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# Asymmetric synthesis of cyclo-archaeol and β-glucosyl cyclo-archaeol†

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An efficient asymmetric synthesis of cyclo-archaeol and β-glucosyl cyclo-archaeol is presented employing catalytic asymmetric conjugate addition and catalytic epoxide ring opening as the key steps. Their occurrence in deep sea hydrothermal vents has been confirmed by chromatographic comparison with natural samples.



## Introduction

The domain of the Archaea forms an evolutionary line next to the well-known domains of Bacteria and Eukarya.[1] A number of Archaea colonize unusual ecological niches and grow under extreme conditions including high salinity, anaerobic conditions, temperatures up to 110 °C or around 0 °C, strongly acidic conditions, or extremely high pressures.[2]

The membrane core lipids of the Archaea are unique since they are composed of saturated isoprenoid chains attached to glycerol *via* ether linkages, unlike the conventional ester-based lipids of Bacteria and Eukarya. In addition, the stereochemistry at C-2 of the glycerol is the opposite. The most common structures include the monomeric diphytanylglycerol diethers (*e.g.* archaeol (**1**),[3] Fig. 1) and the dimeric macrocyclic dibiphytanyldiglycerol tetraethers.[2]

Next to dimerization of archaeol to tetraethers, intramolecular cyclisation leads to the macrocyclic diphytanylglycerol diether **2**, termed here "cyclo-archaeol" (macrocyclic archaeol), which was isolated for the first time in 1983 by Comita and Gagosian from *Methanococcus jannashii*, found in deep sea hydrothermal vents.[4] Subsequently, **2** has been detected a number of times,[5] mostly from hydrothermal vent systems, which has led to the *communis opinio* that this lipid is important for membrane integrity at high temperature and pressure.[6] This bears direct significance for application of this type of compound in nanotechnology and biotechnology.[7]

Until recent years, the analysis of archaeal lipids focussed mainly on the core lipids, *e.g.* without the polar head group, as the intact polar lipids are considerably less stable and more difficult to analyse. As the latter are, however, considered as diagnostic for the occurrence of living cells, the study of intact polar lipids containing *e.g.* phosphocholine or carbohydrate residues has intensified.[8]

Since their discovery, the structure of archaeal lipids has fascinated synthetic chemists.[9] The multiple stereocenters in these compounds, virtually devoid of functional groups, are a challenge, as is the formation of the macrocycles. In 1994,

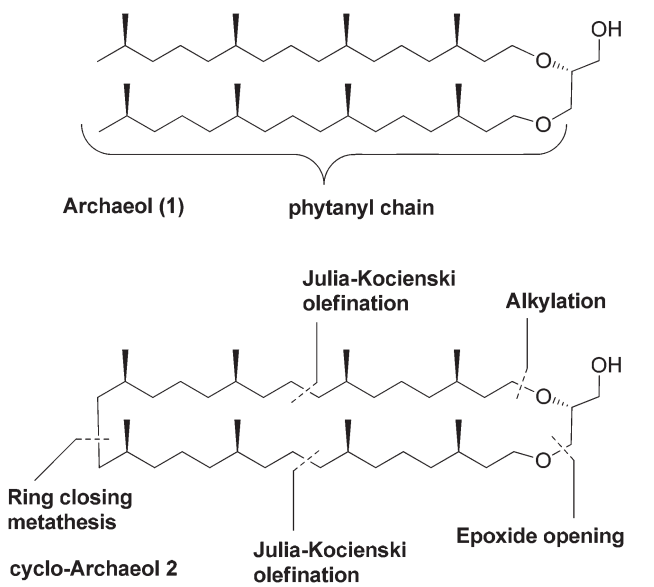


**Fig. 1** Archaeol **1**, and cyclo-archaeol **2**.

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†Electronic supplementary information (ESI) available: $^{1}$H- and $^{13}$C-NMR spectra of all new compounds. GC and HPLC traces of natural and synthetic **2** and **23**. See DOI: 10.1039/c3ob27277j

Kakinuma *et al.* pioneered with the first, and up to this work only, total synthesis of **2**.[10] Synthetic **2** prepared in this way was subsequently used to study its behavior in liposome formation and membrane packing.[11] In their synthesis, the methyl-branched stereocenters originated from the chiral pool (Roche Ester and citronellol). Inspired by this elaborate but also particularly lengthy route, we sought to develop a more efficient approach using asymmetric catalysis in order to bring this compound within reach.

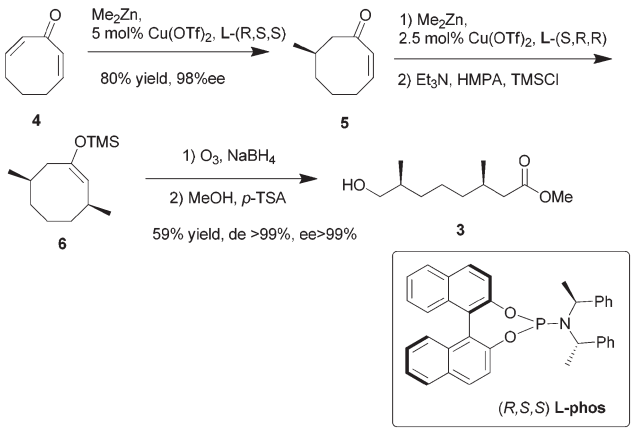
Upon close inspection of the $^{13}$C-NMR spectrum of natural **2**, as reported by Sprott *et al.*,[12] with the one reported for synthetic **2**,[13] it became obvious that the latter spectrum was considerably more complex. Especially in the range between 34 and 36 ppm, where the depicted spectrum of natural **2** shows one signal, synthetic **2** showed several, and also around 32 and 37 ppm, more signals are observed in synthetic **2** compared to natural **2**. Added to this, we realized that synthetic **2** had not been directly compared with a sample of natural **2**, in particular by chromatographic (GC or HPLC) means. So, although the synthetic route seemed unambiguous, there was a clear incentive to shed light on the discrepancy between the $^{13}$C-NMR spectra of natural and synthetic **2**, as prepared by Kakinuma *et al.* and to compare them in terms of chromatographic retention time.

Taken together, we embarked on the development of an efficient synthesis of cyclo-archaeol (**2**), using asymmetric catalysis for the introduction of the methyl substituents. The material prepared in this way would then be compared to natural **2**, isolated from a hydrothermal vent. In addition, we sought to prepare β-glucosyl-**2** (compound **23** in this paper) as this type of compound has been detected in *M. jannaschii*, as well as in hydrothermal vents,[14] but has not been prepared. Both **2** and its β-glucosyl derivative can function as reference compounds and internal standards in the detection and quantification of these compounds.

## Results and discussion

The synthetic approach designed for the preparation of **2** is based on the highly stereoselective synthesis of saturated isoprenoid building block **3**. As **3** will be used fourfold, this leads together with an efficient connection of this building block, to a dramatic simplification of the synthesis c.q. decrease in the number of steps compared to a linear synthesis. For the dimerization of **3** to a phytanyl-type chain, we opted for a Julia–Kocienski olefination followed by double bond reduction (Fig. 1). A non-symmetric coupling is required here as both termini of the phytanyl chain have a different role in the next part of the synthesis.

Contrary to the synthesis of glycerol esters, the stereoselective preparation of the required ether linkages for glycerol has turned out to be far from trivial. Most approaches in the literature use isopropylidene protected glycerol (solketal) as the starting material. In order to reduce steps, we decided to use the inherent reactivity and asymmetry in commercially



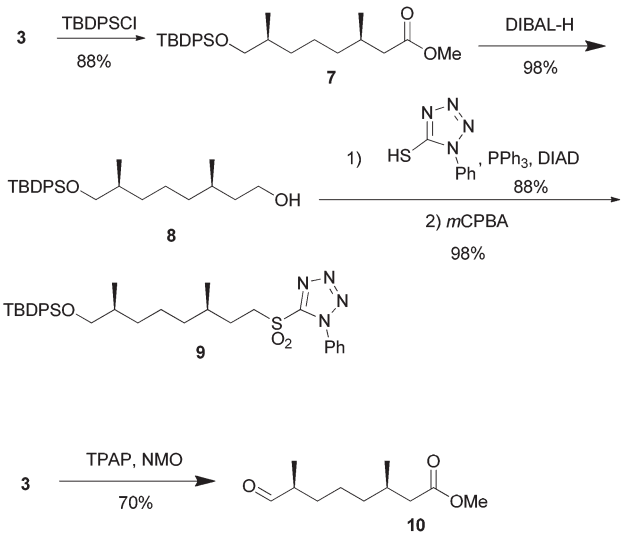

**Scheme 1** Synthesis of building block **3**.

available enantiopure benzyl glycidol. Efficient regioselective epoxide ring opening with the phytanyl chain alcohol, followed by etherification of the resulting secondary hydroxyl function with the second equivalent of the phytanyl chain, would lead in a straightforward manner to an advanced intermediate that upon ring closure, this time in a pseudo-symmetric manner, would directly lead to the 36-membered macrocyclic diether lipid (Fig. 1).

