Total syntheses of (–)-Borrelidin and (–)-Doliculide and the development of the catalytic asymmetric addition of Grignard reagents to ketones
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 2

Catalytic Asymmetric Formal Synthesis of (−)-Borrelidin

In this chapter the asymmetric catalytic formal synthesis of (−)-Borrelidin is described. Iterative copper-catalyzed asymmetric conjugate addition reactions and asymmetric hydrogenation are key strategic elements in this synthesis of Borrelidin.

2.1 Introduction

Borrelidin, an antibiotic discovered as a metabolite of *Streptomyces rochei* and *Streptomyces sp. C2989* (Figure 1) is a biologically intriguing and structurally unique 18-membered macrolide (Figure 2). First isolated by Berger and co-workers in 1949 from a soil sample of *Streptomyces rochei*\(^1\), Borrelidin displayed antibiotic activity against *Borrelia* (a genus of bacteria) and was subsequently identified in related *Streptomyces* species. Keller-Schierlein elucidated the planar architecture of Borrelidin by means of chemical degradation,\(^2\) followed by Anderson et al. who assigned the absolute configuration of its stereocenters by X-ray crystallography.\(^3\)

![Figure 1: Streptomyces sp](image1.png)

![Figure 2: Structure of Borrelidin](image2.png)

Initial biological screening indicated that Borrelidin exhibits broad antiviral\(^4\) and antibacterial activity,\(^5\)\(^6\) which presumably arises from its inhibition of threonyl tRNA synthetase (ThrRS) and protein synthesis.\(^8\)\(^9\)\(^10\)\(^11\) The nitrile, lactone and probably the hydroxyl functions in Borrelidin are essential for antimicrobial activity.\(^13\) More recently, Borrelidin was found to inhibit cyclin-dependent kinase (CDK) and thus displays potent antimitotic properties and anti-tumor activity at low micromolar concentrations.\(^14\) Gene expression profiling of *Saccharomyces cerevisiae* revealed that Borrelidin up-regulated GCN4 leucine\(^15\) zipper mRNA synthesis, and this in turn induced the expression of amino acid biosynthetic enzymes. Equally impressive are reports that Borrelidin inhibits angiogenesis (a key process in the spread of malignant tumors) in rat aorta models at subnanomolar concentrations (IC\(_{50}\)=0.4 ng/mL) through a yet unknown mechanism of action.\(^16\)

Furthermore, Borrelidin was found to interfere with capillary tube formation, possibly through anti-angiogenesis effects that are mediated through the caspase activation pathways. This result implies an alternative biological target...
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for Borrelidin, which may have implications for anticancer therapy.\(^9\) Recently, Borrelidin was found to exhibit potent antimalarial activity against chloroquine-resistant strains, both in vitro and in vivo.\(^{17}\) Borrelidin’s anti-angiogenesis activity is of significance to biological and medicinal research, yet its large-scale study and application have been hampered due to its exorbitant price, owing to its low availability from fermentation based synthesis.

2.2 Reported synthetic strategies

The dense arrangement of stereogenic centers in this 18-membered macrocycle, together with the peculiar and sensitive bis-unsaturated nitrile moiety, has attracted considerable attention of organic chemists.\(^{13,18}\)

\[\text{Scheme 1: General retrosynthetic scheme of Borrelidin}\]

In the retrosynthesis applied by Omura et al.,\(^ {19}\) 1 is disconnected basically into two parts (Scheme 1). The Upper part A, containing the poly-1,3-methyl array flanked by two hydroxy groups, and the Lower part B containing the disubstituted cyclopentyl motif together with the bisunsaturated nitrile. First the groups of Morken\(^ {20}\) and Hanessian\(^ {21}\), reported total syntheses of the compound, closely followed by the groups of Theodorakis\(^ {22}\) and Omura\(^ {19}\) (Table 1). The strategies reported, relied essentially on starting materials from the chiral pool or chiral auxiliaries, albeit with moderate to good enantio and diasteroselectivities (Table 1).
Table 1 Methods for the synthesis of Borrelidin

<table>
<thead>
<tr>
<th>Contributors, year</th>
<th>Upper half</th>
<th>Lower half</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morken et al. 2003</td>
<td>catalysis and chiral pool, dr = 6:1</td>
<td>chiral auxiliaries</td>
</tr>
<tr>
<td>Hanessian et al. 2003</td>
<td>chiral pool, dr = 10:1</td>
<td>chiral pool</td>
</tr>
<tr>
<td>Theodorakis et al. 2004</td>
<td>chiral auxiliaries</td>
<td>enzymes</td>
</tr>
<tr>
<td>Omura et al. 2004</td>
<td>Enzyme catalysis and chiral pool</td>
<td>chiral auxiliaries</td>
</tr>
<tr>
<td>Haddad et al. 1997</td>
<td>chiral pool and catalysis</td>
<td>--</td>
</tr>
<tr>
<td>Negishi et al. 2005</td>
<td>Catalytic, dr = 7:1</td>
<td>--</td>
</tr>
</tbody>
</table>

The first synthetic study towards the upper part (A) of Borrelidin was reported by Haddad and co-workers. More recently, the groups of Negishi and Breit achieved the synthesis of Upper part A, by an iterative catalytic and a chiral reagent based approach, respectively. In view of the need for a more efficient and cost-effective synthesis of Borrelidin and derivatives, we were challenged to develop a route in which all formed chiral centers would be under catalyst control. This "catalytic total synthesis" should lead to a significantly improved overall yield and avoid the tedious separation of diastereomers.

2.3 Strategic synthetic analysis

The disconnection of Borrelidin into upper part A and lower part B was adopted from Omura et al. The synthetic analysis for upper part A (Scheme 2) starts with the formation of the 1,3-dimethyl arrays in compound 13a (the stereochemistry of methyl's is identical, going from 20 to 13a the molecule is turned around). We were keen to apply our iterative catalytic asymmetric conjugate addition approach starting from bifunctional substrate 3 which can be made in three steps from glycol.
Catalytic asymmetric formal synthesis of (–)-Borrelidin

This method has proven its effectiveness in the total synthesis of a variety of natural products containing all-syn deoxypentionate units. Particularly challenging would be the introduction of a methyl with 1,3 anti-stereochemistry at the left end of A, following three syn methyl groups, owing to the intrinsic substrate preference for an all-syn array. The β-hydroxy acid unit was planned to be derived from the corresponding keto ester 20 (Scheme 2) using asymmetric hydrogenation.

In the reported synthesis of part B, the disubstituted cyclopentyl fragment has been invariably prepared using a chiral auxiliary, e.g. menthol, or via kinetic resolution. This, however, requires a lengthy synthesis route with moderate overall yields. After having pursued several routes (see the next paragraphs), it was envisioned, that starting from 36 (Scheme 3), asymmetric hydrogenation would install both chiral centers at once in an anti-relationship (37). Although the reported
enantioselectivities for this transformation were not sufficient, this presented an appealing opportunity and would translate into a significant improvement of the synthesis. Further functional group manipulation would result in aldehyde 26. Finally, we planned a challenging alkene metathesis which starts from 27 in the synthesis of the cyanodiene fragment.

2.4 Results and Discussion

2.4.1 The upper part A: an all-catalytic approach

Earlier work by our group has demonstrated that the CuJosiphos-catalyzed iterative asymmetric conjugate addition of MeMgBr leads to excellent stereochemical control in the synthesis of 1,3-methyl arrays. This has been successfully exploited in the first total synthesis of mycocerosic acid and phthioceranic acid.28,29 Banking on this efficient and robust methodology, 2 (Scheme 2, TBDPS is tert-butyldiphenylsilyl) was chosen as the starting material as it possesses a protected hydroxy function at the terminus of the unsaturated thioester, which remains inert under the iterative reaction conditions (conjugate addition, DIBAL-H reduction, and Wittig or Horner-Wadsworth-Emmons (HWE) reaction). 2 is conveniently prepared from ethylene glycol in three steps.
Substrate 2 (Scheme 4) gives excellent yield, enantioselectivity (96%, 98% ee) and complete regioselectivity in the 1,4-addition of MeMgBr with 1 mol% of CuBr/4. The reaction was conveniently carried out on 15 g scale. Bifunctional building block 3 was reduced to the corresponding aldehyde 5 and extended by HWE reaction to give thioester 6. The nearly exclusive syn-selectivity (syn/anti 98:2) of the second conjugate addition, leading to dimethyl thioester 7a, was deduced from the 1H-NMR spectrum in comparison with anti-dimethyl thioester 7b, prepared using ent-4 (Scheme 4). By repeating once more this sequence of reduction, HWE olefination with (EtO)2P(O)CH2COMe to result in α,β-unsaturated ketone 12.
We were pleased to see that using CuBr/ent-4 as the catalyst, introduction of the fourth methyl group to 12 (Scheme 5) proceeded with excellent anti-selectivity (≥99:1) to give 13a. Remarkably, the use of CuBr/4 resulted in epimer 13b with identical excellent selectivity, demonstrating complete control of the catalyst in steering the chirality of the newly formed stereocenter. Such an overwhelming catalyst control, overriding the strong natural preference of the substrate for syn-addition, is unprecedented. As a consequence of the excellent stereoselectivities obtained throughout this part of the synthesis, the need for laborious separation of diastereomers is completely avoided.

