative and an α-branched aldehyde was realized. This highly convergent synthesis involved two chiral pools, L-malic acid and (+)-camphorsulfonic acid, which are the starting compounds to control the six stereogenic centers present in the C14–C29 fragment of amphidinol 3.

Introduction

Dinoflagellates are a rich source of bioactive secondary metabolites such as brevetoxins, ciguatoxins, maitotoxin, okadaic acid, and palytoxin,[1] which are polyketides with unique structures frequently present in species implicated in seafood poisoning. Recently, amphidinols (AMs), a new class of polyketides, were isolated from dinoflagellates and have been recognized as potent antifungal and hemolytic agents.[2] Up to now, 17 closely related amphidinols have been isolated from dinoflagellates *Amphidinium* species,[3,4] *Amphidinium klebsii* and *Amphidinium carterae*,[2,5] and one of them is amphidinol 3. Other related compounds have been extracted from dinoflagellates such as luteophanols,[6] lingshuiol A,[7] and karatungiol[8] showing cytotoxic and antifungal activities. In addition, carteraol E, an ichthyotoxin, was isolated from *Amphidinium carterae*.[9]

The amphidinol structures are characterized by a skipped polyenic chain and a long irregular polyhydroxy chain, both connected by a fragment containing two pyran rings. As the absolute configuration of the stereogenic centers was elucidated only for amphidinol 3[3b,4b,10] isolated in 1996 from *Amphidinium klebsii*,[4] amphidinol 3 has attracted the attention of synthetic chemists due to its interesting structural features and its potential antifungal and hemolytic activities related to its membrane-permeabilizing activity.[11] We have to point out that amphidinol 3 proved to be a stronger hemolytic agent against human erythrocytes than other well-known antibiotics such as amphotericin B and filipin III. Biological assays have indicated that amphidinol 3 exhibited different mechanisms of action than those for amphotericin B and filipin III, as pores or lesions in biomembranes are formed depending on dosage concentrations.[11]

The syntheses of different fragments of amphidinol 3 have been reported. Polyol,[4a,12] pyranyl[12b,d,13] and polyenic[13e,f,14] fragments have been synthesized and the construction of the most advanced fragment C1–C52 was reported by Rychnovsky and coworkers.[12b] However, no total synthesis has been reported up to now. For our part, we have reported one approach towards the pyranyl fragment,[13a] two approaches to the C53–C67 polyenic fragment[14a,b] as well as two approaches related to the synthesis of the C17–C30[12a] and C18–C30[12b] polyol fragments.

Since we met with difficulties to connect the C17–C30 and C18–C30 fragments with, respectively, the C1–16 and C1–C17 fragments, another disconnection through the C13–C14 bond was envisaged and a new strategy for the synthesis of the fragment C14–C29 (compound **A**) was designed with full control of the stereogenic centers. Our new retrosynthetic analysis of amphidinol 3 is reported in Scheme 1 and is based on two disconnections, the C29–C30 and C52–C53 bonds. These two bonds would respectively be built by using a Suzuki–Miyaura[15] coupling reaction and a Julia olefination.[16] The C1–C29 polyol fragment would be obtained by using a cross-metathesis[17] between fragments C1–C12 and C13–C29 (compound **A′**), and the synthesis of the fragment C14–C29 (compound **A**), bearing six stereogenic centers, would be achieved by a convergent approach involving an optically active β-hydroxyepoxide **B**, 2-TBS-1,3-dithiane **2**, and optically active aldehyde **9**. The connection between these three compounds would be realized by addition of TBS-dithiane **2** to β-hydroxyepoxide **B**, followed by addition of the resulting β-silyloxy-dithiane **C** to aldehyde **9** allowing for the control of the stereogenic center at C24

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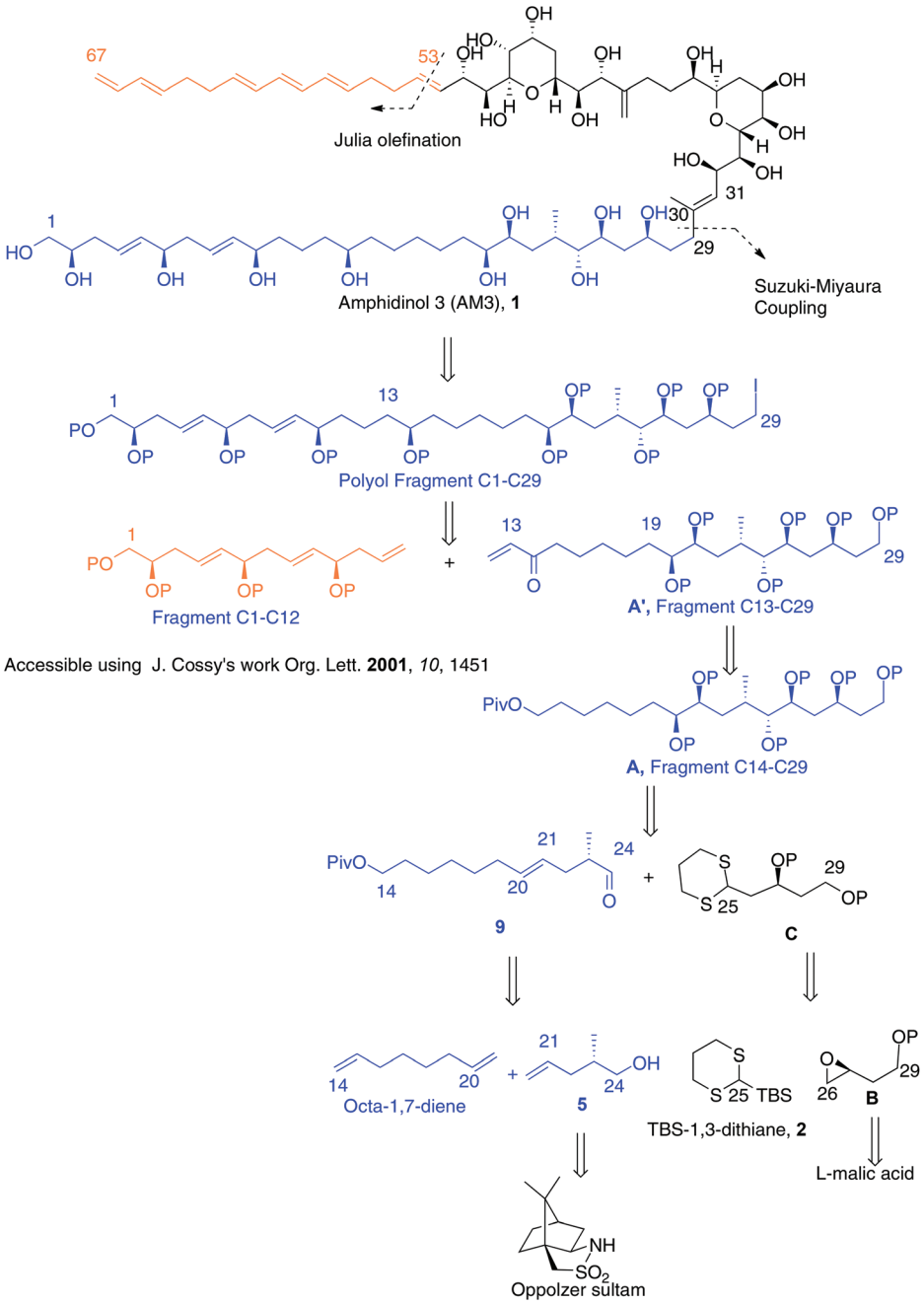


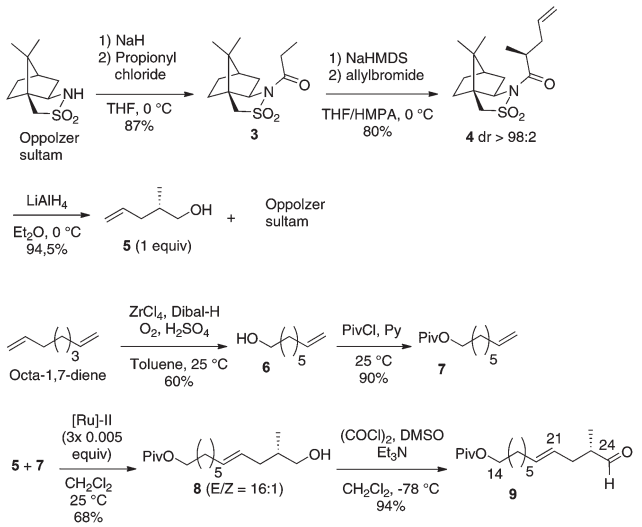
Scheme 1 Retrosynthetic analysis of the fragment C14–C29 of AM3, **1** (compound **A**).

according to a Felkin–Anh model. Aldehyde **9** would be synthesized by using a cross-metathesis between octa-1,7-diene and the enantiomerically pure unsaturated-alcohol **5** which would be available from Oppolzer's sultam[12b,18] and the optically active β-hydroxyepoxide **B** would be accessible from L-malic acid (Scheme 1).