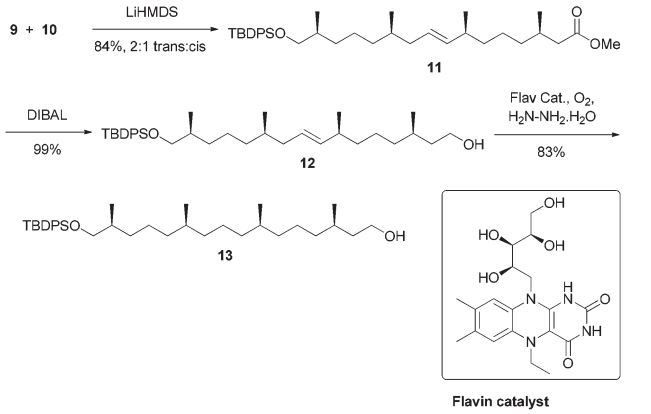
The synthesis started with the preparation of saturated isoprenoid building block **3** (Scheme 1). The synthesis, previously developed by our group,[15] consists of a repeated asymmetric copper-catalyzed conjugate addition of dimethylzinc to cyclooctadienone (**4**) followed by oxidative ring opening, and allows the preparation of the four possible diastereomers of **3** in a highly efficient and stereoselective fashion. Thus, reaction of **4** with dimethylzinc using 5 mol% copper(II) triflate and phosphoramidite **L-phos** as the chiral catalyst gave **5** in 80% yield and 98% enantiomeric excess (ee).

Subsequently, **5** was treated under the same reaction conditions, using in this case 2.5 mol% of the enantiomer of the copper catalyst. Given that protonation of the formed zinc enolate in this reaction would result in a *meso* compound and therefore loss of the chiral information, the enolate was trapped with trimethylsilyl chloride to yield **6**. Ozonolysis of **6** with reductive work-up, followed by esterification of the crude product, gave the saturated isoprenoid unit **3** in 59% yield over three steps, in >99% diastereomeric excess and >99% ee (Scheme 1). This preparation of **3** was optimized and scaled up to batch sizes of 6 to 10 g, and the high overall yield together with the excellent stereoselectivity makes this procedure very suitable for the synthesis of compounds containing this "saturated isoprenoid unit".

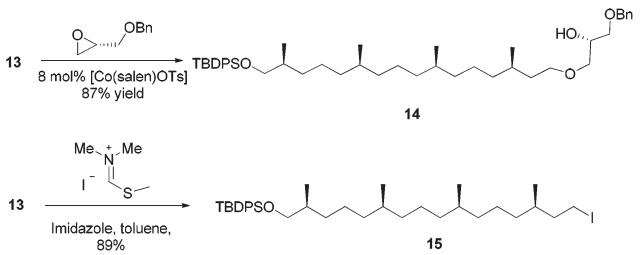
Compounds **9** and **10** (Scheme 2), required for the coupling of the isoprenoid units *via* a Julia–Kocienski olefination, were both synthesized from **3** in a straightforward manner. For the synthesis of the sulfone **9**, the hydroxy group of **3** was first protected with a *tert*-butyldiphenylsilyl group, giving **7** in 88% yield. The ester group was subsequently reduced and the resulting alcohol treated with 1-phenyl-1*H*-tetrazole-5-thiol in a




**Scheme 2** Synthesis of the precursors **9** and **10**.




**Scheme 3** Synthesis of the phytanyl-type chain **13**.




**Scheme 4** Catalytic ring opening of the glycidol and synthesis of **15**.

Mitsunobu reaction. Finally, the thioether was oxidized with *m*CPBA giving the sulfone **9** in very good overall yield from **3**. Aldehyde **10** was obtained by oxidation of **3** with TPAP and NMO in 70% yield.

The Julia–Kocienski olefination between **9** and **10** was carried out at low temperature using LiHMDS as a base. Under these conditions, olefin **11** was obtained in 84% yield as a 2 : 1 *trans–cis* mixture. Although inconsequential since the double bond will be reduced, the stereoselectivity of the reaction was shortly studied. It has been described that the use of bases with different counterions, for instance potassium, leads to higher selectivity for the *trans*-isomer albeit with lower yield.[16] Also in this case the use of KHMDS led to the exclusive formation of the *trans* alkene **11**, but in only 49% yield. Therefore LiHMDS remained the base of choice. Compound **11** was reduced with DIBAL to give alcohol **12** in quantitative yield.

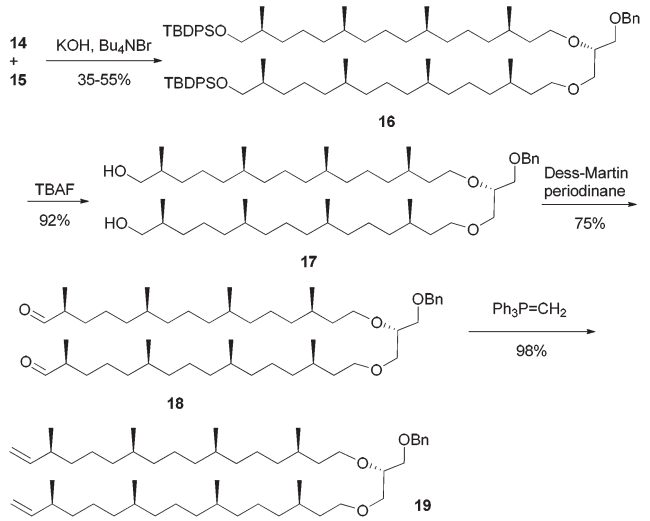
The reduction of the double bond in **12** is not trivial. Transition metals, in particular palladium and nickel, tend to isomerise double bonds, also under hydrogenation conditions. Such an isomerisation followed by reduction would undoubtedly lead to erosion of stereoselectivity, *vide infra*, a phenomenon that would be extremely difficult to detect *a posteriori*.[17] Reduction with diimide (diazene) is one of the few alternatives, and for this reaction a flavin-based catalyst for the controlled oxidation of hydrazine to diimide was chosen.[18] In the presence of hydrazine and under an oxygen atmosphere, the double bond was reduced effectively and alcohol **13** was obtained in 83% yield (Scheme 3).

The next step in the synthesis comprised the regioselective connection of the phytanyl-type chain **13** to two positions of the glycerol head group.[19] Ring opening of epoxides often involves the use of strong Lewis acids, which in the case of glycidol derivatives frequently leads to regioisomeric mixtures. Alternatively, the sodium or cesium alcoholate is used as a powerful nucleophile but this requires an excess of alcoholate in most cases. We decided, therefore, for a novel, different approach. Based on the work of Jacobsen *et al.* using cobalt salen complexes for the hydrolytic kinetic resolution of epoxides,[20,21] we envisioned that the same approach would hold for epoxide ring opening with alcohols. Indeed, Jacobsen *et al.* have described the use of phenols and simple alcohols for the kinetic resolution of terminal epoxides catalyzed by cobalt salen complexes,[22] though the use of these catalysts for the ring opening of epoxides with more complex alcohols has not been described until now.[23]

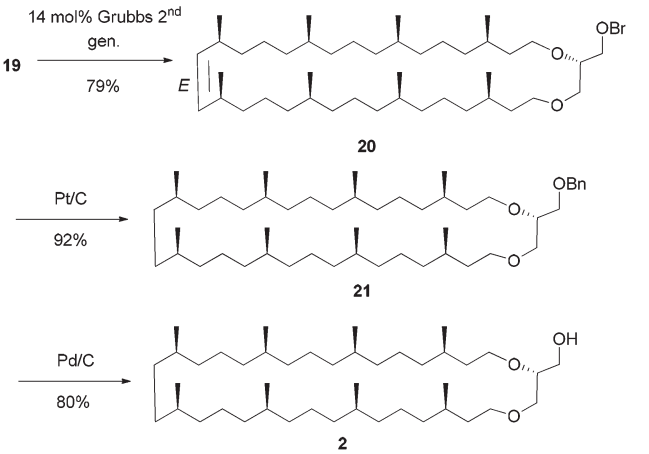
To make the most effective use of the precious **13**, we decided to carry out the ring opening on commercially available enantiopure benzyl glycidyl ether. When the reaction was carried out in the presence of catalytic [Co(salen)OAc], the most commonly used catalyst in the kinetic resolution of terminal epoxides, only starting materials were recovered together with varying amounts of benzyl glycerol, formed due to the presence of trace amounts of water. However, changing the counterion of the catalyst from acetate to tosylate[24] resulted in the formation of compound **14** in a rewarding 87% yield (Scheme 4). This reaction proceeds with complete regioselectivity and is carried out under solvent free conditions, representing a useful and alternative method for the regioselective epoxide ring opening with (complex) alcohols.

