Synthesis of Methyl-Branched Lipids from Mycobacterium tuberculosis

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This chapter describes a new strategy for the construction of phenylphthiocerol, a substructure of Mycosides (phenolic glycolipids). Mycosides are outer membrane lipids of mycobacteria and play an important role in the virulence of mycobacteria. Hetero asymmetric allylic alkylation, cross-metathesis and Sharpless epoxidation reactions are key strategic elements in the synthesis towards phenylphthiocerol and eventually mycosides.**

5.1 Introduction

Mycosides (phenolic glycolipids) are a class of outer membrane waxy lipids which are present in all pathogenic mycobacteria with the exception of *Mycobacterium gastri*. Mycosides typically consist of a long chain p-glycosylated, 3-methoxy, 4-methyl, 9,11-dihydroxy glycol (glycosyl phenolphthiocerol) containing scaffold di-esterified with di-, tri-, and tetramethyl-branched acyl chains (mycocerosates, Chapter 2).¹ Mycoside B (Figure 1) is an example of a mycoside and is found in virulent *Mycobacterium bovis* (*M. bovis*). Phthiocerol dimycocerosate A (PDIM A, Figure 1), a closely related structure to mycosides, is found in virulent *Mycobacterium tuberculosis* (*M. tuberculosis*) and contains a phthiocerol backbone instead of the phenolphthiocerol.

The structure and absolute configuration of mycocerosic acid were proposed by Polgar and Smith in 1963.² We have recently reported the first catalytic asymmetric synthesis of mycocerosic acid and we have confirmed its structure and absolute configuration (Chapter 2).³ Phthiocerol was first reported by Anderson and Stodola in 1936⁴ and the basic structure was elucidated by Stenhagen and co-workers⁵ in 1956. The stereochemistry of phthiocerol and phenolphthiocerol has been studied extensively over the last decades.⁶,⁷,⁸,⁹,¹⁰ More recent studies, involving MALDI-TOF and ¹H-NMR analysis, support this overall structural assignment,¹¹ but rigorous confirmation by chemical synthesis was lacking.¹² We recently confirmed the stereochemistry and absolute configuration by reporting the first synthesis of PDIM A.¹³

Mycoside B is one of the lipids present in the cell envelope of *Mycobacterium bovis* (*M. bovis*), the causative agent of tuberculosis in cattle (known as bovine tuberculosis). Being related to *M. tuberculosis*, *M. bovis* can jump the species barrier and cause tuberculosis in humans.¹⁴ The complete structure of Mycoside B was first described by Demarteau-Ginsburg and Lederer in 1963.¹⁵

It is noteworthy to mention that there are several anomalies in the stereochemistry of phenolphthiocerol and phthiocerol in some mycobacteria species. *Mycobacterium marinum* and *Mycobacterium ulcerans* produce phthiocerols that contain mycocerosic acid residues with the
opposite stereochemistry, all-$S$, compared to the more commonly found all-$R$ configuration. The 9,11-dihydroxy moiety (1,3-diol), which is typically found as the $R,R$-threo (anti) configuration, is only observed as the erythro or syn-diol in $M. \text{marinum}$. The absolute configuration of these syn-diols is still unknown. The C-4 methyl branch is also of the opposite configuration ($R$) compared to that in the other mycobacteria ($S$).$M. \text{marinum}$ and $M. \text{ulcerans}$ do, however, differ at their C-3 center. $M. \text{ulcerans}$ produces phthiocerols with a carbonyl functionality at the C-3 position compared to a hydroxy functionality (methoxy) in $M. \text{marinum}$. 

Figure 1: Molecular structures of phthiocerol containing PDIMA ($M. \text{tuberculosis}$) and phenylphthiocerol containing Mycoside B ($M. \text{bovis}$).

Until recently, little was known about the biosynthesis of (phenol)phthiocerol. Due to the availability of several mycobacterial genomes, at the moment tremendous progress is made toward clarifying their biosynthetic pathways. This was recently extensively reviewed by Onwueme et al. and new enzymes involved in the biosynthetic pathway.
have been discovered. The proposed general biosynthetic pathway for (phenol)phthiocerol is depicted in Scheme 1.

Scheme 1: Biosynthetic pathway for DIMs, $R = \text{CH}_3(\text{CH}_2)_5\text{CH}-$ or $\text{HO}\text{PhCH}_2\text{CH}_2-$, $\text{AT} = \text{acyltransferase}, \text{KS} = \text{keto-acyl synthase}, \text{KR} = \text{ketoreductase}, \text{DH} = \text{dehydratase}, \text{ER} = \text{enoyl reductase}.$

After we successfully synthesized PDIM A (synthesis of phthiocerol by Dr. Eva Casas Arce) we decided to embark on the first asymmetric synthesis.
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of the related, but considerably more complex phenolphthiocerol based Mycoside B (Figure 1, 1), starting with the synthesis of phenolphthiocerol (2).

5.2 Retrosynthetic analysis of phenolphthiocerol

As outlined in the retrosynthetic scheme (Scheme 2), we were interested in a new strategy for the efficient construction of the anti-1,3 diol unit which is present in phenolphthiocerol. We planned to use a Sharpless epoxidation on 4 followed by reductive opening of the resulting epoxide to obtain the desired anti-1,3 diol structure in 2. In order to synthesize allylic alcohol 4, a cross coupling metathesis of building blocks 5 and 6 was envisioned. The key step for the formation of allylic alcohol 5 would be the hetero asymmetric allylic alkylation of 8 using alkylmagnesium bromide 7. On the other hand, building block 6 could be obtained by a reduction, olefination sequence of methyl ester 9.
Scheme 2: Retrosynthetic analysis of phenylphthiocerol (2)

5.3 Synthesis of PDIM A

In 2006 we reported the first total synthesis of PDIM A. Enantioselective addition of 2-methyl-3-butyne-2-ol to aldehyde 10 in the presence of Zn(OTf)$_2$, Et$_3$N, and (+)-N-methylephedrine$^{37}$ allowed for the formation of propargylic alcohol 11 (Scheme 3) with excellent selectivity (95% de).$^{28}$ The hydroxy group in 11 was protected as a silyl ether, and the alkyne moiety was deprotected under basic conditions to afford 12. Alkylation of the corresponding alkynyllithium compound using CH$_3$(CH$_2$)$_2$Br in the presence of NaI afforded the protected propargylic alcohol.$^{29}$ Finally, treatment with tetrabutylammonium fluoride (TBAF) led to the formation of deprotected alcohol 13. We were pleased to observe regioselective hydrosilylation of propargylic alcohol 13 with benzyldimethylsilane.
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(BDMSH) catalyzed by \([\text{Cp}^\ast\text{Ru(MeCN)}_3\text{PF}_6]\), following the protocol described by Trost.\(^{30}\)

1. TIPSOTf, 2,4-lutidine, CH\(_2\)Cl\(_2\), 0 °C, 95%
2. NaH, toluene, 96%

1. nBuLi, THF, CH\(_3\)(CH\(_2\))\(_2\)Br, NaI, 87%
2. TBAF, THF, 0 °C, 92%

Scheme 3: Key steps in the synthesis of PDIM A.