We have to point out that the control of the stereogenic centers at C20 and C21 would be realized by utilizing AD-mix-α for the dihydroxylation of the double bond, resulting from a cross-metathesis and the stereogenic center at C25 would be controlled by a diastereoselective 1,2-*anti*-reduction of the ketone obtained after hydrolysis of the thioketal.

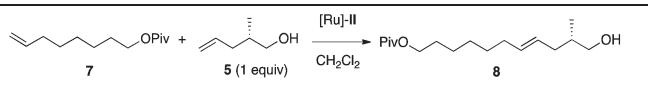
Results and discussion

The synthesis of aldehyde **9** was planned using a cross-metathesis between protected octenol **7** and pentenol **5** (Scheme 2). The access to **5**[18b] was achieved starting from Oppolzer's sultam, by treatment with NaH followed by addition of



Scheme 2 Synthesis of aldehyde **9** (fragment C14–C24).

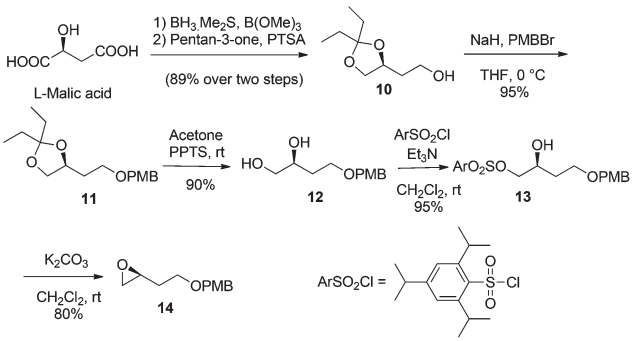
Table 1 Screening of the conditions for the preparation of unsaturated alcohol **8**



Entry	7 (equiv.)	[Ru]-**II** (equiv.)	*t* (°C)	Time (h)	*E*/*Z* ratio[a]	Yield[c] (%)
1	3	0.05	25	12	4.6/1	60
2	1	0.05	25	12	5/1	33
3	3	0.05	40	12	1/1	55
4	3	0.01	25	36	14/1	40
5	5	3 × 0.005[b]	25	168	16/1	68[b]

All experiments were performed in CH_2Cl_2 and monitored by GC/MS until disappearance of **5**. [a] The *E*/*Z* ratio was determined by analysis of the ^{1}H-NMR spectra of the crude material. [b] 0.5 mol% of [Ru]-**II** was added every two days. [c] Isolated yields.

propionylchloride. The resulting amide **3** was then alkylated with allylbromide giving **4** with an excellent diastereomeric ratio (dr > 98 : 2) after recrystallisation. After cleavage of the chiral auxiliary, the optically active unsaturated alcohol **5** was isolated in 95% yield, with an enantiomeric excess up to 96%. The second partner of the cross-metathesis, compound **7**, was prepared by applying a mono-hydroalumination/oxidation sequence to octa-1,7-diene. The obtained alcohol **6** was then protected as a pivaloyl ester **7**. Having **5** and **7** in hand, these two compounds were involved in a cross-metathesis using the Grubbs catalyst, [Ru]-**II**.[19] A screening of the conditions for the cross-metathesis between **5** and **7** was achieved and the best isolated yield (68%) and *E*/*Z* ratio (16/1) in **8** were obtained when [Ru]-**II** was added portionwise (3 × 0.005 equiv.) over one week at 25 °C in CH_2Cl_2 with the use of an excess of **7** (5 equiv.) (Table 1, entry 5) and when lower amounts of **7** were used, lower yields were obtained (Table 1, entries 1 and 2). Worthy of note is the *E*/*Z* ratio of **8** which was highly

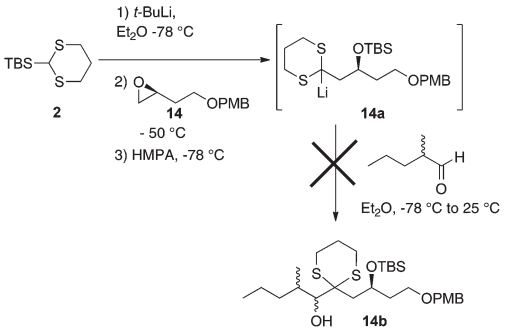


Scheme 3 Preparation of epoxide **14** (fragment C24–C29).

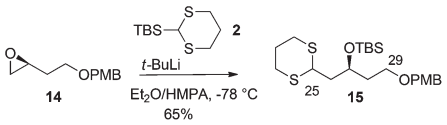
dependent on the amount of catalyst present in the reaction medium (Table 1, entries 1, 4 and 5) and when the temperature was increased, the *E*/*Z* ratio of **8** was dramatically decreased (Table 1, entries 1 and 3). After a Swern oxidation, the unsaturated alcohol **8** was converted to aldehyde **9** in 94% yield. Thus, compound **9** was obtained in seven steps with 42% overall yield from Oppolzer's sultam, which was recycled.

The second fragment, epoxide **B**, was prepared stereospecifically from L-malic acid in six steps (Scheme 3). L-Malic acid was fully reduced ($BH_3{\cdot}Me_2S$, $B(OMe)_3$) and the 1,2-diol of the resulting triol was selectively protected as a ketal (pentan-3-one, PTSA), leading to **10** (89%) which after transformation of its primary alcohol to a *p*-methoxybenzyl ether (NaH, PMBBr, THF, 0 °C) produced **11** in 95% yield. Acid-catalyzed hydrolysis of **11** to diol **12** and the subsequent selective transformation of the primary alcohol to a 2,4,6-triisopropylphenylsulfonate[20] produced **13** which, under basic conditions (K_2CO_3, CH_2Cl_2, rt), delivered the optically active epoxide **14** (80%).[21] Thus, epoxide **14** was obtained in 58% overall yield from L-malic acid.

Our first goal was to perform with compounds **9** and **14** a three components linchpin process exploiting anion relay chemistry (ARC) starting from linchpin TBS-1,3-dithiane **2** and giving access to the C14–C29 fragment of amphidinol 3. Based on the precedent of L. Tietze,[22] A. B. Smith[23] reported that lithiation of silyldithiane followed by alkylation with an epoxide afforded an intermediate oxyanion which upon treatment with HMPA undergoes 1,4-Brook rearrangement,[23a] generating a new reactive dithiane anion which reacts with a second different epoxide giving 1,5 diol monoprotected as a silyl ether. Following this result, we wanted to explore in this process the use of an aldehyde as a second electrophile instead of an epoxide. The first test has been realized starting from TBS-1,3-dithiane **2**; treatment with *t*-BuLi in Et_2O at −78 °C followed by addition of epoxide **14** and HMPA should give the lithiated species **14a**, and then we added 2-methyl-pentanal as a model α-branched aldehyde. But in our hands no trace of coupling product **14b** has ever been detected showing that the extension of this linchpin process with epoxide and aldehyde is not straightforward (Scheme 4).



Scheme 4 Linchpin process with epoxide **14** and 2-methyl-pentanal.

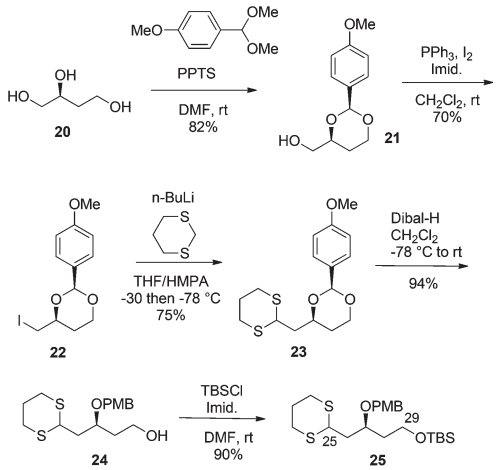


Scheme 5 Preparation of functionalized dithiane **15**.

Therefore we decided to follow this reaction step by step. Treatment of epoxide **14** with lithiated TBS-1,3-dithiane in a mixture of Et_2O–HMPA (3/1) at −78 °C afforded, after Brook rearrangement, the optically active 1,3-dithiane **15** in 65% yield (Scheme 5).