In order to connect the second equivalent of the phytanyl side chain, alcohol **13** was converted into iodide **15** using $MeSCH{=}NMe_2^+I^-$ in 89% yield (Scheme 4), following a recently developed procedure by Ellwood and Porter.[25] Not unexpectedly, alkylation of alcohol **14** with iodide **15** proved to




**Scheme 5** Synthesis of RCM precursor **19**.




**Scheme 6** Synthesis of cyclo-Archaeol **2**, the alkene in **20** has the *E*-configuration.

be a challenging reaction. After testing various reaction conditions, best results were obtained when a mixture of the starting materials was treated with freshly ground KOH and catalytic tetrabutylammonium bromide under solvent free conditions. This provided in a slow reaction the desired product **16** with moderate though reproducible yields varying from 35% to 55% (Scheme 5), comparable to the literature.[10]

Compound **16** contains the carbon skeleton of archaeol and cyclo-archaeol, and the final steps were devoted to the functionalization of **16** in order to carry out the ring-closing metathesis. For this, after deprotection of the silyl groups of **16**, diol **17** was oxidized with Dess–Martin periodinane giving aldehyde **18**, which was subjected to a Wittig reaction that afforded alkene **19** in an excellent 98% yield (Scheme 5).

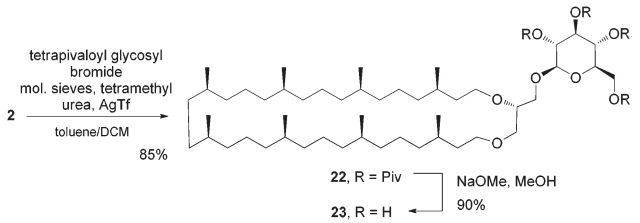
The ring closing metathesis of **19** was carried out using a second generation Grubbs catalyst. When this reaction was carried out in refluxing $CH_2Cl_2$ under dilution conditions, using a catalyst loading of 14%, compound **20** was obtained in 79% yield as a single alkene isomer (Scheme 6). The geometry of the double bond is *trans* (*E*), as deduced from $^1$H-NMR spectroscopy. The current protocol is somewhat more efficient than the one reported by Kakinuma *et al.* using a first generation Grubbs catalyst,[26] in the sense that the catalyst loading is halved, and **19** was obtained as a 7 : 1 *E*/*Z* mixture in the previous case.

Applying the same reduction protocol, with the flavin catalyst, as in the reduction of compound **12** (Scheme 3) for the reduction of **20**, a very low conversion was observed. Even with stoichiometric flavin, the reaction could not be brought to completion. This is remarkable as the actual reducing agent is the very small diimide and we have shown previously that also sterically hindered double bonds are reduced with this method and the method is even applicable in solid phase organic synthesis.[17] The best alternative in our hands turned out to be platinum on carbon, as Pt is known to be considerably less active in double bond isomerization compared to palladium. With atmospheric pressure of hydrogen, **21** was obtained in 92% yield, an additional argument that the double bond is not particularly sterically hindered. Finally, subsequent removal of the benzyl protecting group with Pd/C provided the final product **2** in 80% yield (Scheme 6).

The $^{13}$C-NMR of **2** prepared in this way corresponds to the $^{13}$C-NMR of natural **2**[12] and lacks the additional signals present in the spectrum reported by Kakinuma *et al.*[13] Most probably, the reduction of the double bond with Pd/C in that synthesis leads to a mixture of isomers (*e.g.* epimers) *via* partial isomerization of the double bond followed by reduction of the subsequently formed triple substituted alkene. This hypothesis was strengthened by an experiment in which a small amount of **20** was treated under the same conditions ($H_2$, Pd/C) and provided a $^{13}$C-NMR spectrum almost identical to the reported one by Kakinuma *et al*.

Synthetic **2** was used to confirm its presence in hydrothermal vents. The sample analysed was collected from the Rainbow hydrothermal vent field (RHF) located on the Mid-Atlantic Ridge. RHF has been characterized as an ultra-mafic hydrothermal system with fluids that are known to reach up to 360 °C and contain abundant $H_2$, $CH_4$ and $CO_2$.[27] Samples were collected during a sampling campaign in 2008 using the ROV Jason. The sample is composed of material from the interior of a vent chimney collected at a depth of 2293 meters below the sea level. Analysis by GC showed that synthetic **2** and natural **2** co-eluted (see ESI†). Furthermore, their mass spectra were identical (Scheme 7).

In order to determine whether also the presence of β-glucosyl-**23** could be confirmed in the hydrothermal vents, this compound was prepared from **2**. Glycosylation of archaeal ether lipids has been studied before,[28] and **1** has been glycosylated with gentiobiose.[29] In order to assure stereoselective glycosylation, a per-esterified glucosyl bromide was selected as the donor in a Koenigs–Knorr glycosylation. As tetra-acetylglucosyl bromide gave disappointing yields due to *ortho*-ester formation, tetrapivaloyl glucosyl bromide was applied, together




**Scheme 7** Glycosylation of cyclo-Archaeol **2**.

with molsieves to catch adventitious water, tetramethyl urea, and silver triflate as the activator.[30] This led to the desired product **22** in a rewarding 85% isolated yield. Final deprotection by methanolysis gave **23** in excellent yield. The NMR spectral data of **23** are in very good agreement with literature data.[12] Synthetic **23** was used to confirm the presence of **23** in sediment collected from the Rainbow hydrothermal vent field. Analysis by HPLC/ESI/$MS^n$ showed that synthetic **23** and natural **23** co-eluted with a retention time of around 10.2 min and yielded identical mass spectra on both $MS^1$ as well as $MS^2$ (see ESI†).

## Conclusions

An efficient synthesis of cyclo-archaeol has been developed. Key steps are the quadruple use of an isoprenoid building block, in turn prepared by copper-catalyzed asymmetric addition of dimethylzinc, organocatalytic carbon–carbon double bond reduction, and application of the Jacobsen catalyst for the regioselective ring opening of benzyl-protected glycidol. This synthesis is considerably more efficient than the previously reported route. It was discovered that the earlier reported double bond reduction with $H_2$ and Pd/C in the final stages of the synthesis leads to significant epimerization of the methyl-substituents. This could be avoided by the use of Pt/C instead. Synthetic cyclo-archaeol **2** was used to confirm its presence in samples taken from hydrothermal vents. Furthermore, β-glucosyl-cyclo-archaeol **23** was prepared for the first time and shown to occur in hydrothermal vents.

## Experimental

All reactions were performed using oven or flame-dried glassware and dry solvents. Solvents were distilled prior to use: $Et_2O$ and THF (Na/benzophenone), DCM ($CaH_2$). All other reagents were purchased from Sigma Aldrich, Acros, TCI Europe, Alfa Aesar, Chempur or Fluorochem, and used without further purification unless noted otherwise.

$^1$H- and $^{13}$C-NMR spectra were recorded on a Varian AMX400 or a Varian 400-MR (400, 100.59 MHz, respectively). Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: $\delta$ 7.26 for $^1$H, $\delta$ 77.0 for $^{13}$C). Data are reported as follows: chemical shifts ($\delta$), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants $J$ (Hz), and integration.

High resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL or on an AEI-MS-902 spectrometer. HPLC analysis was performed on an Alltima HP Silica 3 μ 100 mm × 2.1 mm column (Grace Davison Discovery Sciences) with an ELS detector (ELSD).

Flash chromatography was performed using SiliCycle silica gel type SiliaFlash P60 (230–400 mesh) as obtained from Screening Devices or with automated column chromatography using a Reveleris flash system purchased from Grace Davison Discovery Sciences. TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), $H_2O$ (500 mL) and $H_2SO_4$ (25 mL)) or a $KMnO_4$ stain ($K_2CO_3$ (40 g), $KMnO_4$ (6 g), $H_2O$ (600 mL) and 10% NaOH (5 mL)).

**4**.[31] Cyclooctanone (10 g, 79 mmol) was dissolved in DMSO (1.2 L) and IBX (89 g, 317 mmol) was added. The resulting solution was heated to 70 °C and stirred for 48 h. The solution was poured into an Erlenmeyer containing a saturated solution of $NaHCO_3$ upon which iodosobenzoic acid precipitated. The precipitate was filtered and washed with diethyl ether. The water–DMSO solution was extracted with diethyl ether and the collected organic layers were dried with $MgSO_4$. The crude product was purified by silica gel chromatography (pentane–ether 4 : 1) to give **4** (6.70 g, 69% yield) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.41–6.31 (m, 4H), 2.42–2.36 (m, 4H), 1.77 (dt, $J$ = 15.2, 6.7 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 193.8 (CO), 141.9 (2CH), 136.2 (2CH), 27.4 ($CH_2$), 25.2 ($2CH_2$) ppm.