This reaction represents a versatile method in natural product synthesis.\(^{30,31}\) It afforded a mixture of benzyldimethyl silanes (4:1) favoring 14 (69% yield). Fleming-Tamao oxidation,\(^{32}\) using TBAF, KHCO\(_3\) and H\(_2\)O\(_2\), resulted in the formation of the corresponding hydroxy ketones, which could be separated by column chromatography affording 16 as a pure isomer. To selectively produce the anti-1,3-diol, reduction of 16 was carried out with tetramethylammonium triacetoxyborohydride, resulting in 17 with an anti/syn ratio of 88:12.\(^{33}\) Double esterification of phthiocerol...
with mycocerosic acid gave PDIM A (3) in 63% yield (15 steps and 5.6% overall yield) (Scheme 4). 

Although this synthesis is very elegant and it demonstrates the power of state of the art catalytic protocols, we were interested to find a shorter route for the construction of the anti-1,3-diol motif. Therefore, we were interested in constructing the 1,3-diol motif of phenolphthiocerol by applying our earlier developed hetereo asymmetric allylic alkylation reaction combined with cross-metathesis and Sharpless epoxidation reactions (Section 5.2).

5.4 Results and discussion

5.4.1 New enantioselective approach for the construction of 1,3-diols

In order to guarantee the success of the newly designed route for the construction of the anti 1,3-diol motif, the key steps were first studied on model substrates (Scheme 4). Thus, commercially available n-pentadecylmagnesium bromide and dec-1-ene were used instead of Grignard 7 and alkene 6, respectively. Copper/Taniaphos (18) catalyzed hetero asymmetric allylic alkylation of 8 using n-pentadecylmagnesium bromide led to the formation of allylic ester 19 with 78% yield and >98% ee. Cross coupling metathesis with dec-1-ene using Hoveyda-Grubbs 2nd generation catalyst 20 allowed the formation of 21 with excellent yield and selectivity (91% yield, >95% E isomer). Treatment of 21 under basic conditions led to the formation of allylic alcohol 22, which was submitted to a Sharpless epoxidation resulting in the formation of 23 as mixture of anti: syn epoxides (10:1), easily separable by column chromatography.
Scheme 4: Model study on the enantioselective construction of the anti 1,3-diol

Starting with the R-enantiomer of allylic alcohol 22, si-face attack on olefin 22 directed by the titanium D-(-)-diethyl tartrate complex resulted in the desired R,R,R-23 epoxide (Figure 2).
Figure 2: Stereoselectivity in the Sharpless epoxidation reaction.

Finally, reductive opening of anti-23 using Red-Al completed the synthesis of model substrate 24. The selectivity of the reductive epoxide opening was highly dependent on the temperature. Reaction temperatures of –20 and 0 °C resulted in 1:1 and 1:2 mixtures, respectively, favoring the desired 1,3-diol. At room temperature the selectivity improved to 1:6.

5.4.2 Synthesis of the Eastern part of phenylphthiocerol

Olefin 6 was prepared from aldehyde 10, following the protocol we recently disclosed (Scheme 5). Copper/phosphoramide (25) catalyzed asymmetric conjugate addition of Me₂Zn to cycloheptenone (26), followed by in situ ethylation allowed the formation of ketone 27, which was isolated in high yield and with excellent trans selectivity (>20:1) and ee (95%). Baeyer-Villiger oxidation using excess mCPBA followed by treatment of the resulting lactone 28 with K₂CO₃ in MeOH led to the formation of the
linear methyl ester 29. The hydroxyl group of 29 was converted into its methyl ether 9 after which the ester moiety was reduced to the corresponding alcohol 30. Following this protocol, 500 mg of alcohol 30 was prepared. To complete the synthesis of olefin 6, alcohol 30 was oxidized to aldehyde 10 using Dess-Martin reagent. Aldehyde 10 was directly treated with Tebbe’s olefination reagent (31) and olefin 6 was obtained in 89% yield over the last two steps.

Scheme 5: Synthesis of the Eastern part of phenylphthiocerol.
5.4.3 Synthesis of the Western part of phenylphthiocerol

The construction the Western part 5 (Scheme 6) started with the substitution of the hydroxyl group in 16-hydroxyhexadecanoic acid (32) to bromo-derivative 33, followed by formation of the corresponding acyl chloride 34. Friedel-Craft acylation of anisole using 34 led to ketone 35, which was reduced under Clemmensen conditions to complete the synthesis of bromo-derivative 36.\(^\text{39}\)

Formation of the Grignard reagent from bromo-derivative 36 was found to be surprisingly difficult under standard conditions in diethyl ether. Although we managed to observe the formation of the alkyl magnesium species in some cases, in most attempts the starting material was recovered. Bromide 36 was found to be more reactive in refluxing THF and the formed Grignard reagent was more soluble. However, because of the strong

\[ \text{Scheme 6: Synthesis of the Western part of phenylphthiocerol.} \]
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coordinating character (Lewis base) of THF, there is a strong competition between the chiral ligand and the solvent with the copper-catalyst. THF mostly prohibits the enantioselectivity of the asymmetric enantioselective allylic alkylation reaction as well as the enantioselectivity in the enantioselective 1,4-addition reactions. Attempts to perform a solvent exchange by evaporating the THF followed by the addition of diethyl ether were unsatisfactory. The solid Grignard reagent was difficult to dissolve in diethyl ether and the presence of THF could not be ruled out. We therefore decided to use a di-alkyl ether with a higher boiling point compared to diethyl ether so we would have higher reactivity with similar polarity and coordinating character as diethyl ether. Switching to di-n-butyl ether at 100 ºC for 5 h resulted in the desired formation of Grignard reagent. The n-butyl ether solution was then cooled down to approximately 35 ºC after which CH₂Cl₂ was added, immediately followed by cooling to prevent the Grignard reagent to react with the solvent (−55 ºC). Preformed CuBr/Taniaphos (18) complex was added to the solution and substrate 8 was added via a syringe. The copper-catalyzed hetero asymmetric allylic alkylation resulted in Western part 5 in 43% yield over two steps with an ee of >98% (determined via the corresponding Mosher ester of the hydrolyzed allylic alcohol).