With both compounds **9** and **15** in hand, the synthesis of the C14–C29 fragment of amphidinol 3 was undertaken. Unfortunately, the addition of 1,3-dithiane **15** to aldehyde **9** was ineffective when using previously described conditions[24] (*n*-BuLi, with or without HMPA in THF at −50 °C). In order to verify whether the lithiation of 1,3-dithiane **15** was effective, deuterium exchange experiments were performed using different bases and additives[25] and, to our surprise, a low metalation or no metalation was observed. Expecting that the TBS ether at the β position of 1,3-dithiane **15** could affect the acidity of the α hydrogen, 1,3-dithiane **16** bearing a MOM protecting group instead of a TBS ether was prepared.[26] When deuterium exchange was conducted, it was found that *n*-BuLi at −78 °C to 0 °C in THF were the best conditions as 60% deuteration of the dithiane was obtained and when the lithium anion of dithiane **16** was condensed on aldehyde **17**, **18** was isolated in 58% yield (Scheme 6).

The dithiane anion formed under the previously optimized conditions (*n*-BuLi, −78 °C to 0 °C, THF) was added to the optically active aldehyde **9** to afford the expected coupling



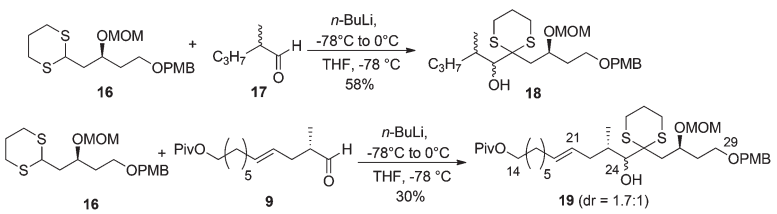
Scheme 7 Synthesis of 1,3-dithiane **25**.

product **19**, but in a low yield of 30%. Furthermore, the diastereoisomeric ratio was not satisfactory (dr = 1.7 : 1).

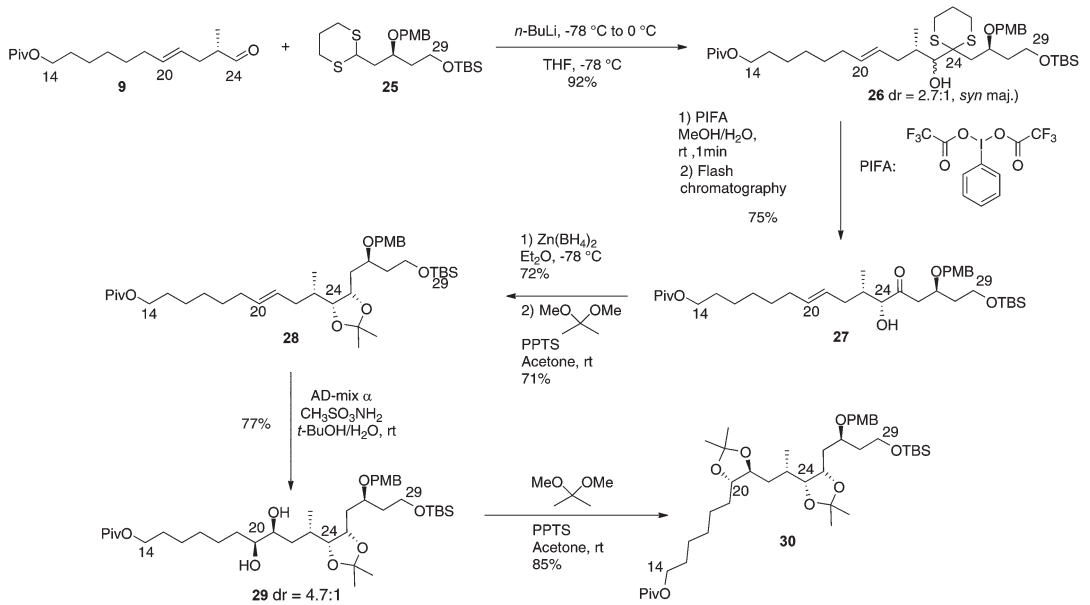
In the course of our study on the addition of dithiane to aldehydes, a closely related work was published by Brimble *et al.*[27] demonstrating that a PMB ether at the δ-position of 1,3-dithiane was interacting with the C–S σ* orbital of the dithiane function,[28] lowering dramatically the acidity of the α-hydrogen. This result was confirmed in our case[29] and we decided to prepare 1,3-dithiane **25** with a PMB protecting group of the C27 hydroxyl.

Starting from the optically active triol **20** readily prepared from L-malic acid (Scheme 3), the selective protection of the 1,3-diol present in **20** as *p*-methoxyphenylacetal (PMP acetal) was realized, leading to **21** which was transformed into the iodo derivative **22** (PPh_3, Imid. I_2, CH_2Cl_2, rt) in 70% yield (Scheme 7). After treatment of **22** with lithiated 1,3-dithiane, **23** was formed in 75% yield. A selective reduction of the six-membered acetal **23** by DIBAL-H[30] at −78 °C in CH_2Cl_2 afforded the resulting primary alcohol **24** which was then protected as a TBS ether in quantitative yield (TBSCl, imid., DMF, rt). Thus, 1,3-dithiane **25** was prepared stereospecifically in seven steps with an overall yield of 40% from L-malic acid.

By addition of lithiated **25** to aldehyde **9** (*n*-BuLi (2.5 equiv.), THF, −78 °C to 0 °C, 1 h and then addition of aldehyde (1 equiv.), −78 °C, 2 h), **26** was obtained with an excellent yield (92%) and with a diastereoselectivity of 2.7 : 1 in favor of the *syn*-isomer according to a Felkin–Anh addition mode (Scheme 8). Oxidative cleavage[31] of the 1,3-dithiane by



Scheme 6 Addition reactions of 1,3-dithiane **16** to aldehydes **17** and **9**.



Scheme 8 Synthesis of the C14–C29 fragment of amphidinol 3.

phenyliodonium bis(trifluoroacetate) (PIFA) led smoothly to a mixture of the two diastereoisomeric ketones *syn*-**27** and *anti*-**27′** (*syn*/*anti*: 2.7/1) which were separated by flash chromatography on silica gel to deliver the optically active ketone **27** (75%). Ketone **27** was then reduced diastereoselectively by $Zn(BH_4)_2$ (Et_2O, −78 °C, 72%) affording the *anti*-1,2-diol which was protected as an acetonide (2,2-dimethoxypropane, PPTS, acetone) producing **28** in 70% yield. A Sharpless dihydroxylation[32] applied to **28**, using AD-mix-α ($CH_3SO_3NH_2$, *t*-BuOH–H_2O, rt), nicely afforded, after 4 days at 0 °C, diol **29** in a 4.7/1 diastereoisomeric ratio. After separation by chromatography, the resulting optically active diol **29** was isolated in 75% yield and then protected as an acetonide (2,2-dimethoxypropane, PPTS, acetone) to afford **30** (85%) with the six stereogenic centers fully controlled.

Conclusion

In conclusion, we have reported herein an efficient and convergent access to the C14–C29 fragment of amphidinol 3 that competes favorably with the previously described synthesis. The target molecule **30**, which corresponds to the fragment C14–C29 **A**, was realized in 12 steps from L-malic acid with 9% overall yield by using as the key step a cross-metathesis to build the C20–C21 bond, and the addition of a dithiane to an epoxide and to an aldehyde to build the C25–C26 and C24–C25 bonds, respectively. The control of the six stereogenic centers was realized by using a Sharpless enantioselective dihydroxylation to control the C20 and C21 stereogenic centers, an alkylation of Oppolzer's sultam to control the C23 stereogenic center, a ring-opening of an optically active epoxide by a 1,3-dithiane lithium anion to control the C27 stereogenic center and the addition of a 1,3-dithiane anion to an α-substituted aldehyde to control the C24 stereogenic center according to a Felkin–Anh addition mode. The latter coupling required careful optimization of the conditions and was closely dependent on the protecting groups.

Experimental section

General

Experimental procedures and spectroscopic and analytical data of the products: reagents and solvents were purchased as reagent grade and used without further purification. THF was distilled over sodium benzophenone ketyl. Dichloromethane was distilled over CaH_2 and acetonitrile over P_2O_5. Flash column chromatography (FC) was performed using silica gel 60 for preparative column chromatography (40–63 mm), unless specifically noted otherwise. Demetalled silica gel was prepared according to a published procedure.[33] Thin layer chromatography (TLC) was performed on glass sheets coated with silica gel 60 F_{254} (otherwise stated), visualization by UV light or through staining with phosphomolybdic acid, $KMnO_4$ or vanillin. Optical rotations were measured using a polarimeter with a sodium lamp and are reported as follows: α_D (*c* g per 100 mL solvent). NMR spectra (^1H and ^{13}C) were recorded at 300 MHz or 400 MHz. Chemical shifts are reported in ppm with the solvent ($CDCl_3$) resonance as the δ 7.26 ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s ap = apparent singlet, mc = multiplet center, coupling constants Hz, integration). Carbon NMR (^{13}C NMR) spectra were also recorded at various field strengths as indicated. Spectra were recorded in $CDCl_3$ using residual undeuterated solvent (77 ppm) as an internal reference. Infrared (IR) spectra were

recorded on a diamond ATR spectrometer using neat samples. Infrared frequencies are reported in wavenumbers (cm^{-1}), and intensities were determined qualitatively and are reported as strong (s), medium (m) or weak (w). Solid Lewis acids were flame-dried in the reaction flask under vacuum and under argon before use.