**5**.[15] Copper(II) triflate (931 mg, 2.6 mmol) and **L-phos** (*R*,*S*, *S*) (2.78 g, 5.1 mmol) were suspended in dry toluene (150 mL) and stirred at room temperature for 30 min under nitrogen. The resulting solution was cooled to −25 °C and dimethylzinc (129 mL, 154 mmol) was added slowly. After stirring for 5 min, **4** (6.29 g, 51.5 mmol) dissolved in 150 mL of toluene was added *via* an addition funnel over 6 h. The reaction mixture was stirred overnight at −25 °C and then poured into a bath containing an aq. solution of saturated $NH_4Cl$ and ice. The mixture was extracted with ether and dried over $MgSO_4$. The crude was purified by silica gel chromatography (pentane–ether 95 : 5) to give **5** (5.70 g, 80% yield, ee > 99%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.33 (dt, $J$ = 12.4, 7.3 Hz, 1H), 6.03 (d, $J$ = 12.4 Hz, 1H), 2.68 (dd, $J$ = 13.9, 5.7 Hz, 1H), 2.61–2.40 (m, 3H), 2.11 (dd, $J$ = 10.5, 4.5 Hz, 1H), 1.73–1.53 (m, 3H), 1.39–1.28 (m, 1H), 1.00 (d, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 204.8 (CO), 141.8 (CH), 133.6 (CH), 50.3 ($CH_2$), 32.3 ($CH_2$), 29.1 (CH), 28.3 ($CH_2$), 22.1 ($CH_3$), 21.8 ($CH_2$) ppm. HRMS-ESI $m/z$ calcd for $C_9H_{15}O$: 139.1117; found: 139.112 [$M^+$ + H]. $[\alpha]_D^{20}$ = +23.3 ($c$ = 0.8, $CHCl_3$). Ee determination: GC Chiraldex B-TA, 30 m × 0.25 mm, $N_2$ flow = 0.5 mL $min^{-1}$, $T_i$ = 50 °C, $T_f$ = 210 °C, rate 10 °C $min^{-1}$, rt 16.69 (*S*), 16.76 (*R*).

**3**.[15] Copper(II) triflate (393 mg, 1.1 mmol) and **L-phos** (*S*,*R*,*R*) (1.17 g, 2.2 mmol) were dissolved in dichloromethane



(136 mL) and the mixture was stirred at room temperature for 30 min under nitrogen. Subsequently, the solution was cooled to −25 °C and dimethylzinc (54 mL, 65 mmol) was added dropwise. After stirring for 5 min, **5** (6.00 g, 43.4 mmol) dissolved in 136 mL of dichloromethane was added *via* an addition funnel dropwise for several hours. The resulting solution was stirred at −25 °C overnight, after which triethylamine (18 mL, 130 mmol), chlorotrimethylsilane (27 mL, 217 mmol) and HMPA (38 mL, 217 mmol) were added. The resulting mixture was stirred for 2 h while slowly warming to rt. The reaction mixture was quenched with water and extracted with $Et_2O$. After removal of the majority of the solvent, the crude was passed through a silica gel column previously deactivated with $Et_3N$ (pentane–ether 2 : 1) and the solvent was evaporated giving **6** as a yellow oil which was used in the next step without further purification. **6** (9.74 g, 43.4 mmol) was dissolved in methanol (36 mL) and $CH_2Cl_2$ (36 mL), and ozone was bubbled through the solution at −78 °C until the solution colored green/blue. The solution was then purged with nitrogen, after which $NaBH_4$ (16.3 g, 430 mmol) was added portionwise and the reaction mixture was allowed to slowly warm to rt. After stirring overnight, the reaction mixture was quenched with 2 M aq. HCl, stirred for 2 h and then extracted with dichloromethane. (3*R*,7*S*)-8-Hydroxy-3,7-dimethyloctanoic acid was obtained as a colorless oil and used in the next step without further purification. To a solution of (3*R*,7*S*)-8-hydroxy-3,7-dimethyloctanoic acid (8.1 g, 43.4 mmol) in MeOH (80 mL) was added *p*-toluenesulfonic acid (370 mg, 2.1 mmol). The reaction was refluxed for 24 h. Subsequently, it was cooled to rt and concentrated, after which aq. $NaHCO_3$ was added and the product was extracted with ether. The crude was purified by silica gel chromatography (pentane–$Et_2O$ 4 : 1) to give **3** (5.1 g, 25.3 mmol, 59% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.66 (s, 3H), 3.55–3.46 (m, 1H), 3.45–3.37 (m, 1H), 2.30 (dd, $J$ = 14.7, 6.1 Hz, 1H), 2.11 (dd, $J$ = 14.7, 8.1 Hz, 1H), 1.95 (dq, $J$ = 13.2, 6.7 Hz, 1H), 1.64–1.57 (m, 2H), 1.44–1.02 (m, 6H), 0.92 (t, $J$ = 7.1 Hz, 6H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.8 (CO), 68.2 ($CH_2$), 51.3 ($CH_3$), 41.6 ($CH_2$), 36.9 ($CH_2$), 35.7 (CH), 33.2 ($CH_2$), 30.3 (CH), 24.2 ($CH_2$), 19.8 ($CH_3$), 16.5 ($CH_3$) ppm. HRMS-ESI $m/z$ calcd for $C_{11}H_{23}O_3$: 203.1641; found: 203.1638 [$M^+$ + H]. $[\alpha]_D^{20}$ = −3.3 ($c$ = 1.2, $CHCl_3$).

**7**.[32] **3** (4.0 g, 19.7 mmol) was dissolved in DMF (33 mL) and 1*H*-imidazole (2.7 g, 39.5 mmol) and *tert*-butylchlorodiphenylsilane (7.7 mL, 30 mmol) were added. The resulting solution was stirred for 16 h at rt, after which TLC showed complete conversion. The solution was diluted with water and extracted with ether. The mixture was purified by silica gel chromatography (5% ether in pentane) to give **7** (7.7 g, 17.5 mmol, 88% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81–7.57 (m, 4H), 7.44–7.35 (m, 6H), 3.66 (s, 3H), 3.50 (dd, $J$ = 9.8, 5.7 Hz, 1H), 3.43 (dd, $J$ = 9.8, 6.3 Hz, 1H), 2.29 (dd, $J$ = 14.7, 5.9 Hz, 1H), 2.09 (dd, $J$ = 14.7, 8.2 Hz, 1H), 1.93 (dt, $J$ = 13.4, 6.8 Hz, 1H), 1.63 (dt, $J$ = 12.7, 6.5, 1H), 1.45–1.10 (m, 6H), 1.05 (s, 9H), 0.91 (d, $J$ = 6.7 Hz, 6H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.7 (CO), 135.6 (4CH), 134.1 (2C), 129.4 (2CH), 127.5 (4CH), 68.8 ($CH_2$), 51.3 ($CH_3$), 41.6 ($CH_2$), 37.0 ($CH_2$), 35.6 (CH), 33.2 ($CH_2$), 30.3 (CH), 26.9 ($3CH_3$), 24.2 ($CH_2$), 19.7 ($CH_3$), 19.3 (C), 16.9 ($CH_3$) ppm. HRMS-ESI $m/z$ calcd for $C_{27}H_{41}O3Si$: 441.2819; found: 441.2974 [$M^+$ + H]. $[\alpha]_D^{20}$ = +3.9 ($c$ = 1.06, $CHCl_3$).

**8**.[32] To a solution of **7** (7.4 g, 16.7 mmol) in THF (85 mL) at −78 °C was added a solution of DIBAL (1 M in dichloromethane, 83 mL, 83.0 mmol) and the resulting mixture was stirred for 2 h at this temperature. The reaction mixture was quenched with aq. $NH_4Cl$ and then diluted with $Et_2O$ and aq. 2 M HCl until a clear solution was obtained. The product was extracted with $Et_2O$, dried over $Na_2SO_4$ and the solvent evaporated giving **8** (6.7 g, 16.4 mmol, 98% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 (dd, $J$ = 7.8, 1.6 Hz, 4H), 7.43–7.33 (m, 6H), 3.72–3.59 (m, 2H), 3.50 (dd, $J$ = 9.8, 5.7 Hz, 1H), 3.43 (dd, $J$ = 9.8, 6.4 Hz, 1H), 1.69–1.48 (m, 3H), 1.44–1.12 (m, 7H), 1.04 (s, 9H), 0.90 (d, $J$ = 6.7 Hz, 3H), 0.86 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 135.6 (4CH), 134.1 (2C), 129.4 (2CH), 127.5 (4CH), 68.9 ($CH_2$), 61.2 ($CH_2$), 39.9 ($CH_2$), 37.4 ($CH_2$), 35.7 (CH), 33.4 ($CH_2$), 29.5 (CH), 26.9 ($3CH_3$), 24.3 ($CH_2$), 19.7 ($CH_3$), 19.3 (C), 16.9 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{26}H_{40}O_2SiNa$: 435.269; found: 435.269 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +1.3 ($c$ = 0.92, $CHCl_3$).