Scheme 5: Synthesis of the upper part (A) of Borrelidin
The conversion of \( 13a \) to alcohol \( 15 \) (Scheme 6) was efficiently accomplished via an optimized Baeyer-Villiger oxidation (BVO) and subsequent hydrolysis. Overall, \( 15 \) was prepared in 33% yield from \( 2 \), a considerable improvement compared to the literature.\(^{19,30-32}\) Protection of the hydroxy group as its tetrahydropyranyl (THP) ether, followed by deprotection of the TBDPS ether and tetrapropylammonium per ruthenate (TPAP) oxidation of the formed alcohol, efficiently produced aldehyde.
18. Reformatsky-type reaction of 18, mediated by SmI$_2$, followed by oxidation of the resulting hydroxy ester afforded the corresponding $\alpha$-keto ester 20. Gratifyingly, catalytic asymmetric hydrogenation of 20 employing 1 mol% of ($R$-)[RuCl(Tol-BINAP)]$_2$(µ-Cl)$_2$[NH$_2$Me$_2$] afforded 21 in 90% yield, with an excellent de of >99%. Admittedly, a catalytic asymmetric Reformatsky reaction would have been of value here, but the current status of that approach does not allow reliable application on more advanced substrates, yet. Protection of 21 with tert-butyldimethylsilyl triflate (TBDMSOTf), followed by basic hydrolysis resulted in 21. This is the first catalytic asymmetric synthesis of the upper part of Borrelidin. This concise “catalytic synthesis” of 21 affords a considerably higher overall yield compared to the reported routes and is amendable to scale-up.

2.4.2 The lower part B: Literature, Challenges, Detouring and Rerouting

2.4.2.1 Chiral auxiliary approach

The synthesis starts from the known chiral diol 24, which is derived from succinic anhydride 22 by Yamamoto asymmetric carbocyclization (Scheme 7). Para-methoxybenzyl (PMB) monoprotection of diol 24 followed by Dess-Martin oxidation gave aldehyde 26. Chelation controlled allylation of 26 with allyltrimethylsilane catalyzed by the Lewis acid MgBr$_2$•Et$_2$O afforded homoallylic alcohol 27 with high yield and excellent stereoselectivity (anti/syn 20:1) as reported by Omura et al. Starting from 27, we envisioned that the use of olefin metathesis could drastically shorten the existing routes to 28 and even avoid protection of the secondary alcohol. Direct and stereoselective installation of the cyanodiene unit via this approach turned out to be impossible however; invariably Z,E-mixtures were obtained. As the cross metathesis of unprotected homoallylic alcohols with methyl acrylate has been documented, we decided to use this as a starting point. We were very pleased to see, that cross-metathesis of homoallylic alcohol 27 with acrylic diethyl acetal using Hoveyda-Grubbs 2$^{nd}$ generation catalyst, followed by careful acidic workup, efficiently produced $E$-28 as the only isomer in 75% isolated yield! Subsequent HWE olefination of 28 with ($O_2$)$_2$P(O)(CH(Br)CN$^{13,36}$ completed the synthesis of fragment 28. The stereoselectivity for the cis nitrile in this reaction is the result of the steric effects; the bromo substituent is bigger than the nitrile and leads to the thermodynamically stable trans product. The overall yield for this present chiral auxiliary route is 23% over 8 steps compared to Omura’s approach with an overall 12% yield over 12 steps.
2.4.2.2 The lower part: a first attempt towards an all catalytic route

The main goal is reminded that comprises the development of catalytic route to the Lower part. The synthetic direction for the catalytic asymmetric synthesis of lower part B was planned via known compound 27 shown in Scheme 8. A proline catalyzed hydroxymethylation of 29 with formaldehyde was planned to give 30. Protection of the primary alcohol followed by 1,2-addition of vinylmagnesium chloride to the ketone would give the corresponding tertiary alcohol 31.
Subsequent acetylation and palladium catalyzed allylic substitution with malonate would result in compound 33. Decarboxylation of 33 under Krapcho conditions followed by selective epoxidation of the alkene and opening of the formed epoxide should result in 35. This would give the desired compound 27 after reduction and alcohol elimination of 35. As previously described, upon subsequent metathesis and HWE reaction of 35 lower part (B) would be obtained.

As said, the synthesis had to commence with a proline catalysed asymmetric α-hydroxymethylation of cyclopentanone 29 (scheme 9) with formaldehyde in DMSO. This reaction is well established with cyclohexanone as the substrate, but disappointingly in the case of cyclopentanone not the desired product 30 but rather dimerization of cyclopentanone took place invariably.
To nevertheless pursue the planned approach and produce an enantiopure, we started a careful study of the asymmetric hydrogenation of 36 (Table 2, Scheme 10). This asymmetric hydrogenation has been reported by Noyori et al.\textsuperscript{38,39} using [RuCl\(_2\)(p-cymene)]\(_2\) and BINAP as the chiral ligand, giving 37 in 98% yield, 92% ee and an anti/syn ratio of 99:1. Catalyst optimization by variation of the ligand (Table 2 and Figure 3) initially failed; the depicted (S\(_S\),S\(_S\),S\(_S\))-phosphoramidite, Josiphos, and Taniaphos all gave incomplete conversion. Tol-BINAP, and xyl-BINAP in combination with 1,2-diphenyl-1,2-ethylenediamine (DPEN) and 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine (DAIPEN), however, gave a significant improvement in ee and dr. Finally, it turned out that by applying 3,5-xyl-BINAP as the chiral ligand in combination with [RuCl\(_2\)(p-cymene)]\(_2\) as the metal precursor, the outcome could be improved to an excellent 98% yield, 97% ee and an anti/syn ratio of >99:1. This strategy is very attractive for natural product synthesis as it provides excellent selectivities and is easily scalable to multi-gram quantities.
Table 2: Catalyst optimization for the asymmetric hydrogenation of 36.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Ruthenium precursor</th>
<th>Yield</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>BINAP</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>95%</td>
<td>96/4</td>
<td>90%</td>
</tr>
<tr>
<td>Phosphoramidite</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>10%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Josiphos</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>30%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Taniaphos</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>25%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>L1</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>90%</td>
<td>97/3</td>
<td>94%</td>
</tr>
<tr>
<td>L2</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>95%</td>
<td>97/3</td>
<td>95%</td>
</tr>
<tr>
<td>Tol-BINAP</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>96%</td>
<td>98/2</td>
<td>94%</td>
</tr>
<tr>
<td>3,5-Xylyl-BINAP</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>98%</td>
<td>99/1</td>
<td>96%</td>
</tr>
<tr>
<td>Tol-BINAP</td>
<td>[RuI₂(p-cymene)]₂</td>
<td>97%</td>
<td>99/1</td>
<td>95%</td>
</tr>
<tr>
<td>3,5-Xylyl-BINAP</td>
<td>[RuI₂(p-cymene)]₂</td>
<td>98%</td>
<td>99/1</td>
<td>97%</td>
</tr>
</tbody>
</table>

Optimized reaction conditions: (R)-3,5-xylyl-BINAP (0.6 mol%), [RuI₂(p-cymene)]₂ (0.25 mol%), 100 bar H₂, CH₂Cl₂, 48 h, 98% yield, anti/syn 99:1, 97% ee; L1= (R)-3,5-Xylyl-BINAP [(R)-DPEN], L2= (R)-3,5-Xylyl-BINAP [(R)-DAIPEN].
Catalytic asymmetric formal synthesis of (−)-Borrelidin

Figure 3: Ligands that were used in asymmetric hydrogenation

Reduction of 37 with LiAlH₄ followed by protection of the formed primary alcohol and oxidation of the remaining secondary alcohol resulted in compound 38 in 75% yield over three steps (Scheme 10). Addition of vinylmagnesium chloride, transmetallated with CeCl₃, to ketone 38 gave the desired tertiary alcohol 39 in 93% yield as a single diastereomer (relative stereochemistry). Without CeCl₃ only starting material was recovered. Acetylation of 39 resulted compound 40 in 89% yield. The key reaction of 40, a palladium(0) catalysed allylic substitution with malonate as the nucleophile, gave the desired compound 41 in 68% yield but as an unexpected 1:1 mixture of E and Z isomers. This could perhaps result from a facile π-π-π palladium allyl complex, stabilized by neighboring oxygen of the substrate (Figure 4).