Synthesis of oct-7-en-1-ol (6)

$ZrCl_4$ (637 mg, 2.83 mmol, 0.03 equiv.) was added to a solution of octa-1,7-diene (10 g, 90.75 mmol, 1 equiv.) in dried hexane (100 mL) under an argon atmosphere. DIBAL-H (1 M in toluene, 90.75 mL, 90.75 mmol, 1 equiv.) was added dropwise at RT (the reaction mixture turning brown) and the reaction mixture was stirred for 7 h at RT. The flask was purged successively with dried air (RT, 1 h) and O_2 (40 °C, 3 h). The solution was treated with H_2SO_4 (10%, 100 mL), stirred for 1 h at RT, and extracted with Et_2O (3 × 50 mL). The combined extracts were washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated, and distilled to afford the alcohol **6** as a colorless liquid (6.9 g, 54.4 mmol, 60%); b.p.: 66–67 °C (8 mmHg) (lit.[34] 64–66 °C 7 mmHg); R_f: 0.11 (EtOAc–cyclohexane 1/9); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 5.82 (m, 1H), 4.95 (m, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.07 (m, 2H), 1.58 (m, 2H), 1.50–0.80 (m, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 139.0, 114.2, 63.1, 33.7, 32.7, 28.8, 28.8, 25.5; IR ν 3550, 3090, 1640, 920.

Synthesis of oct-7-enyl pivalate (7)

Alcohol **6** (4.3 g, 33.5 mmol, 1 equiv.) and PivCl (6.07 g, 50.3 mmol, 1.5 equiv.) were stirred in pyridine (150 mL) for two days. Pyridine was distilled giving a white liquid, which was diluted in water (100 mL), extracted with EtOAc (3 × 50 mL). The combined extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, evaporated, and purified by flash chromatography (EtOAc–cyclohexane 1/100) affording the protected alcohol **7** as a colorless liquid (6.37 g, 30.05 mmol, 90%); R_f: 0.15 (EtOAc–cyclohexane 1/50); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 5.78 (m, 1H), 4.94 (m, 2H), 4.02 (t, J = 6.6 Hz, 2H), 2.03 (m, 2H), 1.59 (m, 2H), 1.45–1.20 (m, 6H), 1.17 (s, 9H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 178.6, 138.9, 114.3, 64.4, 38.7, 33.6, 28.7, 28.6, 28.5, 27.2, 25.7; IR ν 2929, 2858, 1728, 1480, 1460, 1283, 1150, 1034, 994, 909, 771, 726.

(*S*,*E*)-11-Hydroxy-10-methylundec-7-enyl pivalate (8)

7 (6.2 g, 29.24 mmol, 5 equiv.) and **5** (585.7 mg, 5.85 mmol, 1 equiv.) were stirred in DCM (100 mL) at RT for one week. Grubbs II catalyst (3 × 24.8 mg, 0.087 mmol, 0.015 equiv.) was added three times every second day. The reaction mixture was hydrolyzed with a satd. solution of $NaHCO_3$, the aqueous phase was extracted three times with DCM and the organic layers were dried over Na_2SO_4, filtered and the solvents were evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 1/5) affording the cross-coupling product **8** as a mixture of *E* and *Z* (*E*/*Z* 1/16) as a colorless oil (1.12 g, 3.97 mmol, 68%); R_f: 0.42 (EtOAc–cyclohexane 1/3); $[\alpha]_D^{25}$: −2.6° (c = 2.31, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 5.33 (m, 2H), 3.97 (t, J = 6.6 Hz, 2H), 3.40 (m, 2H), 2.1–1.70 (m, 4H), 1.70–1.15 (m, 9H), 1.12 (s, 9H), 0.83 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 178.7, 132.1, 128.2, 68.0, 64.4, 38.7, 36.5, 36.0, 32.4, 29.3, 28.6, 28.5, 27.2, 25.7, 16.4; IR ν 3389, 2928, 1728, 1284, 1153, 1035, 968.

(*S*,*E*)-10-Methyl-11-oxoundec-7-enyl pivalate (9)

DMSO (69.5 μL, 0.98 mmol, 2.4 equiv.) in DCM (1 mL) was added to a solution of $(COCl)_2$ (42 μL, 0.49 mmol, 1.2 equiv.) in DCM (2 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and alcohol **8** (116 mg, 0.41 mmol, 1 equiv.) in DCM (1 mL) was added *via* cannula into the reaction mixture. The reaction mixture was stirred for 30 min, Et_3N (283 μL, 2.04 mmol, 5 equiv.) was added to the solution at −78 °C and the reaction mixture was warmed to RT over 45 min. Hexane (5 mL) was added to the solution and filtered through a pad of silica, and the silica was washed with a mixture of EtOAc and cyclohexane (EtOAc–cyclohexane 1/5). The solvents were distilled under vacuum, and the crude **9** was used without any further purification (108 mg, 0.38 mmol, 94%); R_f: 0.85 (EtOAc–cyclohexane 1/3); $[\alpha]_D^{25}$: +11.6° (c = 0.81, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 9.62 (d, J = 1.4 Hz, 1H), 5.50–5.30 (m, 2H), 4.02 (t, J = 6.6 Hz, 2H), 2.39 (m, 2H), 2.12–1.94 (m, 3H), 1.58 (m, 2H), 1.42–1.28 (m, 6H), 1.12 (s, 9H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 204.9, 178.6, 133.4, 126.2, 64.37, 46.3, 38.7, 33.6, 32.4, 29.2, 28.6, 28.5, 27.2, 25.7, 13.0; IR ν 2931, 1725, 1284, 1154, 969; HRMS ES m/z $(M + Na)^+$: Calcd $C_{17}H_{30}NaO_3$ 305.209, found 305.207.

(*S*)-2-(2,2-Diethyl-1,3-dioxolan-4-yl)ethanol (10)[35]

A solution of L-malic acid (6.0 g, 45 mmol, 1 equiv.) in dry THF (50 mL) was added slowly to a mixture of BMS·THF (30 mL, 5M in THF, 150 mmol, 3.33 equiv.) and trimethyl borate (15.4 mL, 135 mmol, 3 equiv.) at 0 °C. The reaction mixture was stirred overnight and then quenched with MeOH (50 mL). Solvents were evaporated and the crude was co-evaporated with MeOH four times. The crude was then purified by chromatography (DCM–MeOH 9/1), giving the triol as a colorless oil (4.67 g, 44 mmol, 99%).

p-TsOH (365 mg, 2 mmol, 0.05 equiv.) was added to a stirred solution of triol (4.50 g, 46 mmol, 1 equiv.) in dry 3-pentanone (80 mL). The reaction mixture was stirred overnight at room temperature and then quenched with Et_3N (0.25 mL). The solvent was removed and the crude was filtered through a plug of SiO_2 with EtOAc–cyclohexane 7/3, giving the protected 1,2-diol **10**, containing less than 1% of the corresponding protected 1,3-diol as a pale yellow oil (6.5 g, 38.23 mmol, 89%); R_f: 0.30 (EtOAc–cyclohexane 7/3); $[\alpha]_D^{25}$: +2.2° (c = 1.27 $CHCl_3$, lit.[36] $[\alpha]_D^{27}$: +2.2°, c = 1.27 in $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 4.20 (m, 1H), 4.06 (m, 1H), 3.74 (td, J = 5.7 Hz, J = 1.2 Hz, 2H), 3.49 (t, J = 8.1 Hz, 1H), 2.65 (m, 1H), 1.78 (m, 2H), 1.59 (qt, J = 7.5 Hz, 4H), 0.85 (td, J = 7.5 Hz, J = 3.0 Hz, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 112.9, 75.2, 70.1, 60.4, 35.5, 29.9, 29.6, 8.1, 7.9.