**9**.[32] To a solution of **8** (6.8 g, 16.5 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (5.9 g, 33 mmol) in THF (165 mL) was added triphenylphosphine (6.5 g, 24.7 mmol) at 0 °C. Subsequently, DIAD (5.8 mL, 30 mmol) was added dropwise and the solution was stirred while warming up to rt overnight. Then the reaction mixture was quenched with brine, extracted with $Et_2O$ and the organic phase dried over $Na_2SO_4$. After evaporation of the solvent, the mixture was purified by silica gel chromatography (5% ether in pentane) to give 5-(((3*R*,7*S*)-8-((*tert*-butyldiphenylsilyl)-oxy)-3,7-dimethyloctyl)thio)-1-phenyl-1*H*-tetrazole (8.3 g, 14.6 mmol, 88% yield) as a colorless oil. This compound (8.1 g, 14.2 mmol) was dissolved in 80 mL of dichloromethane and *m*CPBA (12.3 g, 71.1 mmol) was added at 0 °C. The solution was allowed to warm up slowly to rt and stirred overnight. Subsequently, the reaction mixture was treated several times with aq. $Na_2S_2O_3$ and the combined aqueous phases were extracted with dichloromethane. The combined organic layers were washed with aq. $NaHCO_3$, brine, dried over $Na_2SO_4$ and the solvent was evaporated giving **9** (8.4 g, 14.2 mmol, 98% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71–7.63 (m, 6H), 7.62–7.55 (m, 3H), 7.44–7.33 (m, 6H), 3.79–3.63 (m, 2H), 3.50 (dd, $J$ = 9.8, 5.8 Hz, 1H), 3.44 (dd, $J$ = 9.8, 6.2 Hz, 1H), 1.94 (ddd, $J$ = 22.0, 11.0, 5.4 Hz, 1H), 1.75 (tdd, $J$ = 13.1, 7.7, 5.3 Hz, 1H), 1.62 (tt, $J$ = 11.5, 5.9 Hz, 2H), 1.47–1.08 (m, 6H), 1.05 (s, 9H), 0.93 (d, $J$ = 6.7 Hz, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 153.7 (C), 135.8 (4CH), 134.3 (2C), 133.3 (C), 131.6 (CH), 129.9 (2CH), 129.7 (2CH), 127.8 (4CH), 125.3 (2CH), 69.0 ($CH_2$), 54.5 ($CH_2$), 36.8 ($CH_2$), 35.8 (CH), 33.4 ($CH_2$), 32.1 (CH), 28.6 ($CH_2$), 27.1 ($3CH_3$), 24.3 ($CH_2$), 19.5 (C), 19.3 ($CH_3$), 17.1 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{33}H_{44}N_4O_3SSiNa$: 627.2795; found: 627.2794 [$M^+$ + Na]. $[\alpha]_D^{20}$ = −3.13 ($c$ = 1.0, $CHCl_3$).

**10**. **3** (3.0 g, 14.8 mmol) was dissolved in 148 mL of dichloromethane and NMO (2.6 g, 22.2 mmol) and TPAP (26.1 mg, 0.74 mmol) were added. The resulting black solution was stirred overnight. Then the solvent was evaporated and the crude reaction mixture was passed through a silica gel column using a mixture of pentane–ether 2 : 1. The solvent was evaporated and **10** (2.1 g, 10.5 mmol, 70% yield) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.59 (d, $J$ = 2.0 Hz, 1H), 3.64 (s, 3H), 2.35–2.22 (m, 2H), 2.11 (dd, $J$ = 14.8, 7.9 Hz, 1H), 1.99–1.88 (m, 1H), 1.72–1.62 (m, 1H), 1.41–1.15 (m, 5H), 1.07 (d, $J$ = 7.0 Hz, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 205.2 (CHO), 173.7 (CO), 51.5 ($CH_3$), 46.4 (CH), 41.7 ($CH_2$), 36.7 ($CH_2$), 30.7 ($CH_2$), 30.3 (CH), 24.4 ($CH_2$), 19.8 ($CH_3$), 13.5 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{11}H_{21}O_3$: 201.149; found: 201.148 [$M^+$ + H]. $[\alpha]_D^{20}$ = +21.25 ($c$ = 1.6, $CHCl_3$).

**11**. LiHMDS (1 M in THF, 9.9 mL, 9.9 mmol) was added dropwise to a solution of **9** (6.0 g, 9.9 mmol) in THF (25 mL) at −78 °C resulting in a yellow solution. The mixture was stirred for 30 min, and subsequently **10** (2.2 g, 10.9 mmol) dissolved in 25 mL of THF was added *via* a cannula and the resulting solution was stirred overnight while slowly warming to rt. The reaction mixture was quenched with water and extracted with ether. The crude was purified by silica gel chromatography using 2% $Et_2O$ in pentane. **11** (4.8 g, 8.3 mmol, 84% yield as a 2 : 1 mixture of $Z$ and $E$ alkenes) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (dd, $J$ = 7.8, 1.6 Hz, 4H), 7.46–7.34 (m, 6H), 5.37–5.10 (m, 2H), 3.66 (s, 3H), 3.52 (dd, $J$ = 9.8, 5.7 Hz, 1H), 3.44 (dd, $J$ = 9.8, 6.4 Hz, 1H), 2.30 (dd, $J$ = 14.7, 6.0 Hz, 1H), 2.10 (dd, $J$ = 14.7, 8.1 Hz, 1H), 2.07–1.89 (m, 3H), 1.88–1.75 (m, 1H), 1.69–1.61 (m, 1H), 1.48–1.13 (m, 13H), 1.06 (s, 9H), 0.97–0.90 (m, 9H), 0.86 (d, $J$ = 6.6 Hz, 3H, $E$ alkene), 0.83 (d, $J$ = 6.6 Hz, 3H, $Z$ alkene). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.7 (CO), 137.5 (CH, $E$ alkene), 136.9 (CH, $Z$ alkene), 135.6 (CH), 134.1 (C), 129.4 (CH), 127.5 (CH), 127.1 (CH, $Z$ alkene), 127.0 (CH, $E$ alkene), 68.9 ($CH_2$), 51.3 ($CH_3$), 41.7 ($CH_2$), 39.9 ($CH_2$), 37.6 ($CH_2$, $Z$ alkene), 37.2 ($CH_2$, $E$ alkene), 36.9 ($CH_2$, $Z$ alkene), 36.9 ($CH_2$, $E$ alkene), 36.8 ($CH_2$), 36.7 ($CH_2$), 35.7 (CH), 34.8 ($CH_2$, $Z$ alkene), 33.4 ($CH_2$, $E$ alkene), 33.2 (CH), 31.6 (CH), 30.3 (CH), 26.9 ($CH_3$), 24.8 ($CH_2$, $Z$ alkene), 24.6 ($CH_2$, $E$ alkene), 24.5 ($CH_2$, $Z$ alkene), 24.4 ($CH_2$, $E$ alkene), 21.3 ($CH_3$, $Z$ alkene), 21.1 ($CH_3$, $E$ alkene), 19.7 ($CH_3$), 19.5 ($CH_3$), 19.3 (C), 16.9 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{37}H_{58}O_3SiNa$: 601.405; found: 601.405 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +2.1 ($c$ = 1.1, $CHCl_3$).

**12**. To a solution of **11** (4.8 g, 8.3 mmol) in 42 mL of THF at −78 °C was added a solution of DIBAL (1 M in dichloromethane, 42 mL, 42 mmol) and the resulting mixture was stirred for 2 h at this temperature. The reaction mixture was quenched with aq. $NH_4Cl$ and then diluted with $Et_2O$ and aq. HCl until a clear solution was obtained. The mixture was extracted with $Et_2O$, dried over $Na_2SO_4$ and the solvent evaporated. **12** (4.5 g, 8.2 mmol, 99% yield as a 2 : 1 mixture of $Z$ and $E$ alkenes) was obtained as a colorless oil without any further purification. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (dd, $J$ = 7.7, 1.5 Hz, 4H), 7.45–7.35 (m, 6H), 5.45–5.11 (m, 2H), 3.67 (br s, 2H), 3.51 (dd, $J$ = 9.8, 5.7 Hz, 1H), 3.44 (dd, $J$ = 9.7, 6.5 Hz, 1H), 2.63 (br s, 1H), 2.40 (br s, 1H), 2.33–1.94 (m, 2H), 1.88–1.75 (m, 1H), 1.67–1.52 (m, 3H), 1.46–1.11 (m, 14H), 1.06 (s, 9H), 0.98–0.86 (m, 9H), 0.83 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 137.5, 136.9, 135.5, 134.0, 132.7, 129.3, 127.4, 126.8, 68.8, 61.1, 47.0, 39.9, 39.9, 37.7, 37.2–36.4, 35.6, 34.7, 33.4, 33.3, 33.1, 31.6, 30.3, 29.4, 29.3, 26.8, 24.7–24.1, 21.3, 21.0, 20.2, 19.5, 19.5, 19.4, 19.2, 18.7, 16.9. HRMS-ESI $m/z$ calcd for $C_{36}H_{58}O_2SiNa$: 573.410; found: 573.410 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +2.12 ($c$ = 0.9, $CHCl_3$).