Figure 4: a) π-π-π Process involving a palladium-tertiary carbon bond. b) Five membered ring formation of the neighboring group oxygen present in the molecule
Decarboxylation of 41 under Krapcho conditions\(^\text{42}\) resulted in 42 in 81% yield, as expected as the same 1:1 mixture of E and Z isomers. Attempts to induce stereoselectivity in the allylic substitution by using the other enantiomer of BINAP failed.

Scheme 10: Synthesis of the lower part of Borrelidin (B) via a catalytic asymmetric approach

81% yield
1:1 mixture of E & Z isomers

Scheme 10: Synthesis of the lower part of Borrelidin (B) via a catalytic asymmetric approach
As a second attempt for the lower part, the synthesis started with compound 38 (Scheme 11). Wittig reaction failed to give 43 directly and although reaction of 38 with Tebbe’s reagent \((\text{Cp}_2\text{Ti}CH_2\text{Cl} \text{AlMe}_2)\) resulted in alkene 44 in 82% yield, cross metathesis of 44 with Grubbs catalyst did not give the desired compound 43. As these route overall required more steps than the previously described chiral auxiliary approach, and due to the disappointing result of the allylic substitution, we considered a new route based on 37.

2.4.2.3 The lower part: A third, successful, approach

With 37 now readily available, we choose for a one-carbon homologation in order to arrive at 26 (Scheme 12). Reduction of 37 to 46 (Scheme 12) was efficiently accomplished via THP-protection of the secondary alcohol and reduction of the ester in 89% yield over two steps. Primary alcohol 46 was PMB-protected (the PMB protecting group was used to compare the formed compound with PMB protected 26 which is a known compound), followed by deprotection of the secondary alcohol with pyridinium \(p\)-toluenesulphonate (PPTS) giving 48, which underwent subsequent tosylation and nucleophilic substitution with cyanide,
resulting in 50. The vicinal stereochemistry of the substituents in 50 was confirmed to be cis, as expected, by $^1$H-NOE experiments. Reduction of syn-50 with DIBAL-H, followed by aqueous work up, led selectively to the desired anti-aldehyde 26 (anti/syn $>15:1$) in 80% yield. This in situ epimerization leading to the required anti-compound was hoped for and indeed takes place readily under the reaction conditions. As described earlier, chelation controlled allylation, metathesis and HWE reaction completed the first catalytic asymmetric synthesis of lower part B. This concise “catalytic synthesis” of B affords a considerably higher overall yield than the reported routes and is readily scaled up.

Scheme 12: Synthesis of the lower part (B) of Borrelidin via a catalytic asymmetric approach

The characterization data of A and B thus synthesized are in excellent agreement with those reported in the literature. The remainder of the synthesis (Scheme 13) can be carried out as described by Omura et al.31.
2.4.3 Coupling and ring closing of the upper and the lower part

As reported by Omura et al.,\textsuperscript{30} the esterification of upper part \textbf{A} and lower part \textbf{B} (Scheme 14) was performed under Yamaguchi conditions to give the corresponding ester 51. This ester was converted into alcohol 52, and subsequently into key intermediate 53 by THP deprotection followed by TPAP oxidation in 72% yield over three steps.

Next, we meticulously explored the \textit{SmI}_2-mediated intramolecular Reformatsky-type reaction of 53 as reported by Omura. In this reaction, bromine radical abstraction is followed by isomerization of the resulting alkenyl radical, intramolecular addition to the aldehyde function and further reduction to the alkoxide. Treatment of 53 with the reported 3:2 ratio of \textit{SmI}_2 and HMPA in THF at –78 °C gave however no desired product observed (mainly debrominated, homo coupling and polymer type products). A series of attempts was made but with no success in obtaining the desired cyclized product. Further investigation is needed to modify the conditions of this Reformatsky type reaction. This will require the freshly prepared \textit{SmI}_2 and perform the reaction by using different concentration of the reaction mixtures.
Scheme 14: Coupling of upper part (A) and lower part of Borrelidin (B)
Catalytic asymmetric formal synthesis of (–)-Borrelidin

2.5 Summary and concluding remarks

In this chapter the first efficient catalytic asymmetric formal total synthesis of Borrelidin \(1\) is described. This synthesis is significantly shorter and produces \(1\) in a much higher yield than reported until now, at least formally. The present approach takes maximum benefit of asymmetric catalysis, in particular the copper-catalyzed asymmetric conjugate addition of methylmagnesium bromide and the ruthenium-catalyzed asymmetric ketone hydrogenation. Due to the excellent stereoselectivities, separation of diastereomers is obsolete. This catalytic approach paves the way for the preparation of Borrelidin analogues, in particular for stereoisomers as well as modifications of the carbon skeleton.

A problem resides, however, in the inability to reproduce the ring closing Reformatsky-type reaction reported by Omura. As this reaction, using a variety of conditions, failed to provide even a trace of the desired product, it must be concluded that this is not the way forward and that an alternative ring closing reaction should be used. This is not hopeless; Omura and co-workers themselves have reported several related ring closures that, albeit with some additional steps, provide Borrelidin using the same upper and lower part.

2.6 Experimental section

General

All reactions were carried out under nitrogen atmosphere using dried glassware. All solvents were dried and distilled before use according to standard procedures. All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by staining with Seebach’s reagent: a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H\(_2\)O (500 mL) and H\(_2\)SO\(_4\) (25 mL). High resolution mass spectra (HRMS) were recorded on a AEI-MS-902 and FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. \(^1\)H, \(^{13}\)C and APT spectra were recorded on a Varian AMX400 (400, 100.59 MHz, respectively) using CDCl\(_3\) as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl\(_3\): \(\delta\) 7.26 for \(^1\)H, \(\delta\) 77.23 for \(^{13}\)C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmid + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Enantiomeric excess was determined by HPLC (Chiralcel OB, 250\(\times\)4.6, 10 µm), (Chiralcel OD, 250\(\times\)4.6, 10 µm) and capillary GC analysis (Chiralcel A-TA column (30 m x 0.25 mm) using a flame ionization detector and compared with racemic products.
Chapter 2

Synthesis of the upper part of Borrelidin

(E)-4-(tert-Butyl-diphenyl-silanyloxy)-but-2-enethioic acid S-ethyl ester (3)

To 20 ml of glycol (358 mmol) in 180 ml of dry THF was added 2.2 g (32.2 mmol) imidazole. Then 9.3 g (33.8 mmol) tert-butyldiphenylsilyl chloride was added to the mixture under nitrogen atmosphere. The resulting mixture was stirred for 24 h at rt, quenched with water and extracted with diethyl ether. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (elu-ent pentane/EtOAc 4:1) to afford 8.5 g (83% yield) of monoprotected glycol a as a colorless oil. A solution of a (8.5 g, 28.3 mmol) and 1.3 equiv of iodoxybenzoic acid (IBX) (10.3 g, 36.3 mmol) in 180 mL of EtOAc was refluxed for 24 h and cooled to rt. IBX and benzoic acid were filtered off through Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give aldehyde b (8.3 g, 27.8 mmol) which was used in the next step without purification. A solution of b (8.3 g, 27.8 mmol) and Ph₃PCHCOSEt (12.2 g, 33.4 mmol) in CH₂Cl₂ (120 mL) was refluxed for 24 h. The solution was concentrated under reduced pressure and purified by flash chromatography (elu-ent pentane/ether 40:1) to afford ĭ as a colourless oil (8.5 g, 80% yield).

1H-NMR (400 MHz, CDCl₃): δ ppm 7.66 (dd, J = 7.7, 1.3 Hz, 4H), 7.43-7.35 (m, 6H), 6.89 (bt, J = 15.3, 3.2 Hz, 1H), 6.55 (dt, J = 14.9, 2.3 Hz, 1H), 4.37-4.32 (m, 2H), 2.98 (q, J = 7.6 Hz, 2H), 1.90 (t, J = 7.3 Hz, 3H), 1.08 (s, 9H).

13C-NMR (100.6 MHz, CDCl₃): δ 190.07 (s), 142.70 (d), 135.40 (d), 132.86 (s), 129.86 (s), 127.80 (d), 126.73 (d), 26.74 (q), 19.45 (s), 14.80 (q).

HRMS, calcd for C₁₈H₁₉O₂SSi (M–tert-butyl) 327.0875 found 327.0875.