(*S*)-2,2-Diethyl-4-(2-(4-methoxybenzyloxy)ethyl)-1,3-dioxolane (11)

10 (6.5 g, 38.2 mmol, 1 equiv.) was stirred in dry THF (100 mL) at 0 °C. NaH (60% in mineral oil, 1.83 g, 45.88 mmol, 1.2 equiv.) was added and the reaction mixture was stirred for 30 min at RT. PMB–Br (9.25 mL, 45.88 mmol, 1.2 equiv.) and Bu_4NI (2.1 g, 5.73 mmol, 0.15 equiv.) diluted in dry THF (100 mL) were added and the reaction mixture was stirred for 6 h at RT. The reaction mixture was hydrolyzed with NH_4Cl (100 mL), and the aqueous phase was extracted three times with EtOAc (100 mL). The organic phases were washed with a saturated solution of Na_2SO_3 and brine, dried with Na_2SO_4, filtered and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 1/4) giving the protected alcohol **11** as a pale yellow oil (10.68 g, 36.3 mmol, 95%); R_f: 0.69 (EtOAc–cyclohexane 1/3); $[\alpha]_D^{25}$: +8.2° (*c* = 1.14, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 6.97 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 111.5 Hz, 4H), 4.40 (s, 2H), 4.10 (qtd, *J* = 6.3 Hz, *J* = 1.5 Hz, 1H), 3.97 (dd, *J* = 6.0 Hz, 1H), 3.71 (s, 3H), 3.44 (m, 3H), 1.85 (m, 2H), 1.59 (td, *J* = 7.5 Hz, *J* = 4.5 Hz, 4H), 0.86 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.2, 132.0, 129.4, 113.8, 112.3, 74.2, 72.7, 70.3, 66.8, 55.2, 33.7, 30.0, 29.8, 8.3, 8.0; HRMS ES *m*/*z* $(M + Na)^+$: Calcd for $C_{17}H_{26}NaO_4$ 317.172, found 317.169.

(*S*)-4-(4-Methoxybenzyloxy)butane-1,2-diol (12)

PTSA (350 mg, 1.83 mmol, 0.2 equiv.) was added to a solution of **11** (2.4 g, 9.2 mmol, 1 equiv.) in MeOH (30 mL). The reaction mixture was stirred for 5 h at RT. Water (10 mL) was added and the reaction mixture was stirred for 4 h at RT. Brine (50 mL) and EtOAc (50 mL) were added. The aqueous phase was extracted three times with EtOAc and the organic phases were washed with a saturated solution of $NaHCO_3$ (50 mL), dried with Na_2SO_4, filtered and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 4/1) giving the diol **12** as white crystals (1.84 g, 8.29 mmol, 90%); R_f: 0.15 (EtOAc–cyclohexane 4/1); $[\alpha]_D^{25}$: −5.2° (*c* = 2.00, $CHCl_3$, lit.[37] $[\alpha]_D^{27}$: −5.2°, *c* = 2.00 in $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.05 (A_2B_2, J_{AB} = 7.7 Hz, $\Delta\nu$ = 109.8 Hz, 4H), 4.24 (s, 2H), 3.85 (m, 1H), 3.78 (s, 3H), 3.60 (m, 2H), 3.51 (AB(ABX), J_{AX} = 3.6 Hz, J_{BX} = 6.3 Hz, J_{AB} = 11.4 Hz, $\Delta\nu$ = 42.0 Hz, 2H), 3.16 (s, 2H), 1.72 (m, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.3, 129.93, 129.4, 113.9, 72.9, 71.1, 67.7, 66.6, 55.3, 32.8; IR ν 3256, 2990, 2942, 2863, 1613, 1513.

(*S*)-2-Hydroxy-4-(4-methoxybenzyloxy)butyl 2,4,6-triisopropylbenzenesulfonate (13)

Dried Et_3N (470 μL, 3.4 mmol, 1.5 equiv.) was added to a solution of **12** (500 mg, 2.25 mmol, 1 equiv.) in dry DCM at RT. The sulfonyl chloride (1.05 g, 3.34 mmol, 1.5 equiv.) was then added; the reaction mixture was allowed to warm to RT and stirred for 36 h. The reaction mixture was hydrolysed with water (2 mL) and stirred for 1 h at RT. The organic phases were washed consequently with water (10 mL), H_2SO_4 1 M (10 mL), water (10 mL) and $NaHCO_3$ (10 mL). The organic phases were dried over Na_2SO_4, filtered and evaporated. The crude oil was purified by chromatography (EtOAc–cyclohexane 1/4), giving the sulfonate **13** as white crystals (1.02 g, 2.14 mmol, 95%); R_f: 0.2 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: −7.3° (*c* = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.18 (s, 2H), 7.03 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 103.7 Hz, 4H), 4.42 (s, 2H), 4.1 (m, 5H), 3.80 (s, 3H), 3.64 (m, 2H), 2.91 (septet, *J* = 6.9 Hz, 1H), 1.80 (m, 2H), 1.25 (d, *J* = 6.6 Hz, 18H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.3, 153.8, 150.8, 129.8, 129.3, 129.1, 123.8, 113.9, 73.0, 72.2, 68.8, 67.4, 55.3, 34.2, 32.6, 29.6, 24.73, 24.71, 23.5; IR ν 3437, 2959, 1614, 1514, 1423, 1337, 1256, 1178, 1072, 1030, 964, 894, 818, 811, 792, 664; HRMS ES *m*/*z* $(M + Na)^+$: Calcd for $C_{27}H_{40}NaO_6S$ 515.244, found 515.243.

(*S*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (14)[38]

K_2CO_3 (940 mg, 6.8 mmol, 2 equiv.) was added to a stirred solution of **13** (1.67 g, 3.4 mmol, 1 equiv.) in dry MeOH. The reaction mixture was stirred overnight at RT. Solvents were removed, giving a pale orange solid. The solid was filtered four times with hot hexane, and the filtrates were dried. The crude was purified by chromatography (DCM), giving the epoxide **14** as a pale yellow oil (572 mg, 2.73 mmol, 80%); R_f: 0.30 (DCM); $[\alpha]_D^{25}$: −14.4° (*c* = 1.0, $CHCl_3$, lit.[38] $[\alpha]_D^{27}$: −13.9°, *c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.07 (A_2B_2, J_{AB} = 8.4 Hz, $\Delta\nu$ = 114.6 Hz, 4H), 4.46 (s, 2H), 3.80 (s, 3H), 3.59 (t, *J* = 6.3 Hz, 2H), 3.05 (m, 1H), 2.77 (t, *J* = 4.8 Hz, 1H), 2.51 (dd, *J* = 2.7 Hz, *J* = 3.0 Hz, 1H), 1.82 (m, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.2, 130.4, 129.2, 113.8, 72.7, 66.7, 55.3, 50.1, 47.1, 32.6; IR (ATR) ν 2859, 1612, 1512, 1244, 1173, 1087, 1032, 818.

(*S*)-(1-(1,3-Dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-yloxy)-(*tert*-butyl)dimethylsilane (15)

To a solution of 1-*tert*-butyl-dimethyl-silyl-(1,3)-dithiane **2**[39] (450 mg, 1.85 mmol, 1 equiv.) in THF (6 mL) at −78 °C was added *tert*-BuLi (1.7 M in heptane, 1.1 mL, 1.85 mmol, 1 equiv.). The reaction mixture was stirred for 1 h at −50 °C and then cooled down to −78 °C. The epoxide **14** (390 mg, 1.85 mmol, 1 equiv.) in THF (6 mL) was added dropwise, and the reaction mixture was stirred for 1 h at −50 °C and cooled down to −78 °C. HMPA (4 mL) was added; the reaction mixture was stirred at RT for 2 h and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted twice with dichloromethane (2 × 10 mL) and the organic phases were washed with brine (10 mL), dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (EtOAc–cyclohexane 1/9) giving the dithiane **15** as an orange oil (533 mg, 1.20 mmol, 65%); R_f: 0.5 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: +8.1° (*c* = 1.02 ($CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.08 (A_2B_2, J_{AB} = 8.6 Hz, $\Delta\nu$ = 116.0 Hz, 4H), 4.43 (s, 2H), 4.10 (m, 2H), 3.82 (s, 3H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.82 (m, 4H), 1.90 (m, 6H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.1, 130.6, 129.3, 113.8, 72.7, 66.4, 66.3, 55.3, 43.9, 42.9, 37.3, 30.5, 30.1, 26.0, 25.9, 18.0, −4.5, −4.6; IR ν 2929, 2855, 2118, 1613, 1513, 1463, 1360, 1248, 1172, 1094, 1039, 928, 835, 775; HRMS ES *m*/*z* $(M + Na)^+$: Calcd for $C_{22}H_{38}NaO_3S_2Si$ 465.192, found 465.192.

(*S*)-2-(4-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)butyl)-1,3-dithiane (16)

To a solution of 1,3-dithiane (689 mg, 5.74 mmol, 3 equiv.) in THF (5 mL) at −78 °C was added *n*-BuLi (1.55 M in hexane, 7.4 mL, 11.48 mmol, 6 equiv.) and DMPU (1.4 mL, 11.48 mmol, 6 equiv.). The reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was then cooled down to −78 °C. The epoxide **14** (402 mg, 1.91 mmol, 1 equiv.) in THF (5 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h at −78 °C and then for 1 h at −10 °C. The reaction was quenched with 10 mL of satd. NH_4Cl. The aqueous phase was then extracted with EtOAc (3 × 10 mL), the organic phases were washed with satd. NH_4Cl (2 × 10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated. The crude was purified by chromatography (cyclohexane–EtOAc 4/1) giving alcohol as a pale yellow oil (520 mg, 1.59 mmol, 83%).