**13**. **12** (2.6 g, 4.7 mmol) was dissolved in 23 mL of EtOH at rt and stirred vigorously. An atmosphere of oxygen was applied (balloon, 1 atm) and, *via* a syringe pump, a solution of **L-flav** (3.2 g, 7.0 mmol) in EtOH (15 mL) was added slowly together with, *via* a second syringe, hydrazine hydrate (2.9 mL, 94 mmol) over a period of 10 h. The reaction mixture was stirred at rt for another 2 h and progress of the reaction was followed by $^1$H NMR (samples were washed with water and extracted with $CH_2Cl_2$). $CH_2Cl_2$ was added, and subsequently the mixture was washed with water. After drying with $Na_2SO_4$, the solvent was evaporated to yield the crude product which was purified by column chromatography (pentane–$Et_2O$ 5 : 1) to give **13** (2.2 g, 3.9 mmol, 83% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (dd, $J$ = 7.8, 1.6 Hz, 4H), 7.45–7.34 (m, 6H), 3.74–3.62 (m, 2H), 3.52 (dd, $J$ = 9.8, 5.7 Hz, 1H), 3.44 (dd, $J$ = 9.8, 6.4 Hz, 1H), 1.70–1.51 (m, 3H), 1.45–1.12 (m, 18H), 1.10–1.02 (m, 3H), 1.06 (s, 9H), 0.93 (d, $J$ = 6.7 Hz, 3H), 0.90 (d, $J$ = 6.6 Hz, 3H), 0.85 (d, $J$ = 6.6 Hz, 3H), 0.84 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 135.6 (4CH), 134.1 (2C), 129.4 (2CH), 127.5 (4CH), 68.9 ($CH_2$), 61.2 ($CH_2$), 40.0 ($CH_2$), 37.5 ($CH_2$), 37.4 ($2CH_2$), 37.3 ($CH_2$), 37.3 ($CH_2$), 35.7 (CH), 33.5 ($CH_2$), 32.8 (CH), 32.8 (CH), 29.5 (CH), 26.9 ($3CH_3$), 24.5 ($CH_2$), 24.4 ($CH_2$), 24.4 ($CH_2$), 19.8 ($CH_3$), 19.75 ($CH_3$), 19.7 ($CH_3$), 19.3 (C), 17.0 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{36}H_{60}O_2SiNa$: 575.425; found: 575.425 [$M^+$ + Na]. $[\alpha]_D^{20}$ = −0.70 ($c$ = 1.0, $CHCl_3$).

**14**. To a round bottom flask containing **13** (488 mg, 0.88 mmol) without any solvent was added (*S*)-2-((benzyloxy)-methyl)oxirane (0.25 mL, 1.63 mmol) and [Co(salen)OTs] (35 mg, 0.04 mmol). An atmosphere of dry oxygen was applied (balloon, 1 atm). The mixture was left to stir for 16 h and then purified by silica gel chromatography (hexane–$Et_2O$ 4 : 1). **14** (533 mg, 0.80 mmol, 85% yield) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.65 (m, 4H), 7.45–7.27 (m, 11H), 4.57 (s, 2H), 3.98 (br s, 1H), 3.59–3.40 (m, 8H), 2.47 (br d, $J$ = 3.1 Hz, 1H), 1.70–1.47 (m, 4H), 1.46–1.14 (m, 20H), 1.06 (s, 9H), 0.92 (d, $J$ = 6.7 Hz, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H), 0.85 (d, $J$ = 5.9 Hz, 3H), 0.83 (d, $J$ = 6.0 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 138.0 (C), 135.6 (CH), 134.1 (C), 129.4 (CH), 128.4 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 73.4 ($CH_2$), 71.8 ($CH_2$), 71.4 ($CH_2$), 70.0 ($CH_2$), 69.5 (CH), 68.9 ($CH_2$), 37.5 ($CH_2$), 37.4 ($CH_2$), 37.4 ($CH_2$), 36.6 ($CH_2$), 35.7 (CH), 33.5 ($CH_2$), 32.8 (CH), 32.8 (CH), 29.9 (CH), 26.9 ($CH_3$), 24.5 ($CH_2$), 24.4 ($CH_2$), 24.4 ($CH_2$), 19.8 ($CH_3$), 19.7 ($CH_3$), 19.3 (C), 17.0 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{46}H_{72}O_4SiNa$: 739.509; found: 739.509 [$M^+$ + Na]. $[\alpha]_D^{20}$ = −0.3 ($c$ = 1.2, $CHCl_3$).

**15**. To a solution of **13** (498 mg, 0.90 mmol) in toluene (5 mL) at 85 °C was added *N*,*N*-dimethyl-*N*-(methylsulfanylmethylene)ammonium iodide (313 mg, 1.35 mmol) and imidazole (30 mg, 0.45 mmol). The mixture was stirred at 85 °C for 16 h and subsequently cooled to rt and the solvent evaporated. The crude mixture was purified by silica gel chromatography using 2% of $Et_2O$ in pentane to give **15** (500 mg, 0.75 mmol, 85% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68–7.63 (m, 4H), 7.43–7.33 (m, 6H), 3.50 (dd, $J$ = 9.8, 5.7 Hz, 1H), 3.42 (dd, $J$ = 9.8, 6.4 Hz, 1H), 3.27–3.20 (m, 1H), 3.15 (ddd, $J$ = 9.5, 8.2, 7.3 Hz, 1H), 1.93–1.80 (m, 1H), 1.69–1.57 (m, 2H), 1.57–1.48 (m, 1H), 1.46–1.02 (m, 20H), 1.04 (s, 9H), 0.91 (d, $J$ = 6.7 Hz, 3H), 0.86 (d, $J$ = 6.6 Hz, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H), 0.83 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 135.6 (CH), 134.1 (C), 129.4 (CH), 127.5 (CH), 68.9 ($CH_2$), 40.9 ($CH_2$), 37.4 ($CH_2$), 37.3 ($CH_2$), 37.2 ($CH_2$), 36.6 ($CH_2$), 35.7 (CH), 33.9 (CH), 33.5 ($CH_2$), 32.8 (CH), 26.9 ($CH_3$), 24.5 ($CH_2$), 24.4 ($CH_2$), 24.2 ($CH_2$), 19.8 ($CH_3$), 19.3 (C), 18.8 ($CH_3$), 17.0 ($CH_3$), 5.4 ($CH_2$). HRMS-ESI $m/z$ calcd for $C_{36}H_{60}OISi$: 663.345; found: 663.346 [$M^+$ + H]. $[\alpha]_D^{20}$ = −6.32 ($c$ = 1.1, $CHCl_3$).

**16**. To a mixture of **14** (275 mg, 0.38 mmol), **15** (280 mg, 0.42 mmol) and tetra-*n*-butylammonium bromide (71 mg, 0.19 mmol) was added freshly ground potassium hydroxide (65 mg, 1.15 mmol). The reaction mixture was stirred for 48 h at 42 °C. Then it was quenched with water, extracted with $Et_2O$ and the residue purified by silica gel chromatography using 2% of $Et_2O$ in pentane to give **16** (263 mg, 0.21 mmol, 55% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 (dd, $J$ = 7.8, 1.6 Hz, 8H), 7.43–7.28 (m, 16H), 4.54 (s, 2H), 3.65–3.38 (m, 13H), 1.68–1.01 (m, 48H), 1.04 (s, 9H), 0.90 (d, $J$ = 6.7 Hz, 6H), 0.85 (d, $J$ = 6.6 Hz, 6H), 0.83 (d, $J$ = 4.8 Hz, 6H), 0.81 (d, $J$ = 4.8 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 138.4 (C), 135.6 (CH), 134.1 (C), 129.4 (CH), 128.3 (CH), 127.5 (CH), 127.5 (CH), 127.5 (CH), 77.9 (CH), 73.3 ($CH_2$), 70.8 ($CH_2$), 70.3 ($CH_2$), 70.0 ($CH_2$), 68.9 ($CH_2$), 68.9 ($CH_2$), 37.5–37.4 ($CH_2$), 37.1 ($CH_2$), 36.6 ($CH_2$), 35.7 (CH), 33.5 ($CH_2$), 32.8 (CH), 32.8 (CH), 29.9 (CH), 29.8 (CH), 26.9 ($CH_3$), 24.5 ($CH_2$), 24.4 ($CH_2$), 19.8–19.7($CH_3$), 19.3 (C), 17.0 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{82}H_{130}O_5Si_2Na$: 1273.935; found: 1273.938 [$M^+$ + Na]. $[\alpha]_D^{20}$ = −0.83 ($c$ = 0.9, $CHCl_3$).