(-)-(R,S)-Josiphos 4-CuBr complex (67.7 mg, 0.091 mmol, 1 mol%) was dissolved in t-BuOMe (50 mL) under nitrogen. The solution was cooled to –78 °C and methylmagnesium bromide (3.64 ml, 10.93 mmol, solution in diethyl ether) was added drowse over 10 min. After stirring for 10 min, a solution of thioester 2 (3.5 g, 9.11 mmol) in t-BuOMe (15 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at –75 °C for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (elu-ent pentane/ether 40:1) to afford 3 as a colourless oil (3.50 g, 96% yield, 98% ee)
Catalytic asymmetric formal synthesis of (–)-Borrelidin

1,4- addition on 15 g scale:
(R,SFe)-Josiphos 4•CuBr complex (290 mg, 0.39 mmol, 1 mol%) was dissolved in t-BuOMe (214 mL) under nitrogen. The solution was cooled to –85 °C and methylmagnesium bromide (15.6 ml, 46.84 mmol, solution in diethyl ether) was added dropwise over 20 min. After stirring for 20 min, a solution of thioester 2 (15 g, 39.0 mmol) in t-BuOMe (64 mL) was added via syringe pump over 2 h. The reaction mixture was stirred at –85 °C for 22 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford 3 as a colourless oil (95 % yield, 98% ee).

E.e. and absolute configuration of 3 were determined by removal of the tert-butyldiphenylsilyl group. To 20 mg (0.05 mmol) of 3 in 0.5 ml of THF under nitrogen and to the mixture (0.1 mmol, 2 eq) of TBAF were added and stirred for 3-4h. The reaction mixture was filtered over a silica plug (eluent pentane/ether 2:1) to afford 3a. The enantiomeric excess was determined by GC analysis [Chiraldex AT-A (30.0 m x 0.25 mm), 1.0 ml/min, initial temp. 50 °C then 5 °C/min to final temp. 170 °C, 19.5 min (major), 19.7 (minor), shows 98% ee]. As an alternative method for e.e determination: To (103 mg, 0.25 mmol) 3 in 4 ml THF, LiAlH₄ (1M in THF, 3 eq, 0.77 ml) was added at 0 °C and stirred the reaction mixture 2h at rt. After workup to afford a crude compound 3b. To 3b in 2 ml pyridine, Benzoyl chloride (3.5 eq, 126 mg) was added, and the reaction mixture was heated to reflux for 4h and allowed to warm the reaction mixture to rt. To the crude 5 ml toluene was added, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 50:3) to afford 3c as a colorless oil. Determination of enantiomeric excess was achieved by HPLC (Chiralcel OB, 250*4.6, 10 μm), Eluent 95/5 heptane/IPA, 23.38 min (major), 28.78 min (minor) 98% ee. [Į]D = –8.5 (c = 1.7, CHCl₃).

1H-NMR (400 MHz, CDCl₃): δ 7.66 (dd, J = 6.8, 1.4 Hz, 4H), 7.47-7.35 (m, 6H), 3.54 (dd, J = 10.0, 5.3 Hz, 1H), 3.46 (dd, J = 9.9, 6.3 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.83 (dd, J = 14.5, 5.3 Hz, 1H), 2.38 (dd, J = 14.5, 8.4 Hz, 1H), 2.28 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.15 (s, 9H), 0.97 (d, J = 6.0 Hz, 3H). 13C-NMR (100.6 MHz, CDCl₃): 199.2 (s), 135.62 (d), 133.63 (s), 129.58 (d), 127.50 (d), 67.90 (t), 47.75 (t), 33.76 (d), 26.84 (q), 23.27 (t), 19.28 (s), 16.40 (q), 14.86 (q). HRMS, calcd for C₁₉H₂₃O₂SSi (M-tert-butyl) 343.1188 found 343.1183.
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The combined organic phases were dried over MgSO₄, concentrated under reduced pressure to yield crude aldehyde and purified by flash chromatography (eluent pentane/ether 40:1) to give 5 which was used in the next step without complete removal of the eluent. A solution of 5 and (EtO)₂POCH₂COEt (2.5 g, 10.42 mmol, 1.5 eq) dissolved in THF (40 mL) under nitrogen and cooled to 0 °C was added slowly at 0 °C to the reaction mixture and mixture was stirred for 10 min at rt. Then the aldehyde was dissolved in 5 mL THF and the reaction mixture is stirred at rt for 10 h. the reaction mixture was washed with distilled water and extracted with diethyl ether. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude olefin. Purification by flash chromatography (eluent pentane/ether 40:1) afforded α,β-unsaturated thioester 6 as a colourless oil (2.4 g, 81% yield over 2 steps). [α]D₂₅ = –6.25 (c = 1.81, CHCl₃).

1H-NMR (400 MHz, CDCl₃): 7.65 (d, J = 7.9 Hz, 4H), 7.49-7.35 (m, 6H), 6.87 (dt, J = 15.4, 7.6 Hz, 1H), 3.53 (dd, J = 10.0, 5.4 Hz, 1H), 3.46 (dd, J = 10.0, 6.4 Hz, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.05 (m, 1H), 1.92-1.84 (m, 1H), 1.29 (t, J = 7.4 Hz, 3H), 2.44 (m, 1H), 2.05 (m, 1H), 1.41 (m, 1H), 1.29 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H).

13C-NMR (100.6 MHz, CDCl₃): 190.1 (s), 143.89 (d), 135.60 (d), 133.70 (s), 129.95 (d), 129.61 (d), 127.64 (d), 68.07 (t), 35.97 (t), 35.42 (d), 26.86 (q), 23.03 (t), 19.29 (s), 16.46 (q), 14.91 (q). HRMS, calcd for C₂₁H₂₅O₂SSi (M–tert-butyl) 369.1331 found 369.1345.

(−)-(3R,5S)-6-(tert-Butyl-diphenyl-silanyloxy)-3,5-dimethyl-hexanethioic acid S-ethyl ester (7a)

TBOSE (R,S)-Josiphos 4•CuBr complex (70 mg, 0.0951 mmol, 1 mol%) was dissolved in t-BuOMe (45 mL) under nitrogen. The mixture was cooled to –75 °C and methylmagnesium bromide (11.43 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester 6 (4.05 g, 9.51 mmol) in t-BuOMe (18 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at –75 °C for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with 3 portions of diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluuent pentane/ether 40:1) to afford 7b as a colourless oil (3.75 g, 90% yield), syn/anti ratio by NMR = 98.2. [α]D₂₅ = –4.86 (c = 1.53, CHCl₃). 1H-NMR (400 MHz, CDCl₃): 7.68 (dd, J = 7.6, 1.5 Hz, 4H), 7.41 (m, 6H), 3.50 (dd, J = 9.9, 5.5 Hz, 1H), 3.43 (dd, J = 9.5, 6.4 Hz, 1H), 2.87 (q, J = 7.4 Hz, 2H), 2.52 (dd, J = 14.4, 5.1 Hz, 1H), 2.25 (dd, J = 14.4, 8.8 Hz, 1H), 2.08 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.24 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 1.03 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). 13C-NMR (100 MHz, CDCl₃): 199.3 (s), 135.7 (d), 133.94 (s), 129.50 (d), 127.57 (d), 68.74 (t), 51.19 (t), 40.79 (t), 33.16 (d), 28.69 (t).
Catalytic asymmetric formal synthesis of (–)-Borrelidin (d), 26.88 (q), 23.26 (t), 20.28 (q), 19.29 (s), 17.54 (q), 14.82 (q). HRMS, calcld for C_{22}H_{29}O_{2}SSi (M–tert-butyl) 385.1658 found 385.1668.

(–)-(3S,5S)-6-(tert-Butyl-diphenyl-silanyloxy)-3,5-dimethyl-hexanethioic acid S-ethyl ester (7b)

To a stirred mixture of 7a (1.23 g, 2.79 mmol) in CH_2Cl_2 (50 mL) was added DIBAL-H (3.62 mL, 3.62 mmol, 1.0 M solution in CH_2Cl_2) at –65 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was washed with 45 mL saturated aqueous NaCl solution and stirred for 30 min. The phases were separated and the aqueous layer was extracted CH_2Cl_2. The combined organic phases were dried over MgSO_4, concentrated under reduced pressure to yield crude aldehyde and purified by flash chromatography (eluent pentane/ether 40:1) to afford 8 which was used in the next step without complete removal of the eluent. A solution of 8 and (EtO)_{2}POCH_2COSEt (1.01 g, 4.186 mmol, 1.5 eq) dissolved in THF (20 mL) under nitrogen and cooled to 0 °C. (2.09 mL, 3.34 mmol, 1.2 eq) n-Butyllithium (1.6 M in hexane) was added slowly at 0 °C to the reaction mixture and mixture was stirred for 10 min at rt. Then the aldehyde was dissolved in 2 mL THF.
was slowly added and the reaction mixture stirred at rt for 10 h. The reaction mixture was washed with distilled water and extracted with diethyl ether. The combined organic phases were dried over MgSO$_4$ and concentrated under reduced pressure to yield crude olefin. Purification by flash chromatography (eluent pentane/ether 40:1) afforded a $\beta$-unsaturated thioester 9 as a colourless oil (1.1 g, 84% yield over 2 steps). 