To a solution of alcohol (500 mg, 1.52 mmol, 1 equiv.) in DMF (20 mL) were added DIPEA (2.1 mL, 12.12 mmol, 8 equiv.), *n*-Bu_4NI (565 mg, 1.52 mmol, 1 equiv.) and MOM–Cl (460 μL, 6.08 mmol, 4 equiv.). The reaction mixture was stirred for 16 h at 50 °C and then quenched with 10 mL of satd. NH_4Cl. The aqueous phase was then extracted with EtOAc (3 × 10 mL) and organic phases were washed with satd. NH_4Cl (2 × 10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated. The crude was purified by chromatography (cyclohexane–EtOAc 9/1) affording the protected alcohol **16** as a colorless oil (520 mg, 1.39 mmol, 92%); R_f: 0.31 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: +2.2° (*c* = 0.96, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.05 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 116.9 Hz, 4H), 4.62 (AB, J_{AB} = 6.9 Hz, $\Delta\nu$ = 6.2 Hz, 2H), 4.41 (s, 2H), 4.15 (dd, *J* = 5.7 Hz, *J* = 5.7 Hz, 1H), 3.99 (m, 1H), 3.78 (s; 3H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.36 (s, 3H), 2.82 (m, 4H), 1.95 (m, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.1, 130.4, 129.3, 113.8, 96.3, 72.9, 72.6, 66.3, 55.7, 55.3, 43.6, 40.9, 35.0, 30.3, 30.0, 25.7; IR (ATR) ν 2931, 1512, 1244, 1093, 1030, 916, 818; HRMS ES *m*/*z* $(M + Na)^+$: Calcd for $C_{18}H_{28}NaO_4S_2$ 395.132, found 395.132.

1-(2-((*S*)-4-((4-Methoxybenzyl)oxy)-2-(methoxymethoxy)butyl)-1,3-dithian-2-yl)-2-methylpentan-1-ol (18)

n-BuLi (1.6 M in hexane, 375 μL, 0.56 mmol, 3.75 equiv.) was added over three minutes to a solution of dithiane **16** (112 mg, 0.30 mmol, 2 equiv.) at −78 °C. The reaction mixture was stirred and then warmed to 0 °C over 1 h. 2-Methylvaleraldehyde **17** (19 μL, 0.15 mmol, 1 equiv.) was added *via* cannula to the stirring solution of 2-lithiodithiane at −78 °C and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was hydrolyzed with a satd. solution of NH_4Cl, and the aqueous layer was extracted three times with EtOAc. Organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography (EtOAc–cyclohexane 1/9 and then 1.5–8.5) affording product **18** as a mixture of 4 diastereoisomers as a colorless oil (41.5 mg, 0.088 mmol, 58%); R_f: 0.12 (EtOAc–cyclohexane 1/9); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.08 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 120.3 Hz, 4H), 4.97–4.6 (mixt. of AB, 2H), 4.44 (mixt. of AB, 2H), 4.10 (m, 1H), 3.80 (s, 3H), 3.58 (t, *J* = 6.6 Hz), 3.38 (s, 3H), 3.0–2.55 (m, 4H), 2.37–2.17 (m), 2.08–1.78 (m), 1.76–1.50 (m), 1.50–1.25 (m), 1.12–0.82 (mixt. of d and t, 6H).

(10*S*,*E*)-11-Hydroxy-11-(2-((*S*)-4-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)butyl)-1,3-dithian-2-yl)-10-methylundec-7-en-1-yl pivalate (19)

n-BuLi (1.6 M in hexane, 240 μL, 0.38 mmol, 2.2 equiv.) was added to a stirring solution of dithiane **16** (130 mg, 0.347 mmol, 2 equiv.) in dry THF (5 mL) at −78 °C and the solution turned yellow. The reaction mixture was stirred for 1 h at 0 °C, turned into a pale yellow solution and then cooled down to −78 °C. The aldehyde **9** (49 mg, 0.173 mmol, 1 equiv.) in THF (1 mL) was added *via* cannula into the solution and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was hydrolyzed by a satd. solution of $NaHCO_3$, and the aqueous phase was extracted three times with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4, and filtered and the solvents were removed. The crude was purified by chromatography (EtOAc–cyclohexane 5/95) affording the desired coupling product **19** as a mixture of stereoisomers (dr = 1/1.7) as a pale yellow oil (34 mg, 0.051 mmol, 30%); R_f: 0.52 (EtOAc–cyclohexane 3/7); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 6.99 (A_2B_2, J_{AB} = 8.6 Hz, $\Delta\nu$ = 120.7 Hz, 4H), 5.36 (m, 2H), 4.75–4.58 (m, 2H), 4.36 (s, 2H), 4.02 (m, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 3.76 (m, 1H), 3.73 (s, 3H), 3.51 (t, *J* = 6.6 Hz, 2H), 3.31/3.30 (s, 3H), 2.90–2.45 (m, 4H), 2.40–1.7 (m, 7H), 1.54 (m, 4H), 1.26 (m, 8H), 1.12 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H).

((4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)methanol (21)

p-Anisaldehyde dimethyl acetal (5.75 mL, 33.74 mmol, 0.95 equiv.) and PTSA (337 mg, 1.77 mmol, 0.05 equiv.) were added to a stirring solution of (*S*)-butane-1,2,4-triol **20** (3.78 g, 35.5 mmol, 1 equiv.) in dry DMF (75 mL) at RT. The reaction mixture was stirred under vacuum (15 mbar) until the reaction was complete (1 h). Et_2O (75 mL) was added and the organic phase was then washed three times with a satd. solution of $NaHCO_3$, a satd. solution of NH_4Cl and finally brine. The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 2/8 and then 6/4) affording the protected diol **21** as a pale yellow oil (6.94 mg, 29.1 mmol, 82%); m.p.: 43–45 °C; R_f: 0.22 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: +7.8° (*c* = 1.3, CH_3Cl, lit.[40] $[\alpha]_D^{27}$: +7.2°, *c* = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.15 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 156.9 Hz, 4H), 5.50 (s, 1H), 4.28 (ddd, *J* = 11.1 Hz, *J* = 4.8 Hz, *J* = 0.9 Hz, 1H), 3.98 (m, 2H), 3.80 (s, 3H), 3.67 (m, 2H), 2.11 (t, *J* = 6.3 Hz, 1H), 1.91 (qd, *J* = 12.9 Hz, *J* = 5.1 Hz, 1H), 1.43 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 160.0, 131.0, 127.5, 113.6, 101.2, 77.6, 66.6, 65.6, 55.3, 26.8; IR ν 3433, 2930, 2856, 1614, 1517, 1244, 1172, 1101, 1067, 1027, 825, 777.

(4*S*)-4-(Iodomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (22)

Triphenylphosphine (1.20 g, 4.59 mmol, 1.03 equiv.) and imidazole (364 mg, 5.35 mmol, 1.2 equiv.) were stirred in DCM

(10 mL) at 0 °C. Iodine (1.16 g, 4.59 mmol, 1.03 equiv.) was added at 0 °C (the solution turned dark brown) and the reaction mixture was stirred for 40 min at RT. Alcohol **21** (1.0 g, 4.46 mmol, 1 equiv.) in DCM (10 mL) was added *via* cannula into the stirring solution and the reaction mixture was stirred for 12 h at RT. The reaction mixture was hydrolyzed with a satd. solution of $NaHCO_3$ and a satd. solution of Na_2SO_3. The aqueous phase was extracted three times with Et_2O, and the organic phases were dried over Na_2SO_4, filtered and evaporated. The crude was filtered through a pad of silica (EtOAc–cyclohexane 1/4) affording the desired compound **22** as a colorless oil (31 mg, 0.148 mmol, 70%); R_f: 0.89 (EtOAc–cyclohexane 1/1) $[\alpha]_D^{25}$: +33.6° (c = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.16 (A_2B_2, J_{AB} = 8.4 Hz, $\Delta\nu$ = 161.5 Hz, 4H), 5.48 (s, 1H), 4.27 (m, 1H), 3.94 (m, 2H), 3.80 (s, 3H), 3.27 (AB(ABX), J_{AX} = 6.0 Hz, J_{BX} = 6.0 Hz, J_{AB} = 9.9 Hz, $\Delta\nu$ = 29.3 Hz, 2H), 1.82 (m, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 158.9, 130.8, 126.4, 112.5, 100.1, 75.3, 65.5, 54.1, 30.1, 6.8.