**17**.[13] TBAF (1.0 M in THF, 0.96 mL, 0.96 mmol) was added to a solution of **16** (300 mg, 0.24 mmol) in 1.5 mL of THF and the solution was stirred overnight at rt. Subsequently, the reaction mixture was quenched with aq. $NH_4Cl$ and extracted with $Et_2O$. The residue was purified by silica gel chromatography (pentane–$Et_2O$ 2 : 1) to give **17** (172 mg, 0.22 mmol, 92% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35–7.26 (m, 5H), 4.55 (s, 2H), 3.67–3.36 (m, 13H), 1.69–0.98 (m, 48H), 0.92 (d, $J$ = 6.7 Hz, 6H), 0.86 (d, $J$ = 6.5 Hz, 6H), 0.84 (d, $J$ = 3.2 Hz, 6H), 0.83 (d, $J$ = 3.2 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 138.4 (C), 128.28 (CH), 127.6 (CH), 127.5 (CH), 77.9 (CH), 73.3 ($CH_2$), 70.8 ($CH_2$), 70.3 ($CH_2$), 69.9 ($CH_2$), 68.9 ($CH_2$), 68.4 ($CH_2$), 37.5–37.3 ($CH_2$), 37.1 ($CH_2$), 36.6 ($CH_2$), 35.8 (CH), 33.5 ($CH_2$), 32.8 (CH), 32.7 (CH), 29.9 (CH), 29.8 (CH), 24.4 ($CH_2$), 24.4 ($CH_2$), 24.4 ($CH_2$), 19.8–19.7($CH_3$), 16.6 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{50}H_{94}O_5Na$: 797.699; found: 797.698 [$M^+$ + Na]. $[\alpha]_D^{20}$ = −3.34 ($c$ = 0.9, $CHCl_3$).

**18**.[26] To a solution of **17** (170 mg, 0.22 mmol) in $CH_2Cl_2$ (2.5 mL) was added Dess–Martin periodinane (15 wt% in dichloromethane, 1.2 mL, 0.56 mmol). The reaction mixture was stirred at room temperature for 1 h and then saturated aqueous $Na_2S_2O_3$ was slowly added. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine. After evaporation of the solvent, the residue was purified by silica gel chromatography (pentane–$Et_2O$ 10 : 1) to give **18** (131 mg, 0.17 mmol, 76% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.61 (d, $J$ = 2.0 Hz, 2H), 7.36–7.26 (m, 5H), 4.55 (s, 2H), 3.68–3.39 (m, 9H), 2.34 (qd, $J$ = 6.8, 2.0 Hz, 2H), 1.77–1.45 (m, 7H), 1.45–0.99 (m, 39H), 1.09 (d, $J$ = 7.0 Hz, 6H), 0.88–0.82 (m, 18H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 205.3, 138.4, 128.3, 127.5, 127.5, 77.94, 73.3, 70.9, 70.3, 69.9, 68.9, 46.3, 37.52, 37.4, 37.3, 37.1, 37.0, 36.6, 32.8, 32.6, 30.9, 29.9, 29.8, 24.4, 24.4, 24.4, 19.7, 19.6, 13.3. HRMS-ESI $m/z$ calcd for $C_{50}H_{90}O_5Na$: 793.668; found: 793.667 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +12.8 ($c$ = 1.3, $CHCl_3$).

**19**.[26] To a solution of methyltriphenyl-phosphonium bromide (271 mg, 0.76 mmol) in 4 mL of THF was added KHMDS (0.5 M in toluene, 1.4 mL, 0.71 mmol) under an atmosphere of nitrogen at rt and stirred for 1 h. Then a solution of **18** (130 mg, 0.17 mmol) in 4 mL of THF was added and the reaction mixture was stirred at room temperature for 1 h. Subsequently, the reaction mixture was quenched with an aqueous solution of $NH_4Cl$ and extracted with $Et_2O$. The residue was purified by silica gel chromatography (pentane–$Et_2O$ 95 : 5) and **19** (114 mg, 0.15 mmol, 87% yield) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36–7.26 (m, 5H), 5.69 (ddd, $J$ = 17.6, 10.3, 7.5 Hz, 2H), 4.98–4.92 (m, 2H), 4.90 (d, $J$ = 10.3 Hz, 2H), 4.55 (s, 2H), 3.66–3.42 (m, 9H), 2.14–2.07 (m, 2H), 1.67–1.46 (m, 4H), 1.42–1.01 (m, 42H), 0.98 (d, $J$ = 6.7 Hz, 6H), 0.86 (d, $J$ = 6.6, 6H), 0.84 (d, $J$ = 6.5 Hz, 12H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 145.0 (CH), 138.4 (C), 128.3 (CH), 127.5 (CH), 127.5 (CH), 112.2 ($CH_2$), 77.9 (CH), 73.3 ($CH_2$), 70.8 ($CH_2$), 70.3 ($CH_2$), 69.9 ($CH_2$), 68.9 ($CH_2$), 37.7 (CH), 37.5 ($CH_2$), 37.5 ($CH_2$), 37.4 ($CH_2$), 37.1 ($CH_2$), 37.0 ($CH_2$), 36.6 ($CH_2$), 32.8 (CH), 32.7 (CH), 29.9 (CH), 29.8 (CH), 24.6 ($CH_2$), 24.5 ($CH_2$), 24.4 ($CH_2$), 20.2 ($CH_3$), 19.8 ($CH_3$), 19.7 ($CH_3$), 19.7 ($CH_3$). HRMS-ESI $m/z$ calcd for $C_{52}H_{94}O_3Na$: 789.710; found: 789.710 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +7.02 ($c$ = 1.0, $CHCl_3$).

**20**.[26] To a solution of **19** (50 mg, 0.07 mmol) in 32 mL of $CH_2Cl_2$ was added a 2nd generation Grubbs catalyst (5.4 mg, 0.01 mmol) and the mixture was refluxed for 48 h. Subsequently the solvent was evaporated and the residue purified by silica gel chromatography with 7% of $Et_2O$ in pentane to give **20** (40 mg, 0.05 mmol, 78% yield as a single isomer) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38–7.27 (m, 5H), 5.11 (dd, $J$ = 5.1, 2.5 Hz, 2H), 4.55 (s, 2H), 3.67–3.44 (m, 9H), 2.01 (br s, 2H), 1.64–1.53 (m, 4H), 1.43–0.98 (m, 42H), 0.94 (d, $J$ = 6.7 Hz, 6H), 0.87 (d, $J$ = 6.5 Hz, 6H), 0.84 (d, $J$ = 6.5 Hz, 6H), 0.83 (d, $J$ = 6.5 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$, due to overlapping signals the reported number of signals does not

correspond to the expected number) $\delta$ 138.4 (C), 134.9 (CH), 128.3 (CH), 127.5 (CH), 127.5 (CH), 77.9 (CH), 73.3 ($CH_2$), 71.4 ($CH_2$), 70.3 ($CH_2$), 69.7 ($CH_2$), 68.6 ($CH_2$), 37.8 ($CH_2$), 37.5–37.2 ($CH_2$), 37.0 ($CH_2$), 36.6 ($CH_2$), 32.8 (CH), 32.8 (CH), 29.7 (CH), 29.7 (CH), 29.6 (CH), 25.0 ($CH_2$), 24.5 ($CH_2$), 21.8 ($CH_3$), 19.8 ($CH_3$), 19.8 ($CH_3$). HRMS-ESI *m*/*z* calcd for $C_{50}H_{91}O_3$: 739.696; found: 739.696 [$M^+$ + H]. $[\alpha]_D^{20}$ = +6.4 (*c* = 0.6, $CHCl_3$).