$\left[\alpha\right]_D^{25} = - 7.6$ (c = 1.97, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.66 (dd, $J = 7.7, 1.6$ Hz, 4H), 7.41 (m, 6H), 6.83 (dt, $J = 15.4, 7.6$ Hz, 1H), 6.08 (dt, $J = 15.5, 1.4$ Hz, 1H), 3.50 (dd, $J = 9.8, 5.3$ Hz, 1H), 3.42 (dd, $J = 9.8, 6.3$ Hz, 1H), 2.94 (q, $J = 7.4$ Hz, 2H), 2.18 (m, 1H), 1.92 (m, 1H), 1.69 (m, 2H), 1.39 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 3H). $^1$C-NMR (100 MHz, CDCl$_3$): 189.97 (s), 144.07 (d), 135.59 (d), 133.93 (s), 129.84 (d), 129.51 (d), 127.57 (d), 68.61 (t), 40.76 (t), 39.45 (t), 33.08 (d), 29.96 (d), 26.86 (q), 23.01 (t), 20.12 (q), 19.28 (s), 17.59 (q), 14.81 (q). HRMS, calcd for C$_{24}$H$_{31}$O$_2$SSi (M–tert-butyl) 411.1814 found 411.1812.

(−)-(3S,5R,7S)-8-(tert-Butyl-diphenyl-silanyloxy)-3,5,7-trimethyl-octanethioic acid S-ethyl ester (10)

$(-)-(3S,5R,7S)$-8-(tert-Butyl-diphenyl-silanyloxy)-3,5,7-trimethyl-octanethioic acid S-ethyl ester (10) was dissolved in t-BuOMe (4 mL) under nitrogen. The mixture was cooled to −75 °C and methylmagnesium bromide (0.836 ml 2.05 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of thioester 9 (980 mg, 2.09 mmol) in t-BuOMe (6 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at −75 °C for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH$_4$Cl was added and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford 10 as a colourless oil (890 mg, 2.09 mmol) in t-BuOMe (6 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at −75 °C for 17 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH$_4$Cl was added and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford 10 as a colourless oil (890 mg, 2.09 mmol). $\left[\alpha\right]_D^{25}$ = −6.8 (c = 1.13, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.67 (dd, $J = 1.7, 7.7$ Hz, 4H), 7.41 (m, 6H), 3.46 (dd, $J = 9.8, 5.1$ Hz, 1H), 3.41 (dd, $J = 9.8, 6.5$ Hz, 1H), 2.87 (q, $J = 7.4$ Hz, 2H), 2.52 (dd, $J = 5.0, 14.3$ Hz, 1H), 2.23 (dd, $J = 8.8, 14.3$ Hz, 1H), 2.10 (m, 1H), 1.72 (m, 1H), 1.49 (m, 1H), 1.36 (m, 1H), 1.25 (t, $J = 7.4$ Hz, 3H), 1.21 (m, 1H), 1.06 (s, 12H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.92 (m, 2H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.84 (d, $J = 6.5$ Hz, 3H). $^1$C-NMR (100.6 MHz, CDCl$_3$): 199.22 (s), 135.60 (d), 134.03 (s), 129.47 (d), 127.54 (d), 68.74 (t), 50.93 (t), 44.71 (t), 41.18 (t), 33.08 (d), 28.59 (d), 27.51 (d), 26.88 (q), 23.24 (t), 20.53 (q), 20.46 (q), 19.29 (s), 17.59 (q), 14.81 (q). HRMS, calcd for C$_{25}$H$_{35}$O$_2$SSi (M–tert-butyl) 427.2142 found 427.2127.
Catalytic asymmetric formal synthesis of (−)-Borrelidin

(−)-(6R,8S,10S,E)-11-(tert-butyldiphenylsilyloxy)-6,8,10-trimethylundec-3-en-2-one (12)

To a stirred mixture of 10 (1.500 g, 3.099 mmol) in CH₂Cl₂ (60 mL) was added DIBAL-H (4.01 mL, 4.01 mmol, 1.0 M solution in CH₂Cl₂) at -65 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched in 45 ml saturated aqueous Rochelle salt (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude aldehyde and purified by flash chromatography (eluent pentane/ether 40:1) to give 11 which was used in the next step without complete removal of the eluent. A solution of 11 and (EtO)₂POCH₂COMe (902.1 mg, 4.648 mmol, 1.5 eq) dissolved in THF (20 mL) under nitrogen and cooled to 0 °C, (2.32 ml, 3.718 mmol, 1.2 eq) n-Butyllithium (1.6 M in hexane) was added slowly at 0 °C to the reaction mixture and mixture was stirred for 10 min at rt. Then the aldehyde was dissolved in 3 mL THF was slowly added and the reaction mixture stirred at rt for 10 h. The reaction mixture was washed with distilled water and extracted with diethyl ether. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford 12 as a colourless oil (1.32g, 92% yield over 2 steps). [α]D = –9.2 (c = 1.12, CHCl₃).

1H NMR (400 MHz, CDCl₃) δ 7.66 (dd, J = 7.9, 1.6, 4H), 7.45 – 7.34 (m, 6H), 6.74 (s, 1H), 6.05 (d, J = 15.9, 1H), 3.46 (ddd, J = 16.2, 9.8, 5.8, 2H), 2.23 (s, 3H), 1.98 – 1.88 (m, 1H), 1.72 (dd, J = 12.0, 6.6, 2H), 1.58 – 1.50 (m, 1H), 1.35 (d, J = 6.7, 1H), 1.20 (s, 1H), 1.05 (s, 9H), 0.96 – 0.77 (m, 13H).

13C NMR (101 MHz, CDCl₃) δ 198.50, 147.42, 135.75, 134.13, 132.61, 129.65, 127.70, 68.83, 44.96, 41.36, 39.58, 33.30, 30.06, 27.77, 27.04, 20.88, 20.59, 19.44, 18.16. HRMS, calcd for C₃₀H₄₄O₂Si (M+Na⁺) 487.3008, found 487.2988.

(−)-(4S,6R,8S,10S)-Josiphos 4•CuBr complex (18.5 mg, 0.0249 mmol, 1 mol%) was dissolved in t-BuOMe (5 mL) under nitrogen. The mixture was cooled to –80 °C and methylmagnesium bromide (0.996 ml 2.44 mmol, solution in diethyl ether) was added dropwise over 10 min. After stirring for 10 min, a solution of enone 12 (1.2 g, 2.49 mmol) in t-BuOMe (7.2 mL) was added via syringe pump over 1.5 h. The reaction mixture was stirred at –80 °C for 18 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH₄Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:1) to afford 13a as a colourless oil (1.01
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g, 85% yield). anti/syn ratio by NMR = > 99:1. $^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J$ = 7.1, 4H), 7.39 (dd, $J$ = 15.8, 8.6, 6H), 3.54 – 3.38 (m, 2H), 2.28 (dt, $J$ = 23.4, 12.6, 2H), 2.11 (s, 3H), 1.72 (dd, $J$ = 12.5, 5.9, 1H), 1.54 (dd, $J$ = 14.5, 8.8, 3H), 1.34 (dt, $J$ = 13.1, 6.5, 1H), 1.05 (d, $J$ = 0.5, 9H), 0.86 (ddd, $J$ = 27.2, 13.6, 6.5, 18H). $^{13}C$ NMR (101 MHz, CDCl$_3$) $\delta$ 208.93, 135.76, 134.22, 129.64, 127.72, 68.94, 52.44, 46.19, 44.10, 41.61, 33.27, 30.58, 27.57, 27.35, 27.07, 26.85, 20.78, 20.38, 19.43, 18.25. HRMS, calcd for C$_{31}$H$_{48}$O$_2$Si (M+Na$^+$) 503.3321 found 503.3315.