5.4.4 End game: towards the total synthesis of Mycoside B

Eastern part 6 and Western part 5 were coupled under cross-metathesis conditions using Hoveyda-Grubbs second generation catalyst (20) (Scheme 7). The reaction was slow and initially resulted in a mixture of the homo-dimer of 6 and the starting materials. The homo-dimer could still react, however, and resulted in the less reactive and desired hetero-coupled product 38 (69% yield, only the E-isomer was observed). Hydrolysis of 38 gave allylic alcohol 4 in 78% yield.

The Sharpless epoxidation was performed under exactly the same conditions as for test substrate 22 and led to the formation of 39 in 72% yield and the same 10:1 ratio favoring the anti-epoxide 39. The diastereomers were separated by flash column chromatography. In the final step epoxide 39 was treated with 5 equivalents of Red-Al at room temperature in THF, similar conditions as were used for epoxide 23. To our great surprise and disappointment, the reductive epoxide ring opening turned out extremely selective, favoring the undesired 1,2-diol 41! The
observed ratio between the 1,3-diol (40) and 1,2-diol (41) was 1:10, respectively, (94% yield).

Scheme 7: Cross metathesis between the eastern and western part followed by Sharpless epoxidation and reductive ring opening.

The reason for this reversed selectivity could be the result of a coordinating effect of the methoxy functionality in 39 (or the more distant MeOPh) which is not present in the test substrate. This seems highly unlikely, however, because there is no coordination site available on the aluminum intermediate species. Moreover the reaction is performed in THF and therefore coordination with the solvent would seem much more
likely and did not lead to selectivity problems with the test substrate. The reaction was only performed once due to the small amount of the available material. The unexpected outcome could thus be an anomaly but is difficult to explain. Alternatively, a radical epoxide ring-opening strategy with \( \text{Cp}_2\text{TiCl} \) and \( \text{t-BuSH} \) in THF could improve the selectivity of epoxide opening as was reported for closely related epoxides.\(^{41}\)

5.5 Conclusions

We developed a highly enantioselective and robust method for the construction of the Eastern part (olefin 6) of Mycoside B by applying a copper/phosphoramidite-catalyzed 1,4-addition reaction on cycloheptenone with \( \text{Me}_2\text{Zn} \). The formed enolate was successfully trapped with ethyl iodide leading to the formation of the trans-product in near perfect stereocontrol. After 6 additional steps olefin 6 was obtained in 34\% overall yield (7 steps).

The western part of Mycoside B was successfully synthesized by a copper-catalyzed asymmetric allylic alkylation reaction with functionalized Grignard reagent 37. We found that the formation of such Grignard reagents works very well at higher temperatures in \( n \)-butyl ether without the loss of enantioselectivity in the allylic alkylation reaction itself. Olefin 5 was obtained in 20\% overall yield in 5 steps with an ee of >98\%.

The cross metathesis of the two functionalized olefins 5 and 6 resulted in the formation of the desired benzyl ester of allylic alcohol 38. This key step in our strategy clearly demonstrates the power of the cross-metathesis reaction in total synthesis.

After the successful Sharpless epoxidation of allylic alcohol 39 we tried selective reductive epoxide ring-opening reaction with Red-Al which failed for unclear reasons. We found that the undesired 1,2-diol was the major product. This is, however, the result of one attempt and needs further investigation. Although this strategy proved to work very well for our test substrate, it unfortunately failed in the synthesis of the more highly functionalized phenolphthiocerol. The strategy presented in this chapter did not lead to the synthesis of Mycoside B, but we did develop effective new strategies and methodologies which can be readily used in the synthesis of complex molecules.
5.6 Experimental

For general experimental procedures, see chapter 2, experimental section.

(2R)-Ethyl-(3S)-methylcycloheptanone (27)

(S,R,R)-25 (146 mg, 0.27 mmol, 1.0 mol%) and Cu(OTf)$_2$ (49 mg, 0.14 mmol, 0.5 mol%) were dissolved in dry toluene (60 mL) and stirred for 30 min under nitrogen at room temperature. The mixture was cooled at −25 °C and Me$_2$Zn (1.2 M in toluene, 34 mL, 40.36 mmol, 1.5 equiv) was added dropwise over 5 min. After stirring for 10 min, a solution of cycloheptenone (3.0 mL, 26.91 mmol) in dry toluene (60 mL) was added over 5 h by syringe pump and the resulting mixture was stirred overnight at −25 °C. Ethyl iodide (22.0 mL, 269 mmol, 10.0 equiv.) and hexamethylphosphoramide (47.0 mL, 269 mmol, 10 equiv.) were added, the mixture was warmed up to 0 °C and stirred for 60 h. The reaction was quenched with aq. NH$_4$Cl (sat.), the mixture extracted with diethyl ether, washed with brine (sat.) and dried (Na$_2$SO$_4$). The solvents were removed under reduced pressure and the product was purified by flash chromatography (pentane/diethyl ether, 50:1) to give 27 (3.44 g, 22.3 mmol, 83%, >95:5 trans:cis, 95% ee for trans) as a colorless oil. [α]$_D$ = −50° (c = 4.9, CHCl$_3$). $^1$H-NMR (CDCl$_3$, 400 MHz) δ = 0.82 (t, $J$ = 7.4 Hz, 3H), 0.99 (d, $J$ = 6.7 Hz, 3H), 1.20 (m, 1H), 1.32–1.69 (m, 6H), 1.83 (m, 2H), 2.27 (m, 1H), 2.55 (td, $J$ = 3.6 Hz, $J$ = 11.8 Hz, 1H) ppm. $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) δ 11.9 (q), 21.0 (q), 24.1 (t), 26.0 (t), 28.0 (t), 35.6 (d), 36.1 (t), 41.2 (t), 61.8 (d), 216.0 (s) ppm. MS (CI) for C$_{10}$H$_{18}$O: m/z = 172.2 [M+NH$_4$]$^+$, HRMS(EI) calculated for C$_{10}$H$_{18}$O $^{154.1358}$, found 154.1353.
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**(8R)-Ethyl-(7S)-methyloxocan-2-one (28)**