(4*S*)-4-((1,3-Dithian-2-yl)methyl)-2-(4-methoxyphenyl)-1,3-dioxane (23)

1,3-Dithiane (3.28 g, 27.3 mmol, 2.44 equiv.) was dissolved in THF/HMPA (10 mL/0.25 mL) and the solution was cooled down to −30 °C. *t*-BuLi (1.7 M in hexane, 16.0 mL, 27.3 mmol, 2.44 equiv.) was added dropwise and the solution turned dark yellow. The reaction mixture was stirred for 1.5 h at −30 °C and **22** (3.74 g, 11.2 mmol, 1 equiv.) in THF (5 mL) was added *via* cannula to the reaction mixture at −78 °C. The reaction mixture was stirred for 45 min at −78 °C, turned dark brown, and was hydrolyzed with a satd. solution of NH_4Cl. The aqueous layer was extracted three times with Et_2O, dried over Na_2SO_4, filtered and evaporated. The crude was then purified by chromatography giving the corresponding dithiane **23** as a white solid (2.74 g, 8.4 mmol, 75%); R_f: 0.42 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: +44.21° (c = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.16 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 159.0 Hz, 4H), 5.48 (s, 1H), 4.26 (td, J = 9.9 Hz, J = 4.5 Hz, 1H), 4.15 (m, 2H) 3.95 (td, J = 12.0 Hz, J = 2.4 Hz, 1H), 3.80 (s, 3H), 2.85 (m, 4H), 2.11 (m, 2H), 1.88 (m, 3H), 1.52 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.9, 131.3, 127.8, 113.5, 101.0, 73.1, 66.8, 55.3, 42.8, 41.7, 31.3, 30.2, 29.8, 26.0; IR (ATR) ν 2926, 1611, 1517, 1428, 1301, 1246, 1172, 1138, 1088, 1030, 1013, 969, 835, 818, 768; HRMS ES m/z $(M + Na)^+$: Calcd for $C_{16}H_{22}NaO_3S_2$ 349.090, found 349.091.

(*S*)-4-(1,3-Dithian-2-yl)-3-((4-methoxybenzyl)oxy)butan-1-ol (24)

DIBAL-H (1 M toluene, 3.0 mL, 3.0 mmol, 6 equiv.) was added dropwise to a solution of **23** (169 mg, 0.5 mmol, 1 equiv.) in DCM (12 mL) at −40 °C and the reaction mixture was stirred for 4 h at −40 °C until the starting material disappeared on TLC. The reaction mixture was hydrolyzed with a satd. solution of sodium tartrate and the solution was stirred until the two phases were clear. The aqueous layer was extracted three times with DCM, organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 3/7) affording the corresponding alcohol **24** as a colorless oil (160 mg, 0.47 mmol, 94%); R_f: 0.36 (EtOAc–cyclohexane 1/1); $[\alpha]_D^{25}$: −11.2° (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.08 (A_2B_2, J_{AB} = 8.4 Hz, $\Delta\nu$ = 119.2 Hz, 4H), 4.52 (AB, J_{AB} = 11.1 Hz, $\Delta\nu$ = 12.6 Hz, 2H), 4.10 (m, 1H), 3.93 (m, 1H), 3.80 (s, 3H), 3.74 (m, 2H), 2.83 (m, 4H), 2.0 (m, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.3, 130.3, 129.7, 113.9, 74.4, 71.3, 60.1, 55.3, 43.9, 40.0, 36.3, 30.4, 30.3, 25.9; IR ν 3434, 2934, 1612, 1513, 1247, 1174, 1034, 821, 772; HRMS ES m/z $(M + Na)^+$: Calcd for $C_{16}H_{24}NaO_3S_2$ 351.106, found 351.103.

(*S*)-(4-(1,3-Dithian-2-yl)-3-((4-methoxybenzyl)oxy)butoxy)-(*tert*-butyl)dimethylsilane (25)

TBSCl (462 mg, 3.06 mmol, 1.5 equiv.) and imidazole (347 mg, 5.1 mmol, 2.5 equiv.) were added to a stirring solution of alcohol **24** (700 mg, 2.04 mmol, 1 equiv.) in dry DMF (10 mL) at RT and the reaction mixture was stirred overnight. Et_2O (15 mL) was added to the solution and the organic phase was washed three times with a satd. solution of $NaHCO_3$, once with a satd. solution of NH_4Cl and with brine. The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude was purified by chromatography giving the protected alcohol **25** as a colorless oil (840 mg, 1.84 mmol, 90%); R_f: 0.27 (EtOAc–cyclohexane 5/95); $[\alpha]_D^{25}$: −17.6° (c = 1.07 in $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.08 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 121.2 Hz, 4H), 4.49 (AB, J_{AB} = 10.8 Hz, $\Delta\nu$ = 10.8 Hz, 2H), 4.14 (dd, J = 9.0 Hz, J = 5.7 Hz, 1H), 3.86 (m, 1H), 3.80 (s, 3H), 3.69 (td, J = 6.6 Hz, J = 2.4 Hz, 2H), 2.81 (m, 4H), 1.85 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 159.2, 131.0, 129.5, 113.8, 72.8, 71.4, 59.4, 55.3, 44.0, 40.6, 37.6, 30.4, 30.1, 26.0, 25.9, 18.2, −5.3, −5.3; IR (ATR) ν 2929, 1612, 1513, 1246, 1172, 1089, 1035, 832, 774; HRMS ES m/z $(M + H)^+$: Calcd for $C_{22}H_{39}O_3S_2Si$ 443.210, found 443.210.

(10*S*,*E*)-11-(2-((*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)butyl)-1,3-dithian-2-yl)-11-hydroxy-10-methylundec-7-en-1-yl pivalate (26)

n-BuLi (1.6 M in hexane, 1.21 mL, 0.76 mmol, 2.5 equiv.) was added dropwise to a stirring solution of dithiane **25** (337 mg, 0.76 mmol, 2.5 equiv.) in THF (7 mL) at −78 °C and the reaction mixture was stirred for 1 h at −10 °C. The freshly prepared aldehyde **9** (86 mg, 0.304 mmol, 1 equiv.) in THF (5 mL) was added dropwise *via* cannula to the reaction mixture at −78 °C and the reaction mixture was stirred for 2 h at −78 °C. The reaction mixture was hydrolyzed by a satd. solution of $NaHCO_3$ and the aqueous layer was extracted three times with EtOAc. The organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated; the crude was purified by chromatography (EtOAc–cyclohexane 1/9) affording the coupling product **26** as a mixture of non-separable diastereoisomers (r.d. 1/2.7) as a pale yellow oil (210 mg, 0.29 mmol, 92%); R_f: 0.65 (EtOAc–cyclohexane 1/4); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.05 (A_2B_2, J_{AB} = 8.4 Hz, $\Delta\nu$ = 117.9 Hz, 4H), 5.42 (m, 2H), 4.52 (AB, J_{AB} = 10.5 Hz, $\Delta\nu$ = 46.5 Hz, 2H), 4.45 (AB, J_{AB} = 10.5 Hz, $\Delta\nu$ = 17.1 Hz, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.99 (m, 1H), 3.79 (s, 3H), 3.74 (m, 3H), 3.58 (d, J = 4.5 Hz, 1H), 2.73 (m, 4H),

2.28 (m, 3H), 1.88 (m, 8H), 1.60 (m, 2H), 1.32 (m, 6H), 1.42 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H), 0.06 (s, 6H), ^{13}C NMR (75 MHz) ($CDCl_3$) δ 178.6, 132.0, 130.9, 113.8, 113.7, 74.8, 74.7, 70.7, 64.4, 59.7, 59.6, 41.3, 40.4, 38.7, 37.6, 33.8, 33.6, 30.2, 29.6, 28.8, 28.6, 27.3, 26.9, 26.0, 25.9, 25.8, 25.6, 25.0, 24.6, 18.3, 15.7, 15.6, −5.26, −5.29; IR ν 3460, 2929, 2856, 1726, 1514, 1248, 1155, 1091, 1036, 834, 775; HRMS ES m/z (M + Na)$^+$: Calcd $C_{30}H_{68}NaO_6S_2Si$ 747.412, found 747.406.