$^{(-)}$-(4S,6R,8S,10S)-11-(tert-butyldiphenylsilyloxy)-4,6,8,10-tetramethylundecan-2-one (13b)

$^{(-)}$-(2S,4R,6S,8S)-9-(tert-butyldiphenylsilyloxy)-2,4,6,8-tetramethylnonan-1-ol (15)
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pentane/EtOAc 40:4) to afford 15 as a colourless oil (1.5 g, 97% yield). \( \delta^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta 7.69 \) (d, \( J = 7.1, 4H \)), 7.47 – 7.35 (m, 6H), 4.55 (s, 1H), 3.55 – 3.40 (m, 4H), 1.79 – 1.50 (m, 4H), 1.07 (s, 3H), 0.97 – 0.75 (m, 18H).

13C NMR (101 MHz, CDCl\(_3\)) \( \delta 135.83, 134.28, 129.68, 127.76, 69.47, 69.03, 41.71, 40.15, 33.32, 27.61, 27.26, 27.11, 20.81, 20.52, 19.53, 18.25, 16.30.

HRMS, calcd for C\(_{29}\)H\(_{46}\)O\(_2\)Si (M+Na\(^+\)) 477.3165 found 477.3159.

(−)-(2S,4S,6R,8S)-2,4,6,8-tetramethyl-9-(tetrahydro-2H-pyran-2-yloxy)nonan-1-ol (17)

To a stirred mixture of 15 (1.4 g, 3.08 mmol) in CH\(_2\)Cl\(_2\) (30 ml) were added dihydropyran (2.78 ml, 30.8 mmol) and PPTS (77 mg, 0.308 mmol). The resulting solution was stirred at rt for 4 h. The reaction was quenched with sat. aq. NaHCO\(_3\) and after phase separation and extraction of the aqueous phase with CH\(_2\)Cl\(_2\), the combined organic phases were dried over MgSO\(_4\), concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:2) to afford 16 as a colourless oil (1.62 g, 98% yield).

1H NMR (400 MHz, CDCl\(_3\)) \( \delta 4.61 – 4.52 \) (m, 1H), 3.91 – 3.81 (m, 1H), 3.51 (dddd, \( J = 12.9, 9.3, 8.5, 5.2, 3H \)), 3.41 – 3.34 (m, 1H), 3.17 (ddd, \( J = 16.5, 9.4, 6.3, 1H \)), 1.86 – 1.50 (m, 11H), 1.33 – 1.11 (m, 3H), 1.06 (m, 1H), 0.92 – 0.83 (m, 12H). 13C NMR (101 MHz, CDCl\(_3\)) \( \delta 99.19, 98.74, 74.09, 73.63, 68.29, 62.37, 45.96, 41.50, 40.63, 33.21, 30.83, 27.69, 27.27, 25.68, 20.95, 20.48, 19.69, 17.64, 17.00. HRMS, calcd for C\(_{18}\)H\(_{36}\)O\(_3\) (M+H\(^+\)) 301.2664 found 301.2682.

(−)-(4S,6S,8R,10S)-4-methoxybenzyl 4,6,8,10-tetramethyl-3-oxo-11-(tetrahydro-2H-pyran-2-yloxy)undecanoate (20)

To a stirred mixture of 17 (800 mg, 2.66 mmol) in CH\(_2\)Cl\(_2\) (25 mL) were added molecular sieves 4Å (1.5 g), NMO (657 mg, 5.52 mmol) and TPAP (49 mg, 140 μmol). The reaction was stirred at rt for 1 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:2) to afford 18 as a colourless oil.

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(698 mg, 88% yield). To a stirred mixture of samarium iodide (0.1 M solution in THF, 33 mL, 3.3 mmol) were added 18 (198 mg, 0.66 mmol) and 4-methoxybenzyl 2-bromoacetate (187 mg, 0.72 mmol) in THF (3 mL) at –78 °C. The reaction was stirred for 30 min and then treated with hexane (35 mL) followed by silica gel (15 g). The mixture was allowed to warm to rt and stirred for 30 min. The mixture was filtered through a short plug of silica gel, concentrated under reduced pressure and purified by flash chromatography (elucent pentane/EtOAc 50:10) to afford 19 as a colourless oil (284 mg, 90% yield). To a stirred mixture of 19 (215 mg, 0.45 mmol) in CH2Cl2 (4.2 mL) were added molecular sieves 4Å (0.5 g), NMO (111 mg, 0.93 mmol) and TPAP (8.2 mg, 24 μmol). The reaction was stirred at rt for 2 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (elucent pentane/EtOAc 55:7) to afford 20 as a colourless oil (182 mg, 85% yield). [(3S,6S,8R,10S)-(3S,4S,6,8,10-tetramethyl-11-(tetrahydro-2H-pyran-2-yl)oxy)undecanoate (21)] A solution of 20 (152 mg, 0.32 mmol), and (R)-[(RuCl(Tol-BINAP))2(μ-Cl)][NH2Me2] (5.7 mg, 0.0032 mmol) in EtOH (3 mL) was placed in an autoclave and purged with N2 and H2. Hydrogen was introduced (5 bar), and the reaction mixture was stirred at rt for 8 h. After the hydrogen pressure was released, the solution was concentrated under reduced pressure and purified by flash chromatography (elucent pentane/EtOAc 50:10) to afford 21 (137 mg, 90%, anti/syn ratio >99:1). The diastereomeric ratio of 21 was determined by NMR by comparing with the diastereomers prepared by reduction of [E-keto ester 20 with NaBH4, see the NMR spectra); [α]D = −19.2 (c = 0.75, CHCl3). 1H NMR (400 MHz, CDC13) δ 7.31 (s, 2H), 6.90 (s, 2H), 5.09 (s, 2H), 4.58 (s, 1H), 3.94 (s, 1H), 3.81 (s, 5H), 3.53 (d, J = 25.0, 2H), 3.17 (d, J = 36.2, 1H), 2.70 (s, 1H), 2.48 (ddd, J = 19.3, 16.3, 6.3, 3H), 1.82 (s, 3H), 1.60 (s, 8H), 1.25 (s, 3H), 0.88 (s, 16H). 13C NMR (101 MHz, CDCl3) δ 173.60, 159.91, 130.39, 127.92, 114.19, 99.28, 96.88, 74.18, 73.95, 70.72, 66.58, 62.52, 62.27, 55.50, 45.76, 41.08, 40.54, 39.33, 35.25, 30.98, 29.91, 27.38, 25.75, 20.99, 20.60, 19.87, 17.00, 14.70; HRMS, calcd for C28H46O6 (M+ Na+) 501.3192 found 501.3186.
Catalytic asymmetric formal synthesis of (–)-Borrelidin

To a stirred mixture of 21 (125 mg, 0.26 mmol) in CH$_2$Cl$_2$ (2.6 mL) was added 2,6-lutidine (51 μl, 0.44 mmol) followed by TBSOTf (77 μl, 0.34 mmol) at 0°C. The mixture was stirred for 1 h and was quenched with water, after phase separation and extraction of the aqueous phase with CH$_2$Cl$_2$, the combined organic phases were dried over MgSO$_4$, and concentrated under reduced pressure. Crude compound was employed in the next reaction without further purification. To the stirred mixture of this crude in THF (2 mL) and H$_2$O (0.55 mL) at 0°C, LiOH (12 mg, 0.51 mmol) was added and the mixture was stirred for 4 h after quenching with water, phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:12) to afford A as a colourless oil (104 mg, 85% yield over 2 steps). Spectral data of A were consistent with those reported in the literature. [α]$_{25}^D$ = –33.2 (c = 0.25, CHCl$_3$). 1H NMR (400 MHz, CDCl$_3$) δ 4.58 (d, J = 11.4, 1H), 4.02 (d, J = 3.2, 1H), 3.86 (s, 1H), 3.61 – 3.44 (m, 2H), 3.26 – 3.07 (m, 1H), 2.47 (d, J = 6.2, 2H), 1.24 (dd, J = 62.3, 52.6, 12H), 1.37 (s, 1H), 1.25 (s, 3H), 0.89 – 0.84 (m, 21H), 0.07 (dd, J = 7.9, 2.8, 6H). 13C NMR (101 MHz, CDCl$_3$) δ 178.22, 99.10, 98.74, 74.18, 74.00, 72.66, 62.26, 45.93, 40.58, 40.26, 39.47, 36.12, 31.05, 30.85, 29.68, 27.63, 27.35, 26.03, 25.70, 20.86, 19.69, 18.24, 16.83, 15.41, -4.33, -4.46. HRMS, calcd for C$_{26}$H$_{52}$O$_5$Si (M+H$^+$) 473.3657 found 473.3656.