![Chemical Structure](image)

A solution of 27 (3.30 g, 21.39 mmol) in CH₂Cl₂ (15 mL) was added to a suspension of m-chloroperbenzoic acid (70-75%, 25.28 g, 106.95 mmol, 5.0 equiv.) in CH₂Cl₂ (15 mL) and the resulting mixture was heated at reflux for 60 h. The reaction mixture was cooled to room temperature, washed with aq. NaHCO₃ (sat.) and then dried (Na₂SO₄). The CH₂Cl₂ was removed under reduced pressure and the product was purified by flash chromatography (pentane/diethyl ether, 50:1) to give 28 (2.18 g, 12.83 mmol, 60%) as a colorless oil. [α]D = −54° (c = 5.2, CHCl₃).

1H-NMR (CDCl₃, 400 MHz) δ = 0.85 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.28 (m, 1H), 1.41-1.92 (m, 8H), 2.38 (t, J = 2.5 Hz, 2H), 4.28 (td, J = 7.4 Hz, J = 6.4 Hz, 2H), 3.30 (m, 1H), 3.63 (s, 3H) ppm. 13C-NMR (CDCl₃, 100.6 MHz) δ 174.2 (s), 77.3 (s), 51.4 (q), 38.2 (d), 34.0 (t), 31.4 (t), 26.7 (t), 26.2 (t), 25.2 (t), 15.3 (q), 10.3 (q). ppm. MS (Cl) for C₆H₁₃O₂: m/z = 188.2 [M+NH₄]+, HRMS(El) calculated for C₁₀H₁₈O₂·C₂H₅: 141.0915, found 141.0921.

**(7R)-Hydroxy-(6S)-methylnonanoic acid methyl ester (29)**

![Chemical Structure](image)

To a solution of 28 (1.81 g, 10.63 mmol) in methanol (30 mL), activated K₂CO₃ (1.47 g, 10.63 mmol, 1.0 equiv.) was added and the resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with aq. NH₄Cl (sat.) and then dried (Na₂SO₄). The solvent was removed under reduced pressure. The product was then extracted with CH₂Cl₂ and the solution was dried (Na₂SO₄). The solvent was removed under reduced pressure and the product was purified by flash chromatography (pentane/EtOAc, 9:1) to give 29 (1.94 g, 9.57 mmol, 90%) as a colorless oil. [α]D = −9.9° (c = 2.8, CHCl₃).

1H-NMR (CDCl₃, 400 MHz) δ = 0.85 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 1.03-1.68 (m, 9H, 1OH), 2.29 (t, J = 7.2 Hz, 2H), 3.30 (m, 1H), 3.63 (s, 3H) ppm. 13C-NMR (CDCl₃, 100.6 MHz) δ 174.2 (s), 77.3 (s), 51.4 (q), 38.2 (d), 34.0 (t), 31.4 (t), 26.7 (t), 26.2 (t), 25.2 (t), 15.3 (q), 10.3 (q). ppm. MS (Cl) for C₁₁H₂₂O₂: m/z = 220.3
\[ [M+\text{NH}_4]^+ \text{, HRMS(El) calculated for C}_{11}\text{H}_{22}\text{O}_3\text{-C}_2\text{H}_5: 173.1178, found 173.1172.} \]

**\(7R\)-Methoxy-(6S)-methylnonanoic acid methyl ester (9)**

\[
\text{MeO} \quad \text{O} \quad \text{O} \\text{O} \quad \text{Me}\]

To a solution of 29 (1.00 g, 4.94 mmol) in dry DMF (30 mL), Mel (4.62 mL, 74.15 mmol, 15.0 equiv.) and NaH (60%, 1.98 g, 49.43 mmol, 10.0 equiv.) were added at 0 °C. The resulting suspension was stirred overnight under nitrogen at 40 °C, after which the reaction was quenched with H\(_2\)O and the mixture extracted with diethyl ether. The combined organic layers were washed with brine (sat.), dried (MgSO\(_4\)) and concentrated. The product was purified by flash chromatography (pentane/EtOAc, 9:1) to give 9 (983 mg, 4.54 mmol, 92%) as a colorless oil. \([\alpha]_D = -3.1^\circ\) (c = 2.8, CHCl\(_3\)). \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta = 0.81\) (d, \(J = 6.9\) Hz, 3H), 0.89 (t, \(J = 7.4\) Hz, 3H), 1.09 (m, 1H), 1.23 (m, 1H), 1.32-1.50 (m, 4H), 1.54-1.72 (m, 3H), 2.30 (t, \(J = 7.6\) Hz, 2H), 2.84 (m, 1H), 3.31 (s, 3H), 3.65 (s, 3H) ppm. \(^13\)C-NMR (CDCl\(_3\), 100.6 MHz) \(\delta = 174.2\) (s), 86.6 (d), 57.4 (q), 51.4 (q), 34.7 (d), 34.0 (t), 32.2 (t), 27.0 (t), 25.2 (t), 22.3 (t), 14.7 (q), 9.9 (q). ppm.