(10*S*,11*R*,14*S*,*E*)-16-((*tert*-Butyldimethylsilyl)oxy)-11-hydroxy-14-((4-methoxybenzyl)oxy)-10-methyl-12-oxohexadec-7-en-1-yl pivalate (27)

Dithiane **26** (30 mg, 0.041 mmol, 1 equiv.) was dissolved in CH_3OH (0.2 mL), water (0.2 mL) and THF (2 mL). PIFA (27 mg, 0.06 mmol, 1.5 equiv.) was added, the reaction mixture was stirred for one minute, and the reaction mixture was hydrolyzed with a satd. solution of Na_2SO_3. The aqueous phase was extracted three times with EtOAc. Organic phases were dried over Na_2SO_4, filtered, and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 5/95) giving the ketone as a single diastereoisomer **27** (19.6 mg, 0.030 mmol, 75%); R_f: 0.59 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: −19.8° (c = 1.01, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.02 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 106.4 Hz, 4H), 5.45 (m, 2H), 4.45 (AB, J_{AB} = 11.1 Hz, $\Delta\nu$ = 9.17 Hz, 2H), 4.14 (m, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 3.69 (t, J = 5.7 Hz, 2H), 3.41 (d, J = 4.8 Hz, 1H), 2.70 (AB(ABX), J_{AX} = 7.5 Hz, J_{BX} = 4.8 Hz, J_{AB} = 16.2 Hz, $\Delta\nu$ = 72.6 Hz, 2H), 2.0 (m, 6H), 1.65 (m, 4H), 1.33 (m, 6H), 1.19 (s, 9H), 0.89 (s, 9H), 0.66 (d, J = 6.3 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 211.4, 179.1, 159.2, 133.0, 130.3, 129.4, 127.9, 113.7, 78.7, 72.5, 71.7, 64.4, 59.2, 55.2, 43.7, 38.7, 37.2, 36.4, 32.5, 29.7, 29.4, 28.8, 28.6, 27.2, 25.9, 25.8, 18.2, 12.6, −5.3; IR ν 2929, 2856, 1727, 1514, 1462, 1249, 1156, 1092, 836, 776; HRMS ES m/z (M + Na)$^+$: Calcd $C_{36}H_{62}NaO_7Si$ 657.416, found 657.416.

(*S*,*E*)-10-((4*R*,5*S*)-5-((*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)butyl)-2,2-dimethyl-1,3-dioxolan-4-yl)undec-7-en-1-yl pivalate (28)

$Zn(BH_4)_2$ (260 μL, 0.183 mmol mL^{-1}, 0.047 mmol, 1 equiv.) was added dropwise to a solution of the ketone **27** (32 mg, 0.047 mmol, 1 equiv.) in Et_2O (2 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. The reaction mixture was hydrolyzed with water (5 mL). The aqueous phase was extracted three times with Et_2O and the organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 1/9) affording the *trans* 1,2-diol as a single diastereoisomer (r.d. > 98/2) as a colorless oil (22.7 mg, 0.033 mmol, 72%).

PPTS (0.9 mg, 0.003 mmol, 0.1 equiv.) was added to a solution of 1,2-diol (22.7 mg, 0.034 mmol, 1 equiv.) in 2,2-DMP (1 mL) at RT. The reaction mixture was stirred overnight at RT and hydrolyzed with a satd. solution of $NaHCO_3$. The aqueous layer was extracted three times with EtOAc, and the organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 1/9) giving the protected 1,2-diol **28** as a colorless oil (16.0 mg, 0.024 mmol, 71%); R_f: 0.64 (EtOAc–cyclohexane 1/3); $[\alpha]_D^{25}$: −22.6° (c = 1.01, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.05 (A_2B_2, J_{AB} = 6.6 Hz, $\Delta\nu$ = 117.7 Hz, 4H), 5.34 (m, 2H), 4.43 (AB, J_{AB} = 8.4 Hz, $\Delta\nu$ = 28.5 Hz, 2H), 4.11 (m, 1H) 4.09 (t, J = 5.1 Hz, 2H), 3.79 (s, 3H), 3.65 (m, 4H), 2.05–1.70 (m, 5H), 1.70–1.50 (m, 6H), 1.43 (s, 3H), 1.25 (m, 6H), 1.23 (s, 3H) 1.19 (s, 9H), 0.99 (d, J = 4.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 178.6, 159.4, 132.6, 131.0, 129.4, 127.2, 113.8, 107.4, 81.9, 74.4, 73.4, 70.7, 64.4, 59.8, 55.3, 38.7, 37.0, 34.1, 33.1, 32.5, 29.7, 29.4, 28.3, 28.6, 28.4, 27.2, 26.0, 25.8, 18.3, 16.7, −5.2; IR ν 2929, 1729, 1514, 1461, 1249, 1158, 1091, 837, 775; HRMS ES m/z (M + Na)$^+$: Calcd $C_{39}H_{68}NaO_7Si$ 699.463, found 699.458.

(7*S*,8*S*,10*S*)-10-((4*R*,5*S*)-5-((*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)butyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7,8-dihydroxyundecyl pivalate (29)

AD-mix-α (31 mg) and $CH_3SO_2NH_2$ (2 mg) were added to a solution of alkene **28** (16 mg, 0.022 mmol, 1 equiv.) in *t*-BuOH–H_2O (0.5/0.5 mL) at RT and the reaction mixture was stirred at RT for 6 days. The reaction was stopped by addition of sodium sulfite and the yellow color disappeared. The aqueous phase was extracted three times with EtOAc, the organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude was purified by chromatography (EtOAc–cyclohexane 1/4) affording the 1,2-diol **29** as a mixture of diastereoisomers (dr = 4.7/1) as a colorless oil (12.0 mg, 0.017 mmol, 77%); R_f: 0.05 (EtOAc–cyclohexane 1/3); $[\alpha]_D^{25}$: −19.1° (c = 0.45, $CHCl_3$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.01 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 109.7 Hz, 4H), 4.40 (AB, J_{AB} = 11.1 Hz, $\Delta\nu$ = 25.9 Hz, 2H), 4.17 (m, 1H) 4.09 (t, J = 6.3 Hz, 2H), 3.75 (s, 3H), 3.68 (m, 4H), 3.48 (m, 1H), 3.27 (m, 1H), 2.05–1.55 (m, 13H), 1.40 (s, 3H), 1.25 (m, 6H), 1.20 (s, 3H) 1.14 (s, 9H), 1.00 (d, J = 6.3 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 178.8, 159.2, 131.9, 129.4, 113.8, 107.8, 82.5, 75.3, 74.5, 73.35, 71.88, 70.6, 64.4, 59.8, 55.3, 38.80, 38.0, 37.1, 33.6, 29.7, 29.4, 29.3, 28.3, 28.6, 28.1, 27.3, 26.0, 25.6, 18.3, 16.1, −5.2; IR (ATR) ν 3445, 2931, 2857, 2324, 1728, 1514, 1463, 1249, 1158, 1093, 1039, 836, 776.

6-((4*S*,5*S*)-5-((*S*)-2-((4*R*,5*S*)-5-((*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)butyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexyl pivalate (30)

To a solution of **29** (9.0 mg, 0.012 mmol, 1 equiv.) in acetone (1 mL) were added PPTS (0.3 mg, 0.001 mmol, 0.1 equiv.) and 2,2-DMP (15 mL, 0.12 mmol, 10 equiv.) at room temperature. The reaction mixture was stirred for 12 h and hydrolyzed with a satd. solution of $NaHCO_3$. The aqueous phase was extracted three times with EtOAc, and the organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by chromatography (EtOAc–cyclohexane 1/9) affording the compound **30** as a colorless oil (8.0 mg, 0.010 mmol, 85%); R_f: 0.48 (EtOAc–cyclohexane 1/4); $[\alpha]_D^{25}$: −0.13° (c = 0.15 in $CHCl_3$);

^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.05 (A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 118.5 Hz, 4H), 4.44 (AB, J_{AB} = 11.1 Hz, $\Delta\nu$ = 39.9 Hz, 2H), 4.17 (m, 1H) 4.04 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 3.76–3.55 (m, 5H), 3.46 (m, 1H), 2.05–1.55 (m, 11H), 1.44 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H) 1.25 (m, 6H), 1.19 (s, 9H), 1.04 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 178.6, 159.1, 131.1, 129.3, 113.7, 108.1, 107.5, 82.5, 81.3, 77.2, 74.6, 73.5, 70.4, 64.3, 59.9, 55.3, 38.7, 37.6, 37.2, 33.6, 32.5, 31.9, 29.7, 29.4, 29.3, 28.9, 28.6, 28.1, 27.4, 27.3, 27.2, 26.10, 26.0, 25.9, 25.7, 18.3, 16.1, 14.1, −5.2; IR (ATR) ν 2927, 2855, 1730, 1514, 1462, 1248, 1157, 1093, 836, 775; HRMS ES m/z $(M + Na)^+$: Calcd $C_{42}H_{74}NaO_9Si$ 773.499, found 773.497.

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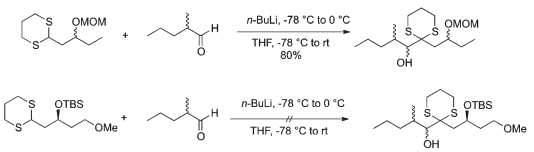

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