Synthesis of the lower part of Borrelidin

(–)-(1R,2R)-methyl 2-hydroxycyclopentanecarboxylate (37)

A solution of 36 (5.0 g, 35.19 mmol), (R)-DM-BINAP (155 mg, 0.211 mmol) and [RuI$_2$(p-cymene)]$_2$ (86 mg, 0.087 mmol) in CH$_2$Cl$_2$ was placed in an autoclave. Hydrogen was introduced (100 bar), and the reaction mixture was stirred at 60°C for 48 h. After the hydrogen pressure was released, the solution was concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 1:1) to afford (1R,2R)-37 (4.99 g, 98%), anti/syn ratio by NMR= 99:1. Enantiomeric excess and absolute configuration were determined by HPLC (Chiralcel OD, 250*4.6, 10 μm), eluent 99/1 heptane/IPA. 23.883 min (major), 29.856 min (minor) shows 97% ee. [α]$_{25}^D$ = –49.8 (c = 2.51, CHCl$_3$). 1H NMR (400 MHz, CDCl$_3$) δ 4.36 (q, J = 6.5, 1H), 3.80 – 3.61 (m, 3H), 2.70 – 2.62 (m, 1H), 2.19 (s, 1H), 2.00 – 1.91 (m, 2H), 1.89 – 1.54 (m, 4H). 13C NMR (101 MHz,
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CDCl₃ δ 175.75, 75.92, 52.46, 51.53, 34.18, 27.52, 22.19. HRMS, calcd for C₇H₁₂O₃ (M-H⁻) 143.0786, found 143.0702.

(−)-(1R,2R)-methyl 2-(tetrahydro-2H-pyran-2-yl)oxy)cyclopentanecarboxylate (37b)

To a stirred mixture of 37 (2.0 g, 13.88 mmol) in CH₂Cl₂ (80 ml) were added dihydropyran (1.39 g, 16.7 mmol) and PPTS (349 mg, 1.38 mmol). The resulting solution was stirred at rt for 4 h. The reaction was quenched with sat. aq. NaHCO₃ solution and after phase separation and extraction of the aqueous phase with CH₂Cl₂, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 50:7) to afford 37b as a colourless oil (3.03 g, 96% yield). [1] [25] D = −51.4 (c = 1.07, CHCl₃).

1H NMR (400 MHz, CDCl₃) δ 4.64 (dt, J = 19.6, 3.8, 1H), 4.46 – 4.35 (m, 1H), 3.91 – 3.78 (m, 1H), 3.73 – 3.61 (m, 3H), 3.53 – 3.40 (m, 1H), 2.79 (d, J = 19.6, 3.8, 1H), 2.10 – 1.86 (m, 2H), 1.81 – 1.60 (m, 6H), 1.51 (dd, J = 11.4, 7.5, 4H).

13C NMR (101 MHz, CDCl₃) δ 175.00, 174.90, 97.65, 97.32, 80.67, 80.36, 61.91, 61.65, 51.07, 50.90, 50.48, 50.10, 33.07, 31.39, 30.45, 28.41, 27.77, 25.03, 22.91, 22.45, 19.14. HRMS, calcd for C₁₂H₂₀O₄ (M+Na⁺) 251.1259 found 251.1253.

(−)-(1S,2R)-2-(tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl)methanol (46)

To LiAlH₄ (731 mg, 19.3 mmol) suspended in dry ether (65 ml) was added dropwise 37a (2.93 g, 12.8 mmol) in dry ether (17 ml) for 1 h under nitrogen. After being stirred for 10 h at rt, the reaction mixture was cooled to 0 °C and water (1.08 ml) was added carefully, followed by the addition of 15% aqueous NaOH (1.08 ml) and water (3.2 ml). The white precipitate was filtered off, and the filtrate was concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 1:1) to afford 46 as a colourless oil (2.38 g, 93% yield). [2] [25] D = −16.2 (c = 1.09, CHCl₃).

1H NMR (400 MHz, CDCl₃) δ 4.66 (ddd, J = 8.4, 5.1, 2.6, 1H), 4.04 – 3.82 (m, 2H), 3.71 – 3.42 (m, 3H), 2.48 (s, 1H), 2.20 – 2.00 (m, 1H), 1.90 – 1.45 (m, 1H), 1.26 – 1.09 (m, 1H). 13C NMR (101 MHz, CDCl₃) δ 98.29, 97.97, 81.26, 80.87, 65.10, 64.70, 63.07, 62.49, 47.75, 33.25, 31.62, 31.03, 30.88, 26.74, 25.31, 25.19, 22.81, 22.10, 19.95, 19.64. HRMS, calcd for C₁₁H₂₀O₃ (M+H⁺) 199.1412, found 199.1328.
Catalytic asymmetric formal synthesis of (–)-Borrelidin

(–)-2-((1R,2S)-2-((4-methoxybenzyloxy)methyl)cyclopentyloxy)tetrahydro-2H-pyran (47)

To a stirred mixture of 46 (2.25 g, 11.26 mmol) in DMF (60 ml) was added sodium hydride (60% in oil, 351 mg, 14.6 mmol) at –20°C. After being stirred for 30 min, to the resulting suspension was added PMBCl (2.11 g, 13.5 mmol) and then warmed to rt. The reaction was quenched with water, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/Ether 50:7) to afford 47 as a colourless oil (3.42 g, 95% yield). [\(\bar{\alpha}\)] D = –31.6 (c = 0.98, CHCl₃). 

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3) & \quad \delta 7.27 (d, J = 1.5, 1H), 7.25 (q, J = 2.4, 1H), 6.89 – 6.84 (m, 2H), 4.65 – 4.59 (m, 1H), 4.45 (d, J = 4.7, 2H), 3.92 (dddd, J = 20.5, 10.2, 8.9, 4.6, 2H), 3.81 – 3.78 (m, 3H), 3.53 – 3.31 (m, 3H), 2.30 – 2.10 (m, 1H), 1.92 – 1.50 (m, 12H), 1.38 – 1.23 (m, 1H). \\
\text{13C NMR (101 MHz, CDCl}_3) & \quad \delta 158.92, 130.61, 129.06, 113.55, 98.42, 96.47, 81.28, 78.84, 72.40, 72.11, 62.73, 61.93, 55.05, 45.95, 33.39, 31.26, 30.97, 27.76, 27.41, 25.47, 22.94, 22.77, 20.03, 19.41. HRMS, calcd for C₁₉H₂₈O₄ (M+Na+): 343.1885 found 343.1875.
\end{align*}\]

(+)-(1R,2S)-2-((4-methoxybenzyloxy)methyl)cyclopentanol (48)

To a stirred mixture of 47 (3.52 g, 11.0 mmol) in EtOH (100 ml) was added PPTS (400 mg, 1.59 mmol), and the resulting solution was stirred at 50°C. After 12 h, the reaction was diluted with water, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 50:12) to afford 48 as a colourless oil (2.49 g, 96% yield). [\(\bar{\alpha}\)] D = +1.2 (c = 1.15, CHCl₃). 

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3) & \quad \delta 7.26 (d, J = 0.7, 1H), 7.24 (s, 1H), 6.92 – 6.81 (m, 2H), 4.50 – 4.42 (m, 3H), 3.97 (q, J = 6.9, 1H), 3.81 (s, 3H), 3.53 – 3.31 (m, 3H), 2.20 (s, 1H), 1.58 (ddd, J = 15.9, 9.1, 5.3, 2H), 1.28 – 1.08 (m, 1H). \\
\text{13C NMR (101 MHz, CDCl}_3) & \quad \delta 159.21, 130.41, 129.69, 113.83, 77.85, 73.55, 72.90, 55.26, 47.60, 34.05, 26.69, 21.92. HRMS, calcd for C₁₄H₂₀O₃ (M-H-) 235.1412, found 235.1328.
\end{align*}\]
To a stirred mixture of 48 (805 mg, 3.40 mmol) and pyridine 3 mL, was added tosyl chloride (1.29 g, 6.8 mmol) at rt under nitrogen, and the mixture was stirred for 12 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 40:20) to afford 49 as a colourless oil (1.29 g, 98% yield). [$\alpha$]$^D_{25}$ = −23.5 (c = 1.18, CHCl$_3$).

$^{1}H$ NMR (400 MHz, CDCl$_3$) δ 7.77 (d, $J$ = 7.6, 2H), 7.28 (s, 1H), 7.26 (s, 1H), 7.17 (d, $J$ = 8.2, 2H), 6.87 (d, $J$ = 8.7, 2H), 4.77 (dd, $J$ = 8.8, 4.4, 1H), 4.34 – 4.26 (m, 2H), 3.84 – 3.77 (m, 3H), 3.23 (d, $J$ = 5.9, 2H), 2.42 (s, 3H), 1.90 – 1.56 (m, 6H), 1.32 (ddd, $J$ = 27.8, 17.8, 10.2, 1H).