MS (CI) for C\(_{12}\)H\(_{24}\)O\(_3\): m/z = 234.2 [M+\text{NH}_4]^+\text{, HRMS(El) calculated for C}_{12}\text{H}_{22}\text{O}_3\text{-OCH}_3 185.1541, found 185.1540.}

**\(7R\)-Methoxy-(6S)-methylnonan-1-ol (30)**

\[
\text{MeO} \quad \text{O} \quad \text{O} \quad \text{OH} \]

To a solution of 9 (600 mg, 2.77 mmol) in dry THF (14 mL) at −78 °C, a solution of DIBAL-H (20% in toluene, 5.0 mL, 5.82 mmol, 2.1 equiv.) was added. The resulting mixture was stirred overnight under nitrogen at −78 °C, after which the reaction was quenched with an aqueous solution of Rochelle salt and followed by extraction with Et\(_2\)O. The combined organic layers were washed with brine (sat.), dried (MgSO\(_4\)) and concentrated. The product was purified by flash chromatography (pentane/EtOAc, 9:1) to give 30 (496 mg, 2.63 mmol, 95%) as a colorless oil. \([\alpha]_D = -3.5^\circ\) (c = 3.3, CHCl\(_3\)). \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta = 0.83\) (d, \(J = 6.8\) Hz, 3H), 0.91 (t, \(J = 7.5\) Hz, 3H), 1.10 (m, 1H), 1.20-1.76 (m, 10H, 1OH), 2.87 (m, 1H), 3.33
To a solution of 30 (545 mg, 2.89 mmol) in dry CH₂Cl₂ (15 mL), Dess-Martin reagent (1.35 g, 3.18 mmol, 1.1 equiv.) was added and the resulting mixture was stirred under nitrogen at room temperature for 30 min. The reaction was quenched with aq. Na₂S₂O₃ (sat.) and aq. NaHCO₃ (sat.) and then the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine (sat.), dried (MgSO₄) and concentrated. The product was purified by flash chromatography (petroleum/EtOAc, 9:1) to give 10 (494 mg, 92% yield) as a colorless oil. The product turned out to be unstable (oxidation to the acid) and was therefore immediately used in the next reaction. [α]D = -5.3° (c = 3.1, CHCl₃). ¹H-NMR (CDCl₃, 400 MHz) δ = 0.79 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H), 1.06 (m, 1H), 1.22 (m, 1H), 1.30-1.47 (m, 4H), 1.50-1.66 (m, 3H), 2.39 (td, J = 1.8 Hz, J = 7.3 Hz, 2H), 2.82 (m, 1H), 3.28 (s, 3H), 9.72 (t, J = 1.8 Hz, 1H) ppm. ¹³C-NMR (CDCl₃, 100.6 MHz) δ 86.5 (d), 62.7 (t), 57.3 (q), 43.8 (t), 34.7 (d), 32.2 (t), 27.0 (t), 22.3 (t), 14.7 (q), 9.8 (q).

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(s, 3H), 3.64 (m, 2H) ppm. ¹³C-NMR (CDCl₃, 100.6 MHz) δ 86.7 (d), 62.7 (t), 57.3 (q), 34.7 (d), 32.7 (t), 27.2 (t), 26.0 (t), 22.3 (t), 14.7 (q), 9.9 (t). MS (Cl) for C₁₁H₂₄O₂: m/z = 206.2 [M+NH₄]⁺, HRMS(EI) calculated for C₁₁H₂₄O₂-OCH₃ 157.1592, found 157.1589.

(7R)-Methoxy-(6S)-methylnonanal (10)

![Chemical Structure]

Freshly prepared aldehyde 10 (100 mg, 0.530 mmol) was dissolved in 10 mL toluene and stirred at rt. Tebbe reagent (2.121 mL, 1.060 mmol, 0.5M in toluene) was added dropwise to the stirred solution over 10 min. The reaction was followed by TLC (CH₂Cl₂) until the reaction was completed (15 min). After quenching with 10 mL of saturated aq. NH₄Cl solution, 10 mL of diethyl ether was added. The phases were separated and the aqueous layer was extracted with three portions of 10 mL diethyl ether. The combined organic phases were dried over MgSO₄ and concentrated.
under reduced pressure to yield crude 6, which was purified by flash chromatography (CH$_2$Cl$_2$) to afford 6 as a colorless oil (87 mg, 89% yield (two steps), $[\alpha]_D = -1.0^\circ$ (c = 1.5, CHCl$_3$)). $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 5.81 (m, 1H), 4.96 (m, 2H), 3.34 (s, 3H), 2.87 (m, 1H), 2.06 (m, 2H), 1.68 (m, 1H), 1.50-1.02 (br, 9H), 0.91 (t, $J = 6.9$ Hz, 3H) 0.83 (d, $J = 6.8$ Hz, 3H).

$^{13}$C-NMR (CDCl$_3$, 100.6 MHz) $\delta$ 139.07 (d), 114.15 (t), 86.70 (d), 57.33 (q), 34.77 (d), 34.13 (t), 33.79 (t), 32.50 (t), 29.26 (t), 27.02 (t), 14.71 (q), 10.08 (q). HRMS(ESI+) calculated for C$_{12}$H$_{25}$O$^+$ (M + H$^+$), 185.1900, found 185.1897.

**16-Bromohexadecanoic acid (33)**

![Chemical Structure](image)

To a solution of 16-hydroxyhexadecanoic acid (1.00 g, 3.67 mmol) in CH$_2$Cl$_2$ (20 mL) cooled to 0 ºC, PPh$_3$ (2.90 g, 11.01 mmol, 3.0 equiv.) and NBS (1.63 g, 9.18 mmol, 2.5 equiv.) were added. The resulting solution was stirred under nitrogen at 0 ºC for 10 min and then warmed to room temperature over 2 h. The reaction mixture was quenched with aq. NaHCO$_3$ (sat.) and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with aq. Na$_2$S$_2$O$_3$ (10% v/v) and brine (sat.), dried (MgSO$_4$), filtered and concentrated. The resulting crude was purified by flash chromatography (pentane/EtOAc, 9:1) to give 33 (935 mg, 76% yield) as a white solid, mp = 67-68 ºC. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ = 1.22-1.35 (m, 20H), 1.41 (m, 2H), 1.62 (m, 2H), 1.85 (qt, $J = 6.9$ Hz, 2H), 2.34 (t, $J = 7.5$ Hz, 2H), 3.40 (t, $J = 6.9$ Hz, 2H) ppm. $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) $\delta$ 180.4 (s), 34.1 (t), 32.8 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.2 (t), 29.0 (t), 28.8 (t), 28.2 (t), 24.6 (t). ppm. MS (El) for C$_{16}$H$_{31}$BrO$_2$: m/z = 333.8 [M$^+$], 335.9 [M+2$^+$]. HRMS(El) calculated for C$_{16}$H$_{31}$BrO$_2$: 334.1507, found 334.1504.