**21**. **20** (38 mg, 0.05 mmol) was dissolved in 3 mL of a 2 : 1 mixture of MeOH–$CH_2Cl_2$ and Pt on charcoal (10 wt%, 10 mg, 0.01 mmol) was added. The mixture was stirred under a hydrogen atmosphere (1 atm, balloon) for 16 h. The suspension was filtered over silica, the solvent evaporated, and the residue was purified by silica gel chromatography using 5% $Et_2O$ in pentane to give **21** (34 mg, 0.04 mmol, 92% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.27 (m, 5H), 4.55 (s, 2H), 3.72–3.42 (m, 9H), 1.64–0.99 (m, 54H), 0.88–0.84 (m, 24H). $^{13}$C NMR (101 MHz, $CDCl_3$, due to overlapping signals the reported number of signals does not correspond to the expected number) $\delta$ 138.4 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 77.9 (CH), 73.3 ($CH_2$), 71.1 ($CH_2$), 70.3 ($CH_2$), 69.8 ($CH_2$), 68.7 ($CH_2$), 37.4 ($CH_2$), 37.3–37.1 ($CH_2$), 37.0 ($CH_2$), 36.6 ($CH_2$), 34.1 ($CH_2$), 33.0 (CH), 32.8 (CH), 32.6 (CH), 29.9 (CH), 29.7 (CH), 24.4 ($CH_2$), 24.2 ($CH_2$), 20.1 ($CH_3$), 20.0 ($CH_3$), 19.9 ($CH_3$), 19.8 ($CH_3$). HRMS-ESI *m*/*z* calcd for $C_{50}H_{91}O_3$: 763.694; found: 763.694 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +2.4 (*c* = 0.8, $CHCl_3$).

**2**.[26] **21** (28 mg, 0.04 mmol) was dissolved in 2 mL of EtOAc and Pd on charcoal (10 wt% Degussa type, 8 mg, 0.01 mmol) was added. The mixture was stirred under a hydrogen atmosphere (1 atm, balloon) for 16 h followed by filtration over silica and evaporation of the solvent. The residue was purified by silica gel chromatography (pentane–$Et_2O$ 5 : 1) to give **2** (21 mg, 0.03 mmol, 80% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.79–3.30 (m, 9H), 2.08 (br s, 1H), 1.66–0.92 (m, 52H), 0.82 (d, *J* = 6.2 Hz, 6H), 0.81 (d, *J* = 6.5 Hz, 6H), 0.78 (d, *J* = 6.5 Hz, 12H). $^{13}$C NMR (101 MHz, $CDCl_3$, due to overlapping signals the reported number of signals does not correspond to the expected number, in addition small signals of residual solvent are present) $\delta$ 78.4 (CH), 71.2 ($CH_2$), 70.0 ($CH_2$), 68.5 ($CH_2$), 63.0 ($CH_2$), 37.3–37.1 ($CH_2$), 37.0 ($CH_2$), 36.5 ($CH_2$), 34.1 ($CH_2$), 33.0 (CH), 32.7 (CH), 32.6 (CH), 29.7 (CH), 29.7 (CH), 29.7 (CH), 24.4 ($CH_2$), 24.2 ($CH_2$), 20.1 ($CH_3$), 20.0 ($CH_3$), 19.9 ($CH_3$), 19.8 ($CH_3$), 19.8 ($CH_3$). HRMS-CI *m*/*z* calcd for $C_{50}H_{91}O_3$: 673.647; found: 673.647 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +6.5 (*c* = 0.8, $CHCl_3$).

**22**. **2** (15 mg, 0.02 mmol) was dissolved in 1 mL of a 1 : 1 mixture of toluene and dichloromethane. Subsequently, 4 Å molecular sieves (14 mg), tetrapivaloyl bromoglucose (40 mg, 0.07 mmol), tetramethylurea (11 μL, 0.09 mmol) and silver triflate (18 mg, 0.07 mmol) were added at 0 °C. The resulting reaction mixture was stirred and allowed to reach slowly rt. Progress of the reaction was followed by TLC (pentane–ether 5 : 5 and pentane–ether 8 : 2) until completion and subsequently the mixture was filtered and purified by column chromatography to give **22** (22.6 mg, 0.02 mmol, 85%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.30 (t, *J* = 9.4 Hz, 1H), 5.10 (t, *J* = 9.7 Hz, 1H), 5.02 (t, *J* = 7.1 Hz, 1H), 4.56 (d, *J* = 7.9 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 4.06 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.81 (dd, *J* = 12.4, 7.3 Hz, 1H), 3.70 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.63–3.51 (m, 4H), 3.51–3.30 (m, 4H), 1.47–0.93 (m, 88H), 0.93–0.72 (m, 24H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 178.0 (C), 177.2 (C), 176.4 (C), 176.4 (C), 101.0 (CH), 77.7 (CH), 72.3 (CH), 72.2 (CH), 71.2 (CH), 71.0 ($CH_2$), 69.9 ($CH_2$), 69.6 ($CH_2$), 68.7 ($CH_2$), 68.1 (CH), 62.0 ($CH_2$), 38.8 (C), 38.7 (C), 38.7 (C), 37.4 ($CH_2$), 37.4 ($CH_2$), 37.3 ($CH_2$), 37.3 ($CH_2$), 37.3 ($CH_2$), 37.2 ($CH_2$), 37.2 ($CH_2$), 37.1 ($CH_2$), 37.1 ($CH_2$), 37.1 ($CH_2$), 37.0 ($CH_2$), 36.6 ($CH_2$), 34.1 ($CH_2$), 34.1 ($CH_2$), 33.0 (CH), 32.8 (CH), 32.8 (CH), 32.7 (CH), 32.6 (CH), 30.3 (CH), 29.8 (CH), 29.7 ($CH_2$), 27.1 ($CH_3$), 27.1 ($CH_3$), 27.1 ($CH_3$), 27.0 ($CH_3$), 24.4 ($CH_2$), 24.2 ($CH_2$), 24.2 ($CH_2$), 20.2 ($CH_3$), 20.1 ($CH_3$), 20.1 ($CH_3$), 20.0 ($CH_3$), 19.9 ($CH_3$), 19.9 ($CH_3$), 19.8 ($CH_3$), 19.8 ($CH_3$). HRMS-ESI *m*/*z* calcd for $C_{69}H_{128}O_{12}$: 1171.928; found: 1171.915 [$M^+$ + Na]. $[\alpha]_D^{20}$ = +4.0 (*c* = 0.5, $CHCl_3$).

**23**. **22** (10 mg, 0.012 mmol) and sodium methoxide (14 mg, 0.36 mmol) were dissolved in methanol (0.5 mL). The reaction mixture was stirred until complete consumption of the starting material (24 h, TLC in pentane–ether 8 : 2). Then, amberlite ($H^+$ form) was added to the reaction mixture and the mixture stirred for an additional 3 min. The solution was then filtered, washing the solid several times with methanol. The solvent was removed under reduced pressure and the crude purified by column chromatography (from pentane–ethyl acetate 5 : 5 to ethyl acetate–methanol 95 : 5), giving 6.4 mg (0.010 mmol, 90% yield) of the product. $^1$H NMR (400 MHz, $CDCl_3$–$CD_3OD$ 9 : 1) $\delta$ 4.21 (d, *J* = 7.3 Hz, 1H), 3.87 (d, *J* = 6.6 Hz, 1H), 3.79 (dd, *J* = 11.1, 8.6 Hz, 1H), 3.68 (dd, *J* = 12.5, 4.8 Hz, 1H), 3.61–3.50 (m, 4H), 3.49–3.39 (m, 4H), 3.39–3.26 (m, 6H), 3.26–3.17 (m, 2H), 1.61–1.40 (m, 4H), 1.39–1.08 (m, 36H), 1.08–0.91 (m, 12H), 0.86–0.68 (m, 24H). $^{13}$C NMR (101 MHz, $CDCl_3$–$CD_3OD$ 9 : 1) $\delta$ 103.2 (CH), 77.6 (CH), 76.0 (CH), 75.8 (CH), 73.3 (CH), 70.1 ($CH_2$), 69.9 (CH), 69.9 ($CH_2$), 69.0 ($CH_2$), 68.3 ($CH_2$), 61.6 ($CH_2$), 37.2 ($CH_2$), 37.1 ($CH_2$), 37.1 ($CH_2$), 37.1 ($CH_2$), 37.1 ($CH_2$), 37.0 ($CH_2$), 36.9 ($CH_2$), 36.9 ($CH_2$), 36.9 ($CH_2$), 36.6 ($CH_2$), 36.3 ($CH_2$), 33.9 ($CH_2$), 33.8 ($CH_2$), 32.8 (CH), 32.6 (CH), 32.6 (CH), 32.4 (CH), 32.4 (CH), 29.6 (CH), 29.5 (CH), 24.2 ($CH_2$), 24.0 ($CH_2$), 23.9 ($CH_2$), 19.9 ($CH_3$), 19.9 ($CH_3$), 19.8 ($CH_3$), 19.7 ($CH_3$), 19.6 ($CH_3$), 19.6 ($CH_3$), 19.5 ($CH_3$), 19.5 ($CH_3$). $CD_3OD$ was added to the NMR sample in $CDCl_3$ in order to improve its resolution. HRMS-ESI *m*/*z* calcd for $C_{49}H_{96}O_8$: 835.691; found: 835.689 [$M^+$ + Na]. $[\alpha]_D^{20}$ = −6.9 (*c* = 0.26, MeOH).

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