**16-Bromohexadecanoyl chloride (34)**

![Chemical Structure](image)

To a solution of 33 (930 mg, 2.77 mmol) in CH$_2$Cl$_2$ (20 mL) cooled at 0 ºC, oxalyl chloride (0.5 mL, 5.54 mmol, 2.0 equiv.) was added. The resulting
mixture was stirred under nitrogen at 0 °C for 10 min and then warmed to room temperature overnight. The solvent was removed under vacuum to give 34 (833 mg, 2.35 mmol, 85%) as a yellowish oil, that was used in the next transformation without further purification. ¹H-NMR (CDCl₃, 400 MHz) δ = 1.21-1.34 (m, 20H), 1.42 (m, 2H), 1.71 (m, 2H), 1.85 (dt, J = 6.9 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H), 3.41 (t, J = 6.9 Hz, 2H) ppm.

16-Bromo-1-(4-methoxyphenyl)-hexadecan-1-one (35)

To a solution of 34 (833 mg, 2.35 mmol) in CH₂Cl₂ (20 mL) cooled to 0 °C, AlCl₃ (470 mg, 3.53 mmol, 1.5 equiv.) was added, followed by anisole (1.3 mL, 11.75 mmol, 5.0 equiv.). The resulting solution was stirred under nitrogen at 0 °C for 10 min and then warmed to room temperature overnight. The reaction mixture was quenched by pouring it into a separation funnel containing ice. After 30 min the organic layer was collected, washed with water until the aqueous extract was neutral, dried (MgSO₄), filtered and concentrated. The resulting crude product was purified by flash chromatography (pentane/diethyl ether, 9:1) to give 35 (820 mg, 82% yield) as a white solid. mp = 65-66 °C. ¹H-NMR (CDCl₃, 400 MHz) δ = 1.15-1.67 (m, 22H), 1.71 (m, 2H), 1.84 (qt, J = 6.9 Hz, 2H), 2.90 (t, J = 7.3 Hz, 2H), 3.39 (t, J = 6.9 Hz, 2H), 3.86 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 9.0 Hz, 2H) ppm. ¹³C-NMR (CDCl₃, 100.6 MHz) δ 199.2 (s), 163.2 (s), 130.3 (d), 113.6 (d), 55.4 (q), 38.3 (t), 34.0 (t), 32.8 (t), 29.6 (t), 29.5 (t), 29.4 (t), 28.7 (t), 28.2 (t), 24.6 (t) ppm. MS (EI) for C₂₃H₄₁BrO₃: m/z = 424.0 [M⁺]⁺, 426.0 [M+2]⁺. HRMS(El) calculated for C₂₃H₄₁BrO₃ 424.1977, found 424.1968.

1-(16-Bromohexadecyl)-4-methoxybenzene (36)

A sample of zinc + mercury amalgam was freshly prepared by suspending Zn powder (853 mg, 13.05 mmol, 15.0 equiv.) and HgCl₂ (119 mg, 0.87
mmol, 1.0 equiv.) in a mixture of water (4.0 mL) and 12 M aq. HCl (2.5 mL). After stirring the resulting suspension for 10 min, a solution of 35 (370 mg, 0.87 mmol) in toluene (5.5 mL) was added. The resulting two-phase mixture was heated and stirred vigorously such that both phases were in frequent contact with the amalgam. After 16 h under reflux, during which two 0.5 mL portions of 12 M aq. HCl were added, the reaction flask was allowed to cool to room temperature and the organic phase was collected, washed with water and dried (MgSO₄). The resulting solution was concentrated and purified by flash chromatography (pentane/diethyl ether, 95:5) to give 36 (315 mg, 0.77 mmol, 88%) as a white solid, mp = 33-34 ºC.

^1^H-NMR (CDCl₃, 400 MHz) δ 1.17-1.37 (m, 22H), 1.44 (m, 2H), 1.59 (m, 2H), 1.87 (qt, J = 6.9 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 3.42 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 6.83 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H). ^1^C-NMR (CDCl₃, 100.6 MHz) δ 157.5 (s), 135.0 (s), 129.2 (d), 113.6 (d), 55.2 (q), 35.0 (t), 34.0 (t), 32.8 (t), 31.8 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.8 (t), 28.2 (t). MS (EI) for C₂₃H₃₉BrO: m/z = 410.2 [M]^+ , 412.2 [M+2]^+ , HRMS(EI) calculated for C₂₃H₃₉BrO 410.2184, found 410.2166.

**(E)-3-Bromoprop-1-enyl benzoate (8)**

Freshly distilled acrolein (2.8 mL, 41.96 mmol) was dissolved in CH₂Cl₂ (40 mL) at 0 ºC and benzoyl bromide (5.0 mL, 41.96 mmol, 1.0 equiv.) was added. The resulting solution was allowed to warm to room temperature and stirred for 72 h. The reaction was quenched by addition of aq. NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried (MgSO₄), filtered and concentrated. The resulting crude was purified by recrystallization from pentane to give the pure E isomer 8 (5.76 g, mmol, 57%) as a white solid.²⁶
(R)-19-(4-Methoxyphenyl)nonadec-1-en-3-yl benzoate (5)

First a solution of the corresponding Grignard reagent of 36 was prepared in n-butyl ether at 100 °C for 5 h (550 mg, 1.335 mmol 34 together with 36 mg, 1.481 mmol Mg(s) in 5 mL n-butyl ether). The solution was cooled to 35 °C, 20 mL CH₂Cl₂ was added and the mixture was stirred vigorously for 1 min after which it was quickly cooled down to –55 °C. A second portion of 20 mL of CH₂Cl₂ was added and stirring was continued for 15 min. A pre-stirred (10 min) solution of (−)-(S,S)-Taniaphos (21.3 mg, 0.031 mmol) and CuBr•SMe₂ (5.1 mg, 0.025 mmol) in 2 mL of CH₂Cl₂ was added and the suspension was stirred for 10 min. Substrate 8 (322 mg, 1.335 mmol) was added dropwise in CH₂Cl₂ (3 mL) over 15 min. The reaction mixture was quenched with 3 mL MeOH after 16 h at –55 °C. A saturated aq. NH₄Cl solution (50 mL) was added, together with 50 mL ether and the mixture was brought to rt and stirred for 30 min. The layers were separated and the water layer was extracted with 2 additional portions of 20 mL ether. The organic layers were combined, dried on MgSO₄ to 35 ºC, 20 mL CH₂Cl₂ was added and the mixture was stirred for 1 min after which it was quickly cooled down to –55 ºC. A second portion of 20 mL of CH₂Cl₂ was added and stirring was continued for 15 min. A pre-stirred (10 min) solution of (−)-(S,S)-Taniaphos (21.3 mg, 0.031 mmol) and CuBr•SMe₂ (5.1 mg, 0.025 mmol) in 2 mL of CH₂Cl₂ was added and the suspension was stirred for 10 min. Substrate 8 (322 mg, 1.335 mmol) was added dropwise in CH₂Cl₂ (3 mL) over 15 min. The reaction mixture was quenched with 3 mL MeOH after 16 h at –55 °C. A saturated aq. NH₄Cl solution (50 mL) was added, together with 50 mL ether and the mixture was brought to rt and stirred for 30 min. The layers were separated and the water layer was extracted with 2 additional portions of 20 mL ether. The organic layers were combined, dried on MgSO₄ and concentrated under reduced pressure and purified by flash chromatography (pentane/diethyl ether, 50:1) to afford 5 as a colorless oil (282 mg, 43% yield).¹H-NMR (400 MHz) δ 8.07 (dd, J = 1.3, 8.4 Hz, 2H), 7.56 (m, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.90 (m, 1H), 5.49 (m, 1H), 5.26 (m, 2H), 3.79 (s, 3H), 2.54 (m, 2H), 1.75 (m, 2H), 1.57 (m, 2H), 1.45-1.20 (m, 26H). An analytical sample of compound 5 was hydrolyzed with KOH in a mixture of EtOH/THF/H₂O to the give allylic alcohol which was used to determine the ee via the Mosher ester (ee >98%). Spectral data allylic alcohol¹H-NMR (CDCl₃, 400 MHz) δ 7.09 (d, J = 7.3 Hz, 2H), 6.82 (dd, J = 1.2, 8.3 Hz, 2H), 5.87 (m, 1H) ppm 5.16 (ddd, J = 13.8, 11.4, 1.1 Hz, 2H), 4.09 (m, 1H), 3.78 (s, 3H) 2.53 (t, J = 7.6 Hz, 2H) ppm 1.60-1.20 (br, 31H).¹³C-NMR (CDCl₃, 100.6 MHz) δ 157.50 (s), 141.31 (d), 134.99 (s), 129.20 (d), 114.50 (t), 113.60 (d), 73.27 (d), 55.23 (q), 37.04 (t), 35.02 (t), 31.75 (t), 29.73 (t), 29.66 (t, 8 x C), 29.59
(t), 29.54 (t), 29.27 (t), 25.32 (t). HRMS(ESI+) calculated for C_{36}H_{62}O_{6}^+ (M – H_{2}O) 371.3308, found 371.3294.

The spectral data of the Mosher ester from S-(+)-Mosher acid chloride and the allylic alcohol. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) δ 5.81 (m) for CH\textsubscript{2}C(O-Mosher)CH=CH\textsubscript{2}. Diastereomers from the product of racemic allylic alcohol with S-(+)-Mosher acid chloride; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) δ 5.81 (m) and 5.71 (m) for CH\textsubscript{2}C(O)CH=CH\textsubscript{2}. (ester formation with S-(+)-Mosher acid chloride results in the R-Mosher ester!).

(3R,4S,11R,E)-3-Methoxy-27-(4-methoxyphenyl)-4-methylheptacos-9-en-11-yl benzoate (38)

![Chemical structure of compound 38](image)

Compound 5 (83 mg, 0.169 mmol) was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (0.5 mL) previously degassed for 30 min by a nitrogen flow and then 6 (47 mg, 0.253 mmol, 1.5 equiv., in 0.2 mL) was added. HG-2 catalyst (2.6 mg, 2.5 mol%) was added and the resulting mixture was refluxed for 3 h. Another portion of HG-2 catalyst (2.6 mg, 2.5 mol%) was added and the resulting suspension was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed under vacuum. The resulting crude was purified by flash chromatography (CH\textsubscript{2}Cl\textsubscript{2}) to give 38 (76 mg, 69% yield, [\alpha]_D = -12.3º (c = 1.14, CHCl\textsubscript{3}) as a pure E isomer). \textsuperscript{1}H-NMR (400 MHz) δ 8.05 (d, J = 7.1 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.78 (m, 1H), 5.47 (m, 2H), 3.79 (s, 3H), 3.32 (s, 3H), 2.85 (m, 1H), 2.54 (m, 2H), 2.05 (m, 2H), 1.78 (m, 1H), 1.67 (m, 1H), 1.56 (m, 2H), 1.50-1.00 (br, 34H), 0.91 (t, J = 7.4 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100.6 MHz) δ 165.86 (s), 157.52 (s), 135.01 (s), 134.36 (d), 132.62 (d), 130.87 (s), 129.50 (d), 129.18 (d), 128.40 (d), 128.21 (d), 113.57 (d), 86.62 (d), 75.61 (d), 57.33 (q), 55.19 (q), 35.01 (t), 34.74 (d), 34.67(t), 32.40 (t), 32.17 (t), 31.73 (t), 29.65 (t, 5 x C), 29.61 (t), 29.58 (t), 29.56 (t), 29.50 (t, 2 x C), 29.39 (t), 29.25 (t), 29.22 (t), 26.93 (t), 25.22 (t), 22.31 (t), 14.68 (q), 10.07 (q). HRMS(ESI+) calculated for C_{43}H_{68}O_{6} 671.5015, found 671.5005.
(3R,4S,11R,E)-3-Methoxy-27-(4-methoxyphenyl)-4-methylheptacos-9-en-11-ol (4)

Benzoyl ester 38 (78 mg, 0.120 mmol) was dissolved in a mixture of MeOH, THF and H₂O (1:1:1, 5 mL) and 10 eq. KOH (67 mg, 1.20 mmol) was added. The mixture was stirred for 17 h at rt. Diethyl ether was added (10 mL) together with 5 mL H₂O. After phase separation and extraction of the aqueous phase with 3 portions of diethyl ether (10 mL), the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (pentane/diethyl ether, 1:1) to afford 4 as a white solid (51 mg, 78% yield). ¹H-NMR (400 MHz, CDCl₃) δ 7.09 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.62 (td, J = 6.7, 15.3 Hz, 1H), 5.45 (dd, J = 7.1, 15.3 Hz, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 2.87 (m, 1H), 2.54 (m, 2H), 2.02 (m, 2H), 1.67 (m, 2H), 1.52-0.92 (br, 38H), 0.91 (t, J = 7.4 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). ¹³C-NMR (CDCl₃, 100.6 MHz) δ 157.50 (s), 134.99 (s), 133.11 (d), 131.93 (d), 129.16 (d), 113.56 (d), 86.66 (d), 73.13 (d), 57.33 (q), 55.16 (q), 37.32 (t), 34.99 (t), 34.76 (d), 32.39 (t), 32.13 (t), 31.72 (t), 29.64 (t, 7 x C), 29.58 (t, 2 x C), 29.55 (t), 29.49 (t), 29.44 (t), 29.24 (t), 26.99 (t), 25.47 (t), 22.32 (t), 14.75 (q), 10.04 (q). HRMS(ESI⁺) calculated for C₃₀H₆₀O₃ (M + Na⁺) 567.4753, found 567.4738.

(R)-1-((2R,3R)-3-((SS,6R)-6-Methoxy-5-methyloctyl)oxiran-2-yl)-17-(4-methoxyphenyl)heptadecan-1-ol (39)

Ti(i-PrO)₄ (28 μL, 0.092 mmol, 1 equiv.) and (–)-D-diethyl tartrate (19 μL, 0.110 mmol, 1.2 equiv.) were dissolved in CH₂Cl₂ (1 mL) containing activated molecular sieves. The resulting mixture was stirred for 5 min at room temperature and then a solution of 4 (50 mg, 0.092 mmol) in CH₂Cl₂
(1.5 mL) was added. After stirring the resulting mixture for 30 min, t-butyldihydroperoxide 5.0-6.0 M in decane (37 µL, 0.184 mmol, 2.0 equiv.) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of D,L-tartaric acid (10%) and the two layers obtained were separated. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried (Na₂SO₄). The solvents were removed under reduced pressure and the crude was purified by flash chromatography (pentane/diethyl ether, 1:1) to give 39 (37 mg, 0.151 mmol, 72%).

¹H-NMR (400 MHz) δ 7.09 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 3.78 (s, 3H), 3.78 (m, 1H), 3.33 (s, 3H), 2.99 (m, 1H), 2.86 (m, 1H), 2.76 (m, 1H), 2.53 (m, 2H), 1.70-1.10 (br, 42H), 0.91 (t, J = 7.3 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H).

¹³C-NMR (CDCl₃, 100.6 MHz) δ 157.50 (s), 135.06 (s), 129.21 (d), 113.61 (d), 86.66 (d), 68.50 (d), 60.96 (d), 57.40 (q), 55.24 (q), 54.90 (d), 35.03 (t), 34.81 (d), 33.55 (t), 32.51 (t), 31.76 (t), 31.63 (t), 29.68 (t, 8 x C), 29.60 (t), 29.55 (t), 29.52 (t), 29.28 (t), 27.33 (t), 26.40 (t), 25.34 (t), 22.37 (t), 14.84 (q), 10.02 (q).

(3R,4S,10S,11R)-3-Methoxy-27-(4-methoxyphenyl)-4-methylheptacosane-10,11-diol (41)

Red-Al 3.5 M in toluene (51 µL, 0.178 mmol, 5.0 equiv.) was added to a solution of 39 (20 mg, 0.036 mmol) in THF (2 mL) and the resulting mixture was stirred at room temperature for 24 h. The reaction was quenched with an aqueous solution of Rochelle salt and the mixture extracted with diethyl ether. The combined organic layers were dried (MgSO₄) and concentrated. The product was purified by flash chromatography (pentane/diethyl ether, 1:1) to give a mixture of diols 40 and 41 in a 1:10 ratio (19 mg, 94%) as a white solid. ¹H-NMR (400 MHz) δ 7.09 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.60 (m, 2H), 3.33 (s, 3H), 2.87 (ddd, J = 4.1, 5.2, 7.5 Hz, 1H), 2.53 (m, 2H), 1.90 (m, 2H), 1.72-1.00 (br, 43H), 0.91 (t, J = 7.4 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). 1,3-diol chemical shift (CHOH) multiplet δ 3.94, 1,2-diol chemical shift (CHOH) multiplet δ 3.60. ¹³C-NMR (CDCl₃, 100.6 MHz) δ 157.52 (s), 164
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135.03 (s), 129.19 (d), 113.59 (d), 86.69 (d), 74.66 (d), 74.60 (d), 57.35 (q), 55.21 (q), 35.01 (d), 34.77 (d), 32.59 (d), 32.56 (d), 31.90 (d), 31.74 (d), 31.21 (d), 31.15 (d), 29.95 (d), 29.90 (d), 29.66 (d, 4 x C), 29.58 (d, 2 x C), 29.50 (d), 29.26 (d), 27.44 (d), 26.00 (d), 25.96 (d), 22.67 (d), 22.32 (d), 14.75 (q), 10.06 (q). HRMS(ESI+) calculated for $\text{C}_{36}\text{H}_{66}\text{O}_{4}$ ($\text{M} + \text{Na}^+$) 585.4859, found 585.4825.
5.7 References


4 Stodola, F. H.; Anderson, R. J. Biol. Chem. 1936, 114, 467-472.


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22 Dr. Eva Casas-Arce worked as a post-doctoral researcher in group of A.J. Minnaard and B. L. Feringa at the Stratingh Institute for Chemistry, Groningen, The Netherlands.


28 The diastereomeric excess was measured by 19F-NMR spectroscopy of the corresponding Mosher esters.


36 By '1H-NMR, only the E-isomer was detected.


38 Since aldehyde 10 decomposes easily, it is convenient to store it as the precursor alcohol 30.