$^{13}C$ NMR (101 MHz, CDCl$_3$) δ 159.21, 144.50, 134.36, 130.50, 129.81, 129.15, 127.92, 113.82, 86.66, 72.63, 70.36, 55.39, 46.04, 32.79, 26.94, 22.95, 21.73. HRMS, calcd for C$_{21}$H$_{26}$O$_5$S (M+Na$^+$) 413.1399 found 413.1385.

To a stirred mixture of 49 (1.22 g, 3.14 mmol) in DMSO (15 mL), was added NaCN (0.310 g, 6.29 mmol) and the resulting solution was stirred at 50 °C. After 12 h, the reaction was diluted with water, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ether 50:10) to afford 50 as a colourless oil (615 mg, 80 % yield). [$\alpha$]$^D_{25}$ = +36.8 (c = 1.05, CHCl$_3$).

$^{1}H$ NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.27 (m, 2H), 6.91 – 6.85 (m, 2H), 4.55 – 4.41 (m, 2H), 3.80 (s, 3H), 3.65 – 3.51 (m, 2H), 3.05 (td, $J$ = 7.4, 4.7, 1H), 2.42 – 2.31 (m, 1H), 2.04 – 1.83 (m, 4H), 1.73 – 1.60 (m, 1H), 1.52 – 1.40 (m, 1H), 1.25 (d, $J$ = 11.1, 1H). $^{13}C$ NMR (101 MHz, CDCl$_3$) δ 159.15, 130.18, 129.34, 121.08, 113.69, 73.07, 71.23, 55.13, 42.52, 32.13, 27.39, 23.51. HRMS, calcd for C$_{15}$H$_{19}$NO$_2$ (M+Na$^+$) 268.1313 found 268.1306.

To a stirred mixture of 50 (500 mg, 2.03 mmol) in CH$_2$Cl$_2$ (30 mL) was added DIBAL-H (4.46 mL, 4.46 mmol, 1.0 M solution in CH$_2$Cl$_2$) at −65 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched with 30 mL saturated aqueous Rochelle salt
Catalytic asymmetric formal synthesis of (–)-Borrelidin (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude aldehyde 26 as a colourless oil (428 mg, 85 % yield). Spectral data of 26 were coincident with those reported in the literature. [α]D⁰ = −25.8 (c = 0.29, CHCl₃). H NMR (400 MHz, CDCl₃) δ 9.65 (d, J = 2.6, 1H), 7.25 – 7.22 (m, 2H), 6.89 – 6.85 (m, 2H), 4.44 (d, J = 1.6, 2H), 3.81 – 3.79 (m, 3H), 3.46 (dd, J = 5.1, 5.8, 1H), 3.33 (dd, J = 9.1, 7.4, 1H), 2.58 – 2.43 (m, 2H), 1.83 (ddt, J = 12.7, 6.6, 5.6, 4H), 1.70 – 1.58 (m, 2H), 1.38 (dd, J = 12.5, 7.8, 1H).

13C NMR (101 MHz, CDCl₃) δ 204.02, 159.33, 130.71, 129.31, 113.96, 73.18, 72.89, 56.00, 55.48, 41.43, 29.59, 26.79, 25.19.

HRMS, calcd for C₁₅H₂₀O₃ (M+Na⁺) 271.1310, found 271.1295.

(+)-(S)-1-((1R,2R)-2-((4-methoxybenzyloxy)methyl)cyclopentyl)but-3-en-1-ol (27)

To a stirred mixture of 26 (1.2 g, 4.83 mmol) in CH₂Cl₂ (40 ml) was added allyltrimethylsilane (1.17 ml, 1.77 mmol) and magnesium bromide diethyl etherate (1.24 g, 4.83 mmol) at 0°C. The reaction was stirred for 10 h at 0°C, then quenched with 2M HCl and stirred for 1 h, after phase separation and extraction of the aqueous phase with CH₂Cl₂, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/Ether 55:10) to afford 27 as a colourless oil (1.2 g, 86% yield). Spectral data of 27 were coincident with those reported in the literature. [α]D⁰ = +6.3 (c = 0.32, CHCl₃). H NMR (400 MHz, CDCl₃) δ 7.26 – 7.21 (m, 2H), 6.86 (dd, J = 7.5, 4.7, 2.3, 2H), 6.05 – 5.99 (m, 1H), 5.15 – 5.03 (m, 2H), 4.44 (qd, J = 11.8, 4.3, 2H), 4.33 (s, 1H), 3.82 – 3.75 (m, 3H), 3.50 (dt, J = 10.0, 4.4, 1H), 3.43 – 3.34 (m, 1H), 3.18 (td, J = 10.0, 4.4, 1H), 2.37 (dd, J = 10.1, 3.9, 1H), 2.16 – 2.00 (m, 2H), 1.82 – 1.51 (m, 5H), 1.23 (td, J = 12.3, 5.5, 2H). 13C NMR (101 MHz, CDCl₃) δ 159.36, 135.87, 129.50, 116.48, 113.90, 75.06, 74.35, 72.96, 55.26, 51.73, 43.98, 40.56, 31.08, 30.03, 24.62. HRMS, calcd for C₁₈H₂₆O₃ (M+H⁺) 289.1882, found 289.1798.

(+)-(5,2E,4E)-2-bromo-7-hydroxy-7-((1R,2R)-2-((4methoxybenzyloxy)methyl)cyclopentyl)hepta-2,4-dienenitrile (B)

A flame dried Schlenk-flask under N₂-atmosphere was charged with 27 (520 g, 1.79 mmol), acrolein diethyl acetal (620 µl, 5.37 mmol) and CH₂Cl₂ (8.5 ml), Hoveyda-Grubbs 2nd generation catalyst (56
mg, 0.089 mmol) was added and the resulting solution was stirred for 18 h at reflux temperature, then quenched with 5 ml water and 0.4 ml formic acid and stirred for 1 h, after phase separation and extraction of the aqueous phase with \( \text{CH}_2\text{Cl}_2 \), the combined organic phases were dried over MgSO\(_4\), concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EiOAc 40:8) to afford 28 as a colourless oil (427 mg, 75 % yield, only E-isomer observed). To a stirred mixture of 28 (150.5 mg, 0.47 mmol) and diethyl bromo (cyano) methylphosphate (360 mg, 1.41 mmol) in MeCN (5 ml) at 0 °C was added DBU (143 mg, 0.94 mmol) and lithium chloride (40 mg, 0.94 mol). The solution was stirred for 4 h, then quenched with sat. aq. NaHCO\(_3\), and after phase separation and extraction of the aqueous phase with EiOAc, the combined organic phases were dried over MgSO\(_4\), concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 40:8) to afford 38 as a colourless oil (916 mg, 75% yield over 3 steps) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.82 – 7.56 (m, 4H), 7.55 –

(S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentanone (38):

To 37 (500 mg, 3.47 mmol) in 15 mL THF, L\(\text{Bu} \text{AlH}_4\) (1 M in THF, 2 eq, 3.9 mL) was added at 0 °C and the reaction mixture stirred at rt for 3 h and quenched with water and aq. NaOH (used a small amounts that is enough to precipitate). Filtration through a Büchner funnel was followed by washing the filter cake twice with EiOAc. The filtrate was dried over MgSO\(_4\), and concentrated under reduced pressure to afford a crude 37a. To the solution of crude 37a in DMF (10 ml) were added imidazole (468 mg, 6.94 mmol) and TBDPSCl (1.35 ml, 5.2 mmol) at 0 °C. The reaction was allowed to warm to rt and stirred for 30 min. After addition of water, the reaction mixture was extracted with EiOAc. The combined organic extracts were dried over MgSO\(_4\) and concentrated to afford the corresponding hydroxyl silylether 37b. To a solution of this secondary alcohol (1.02 g, 2.87 mmol) (total amount from the in DCM (4.5 ml) was added Dess-Martin periodinane (1.75 g, 5.3 mmol). After stirring at rt for 30 min, the reaction mixture was quenched with sat. aq. Na\(_2\)S\(_2\)O\(_3\) and sat. aq. NaHCO\(_3\), followed by extraction with DCM. The combined organic extracts were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. Flash chromatography (5:1 pentane/EiOAc) afforded 38 (916 mg, 75% yield over 3 steps) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.62 – 7.56 (m, 4H), 7.55 –

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7.28 (m, 6H), 3.99 (m, 1H), 3.88 – 3.73 (m, 1H), 2.47 – 1.95 (m, 6H), 1.82 (d, J = 7.9, 1H), 1.04 (l, J = 11.4, 9H). 13C NMR (101 MHz, CDCl3) δ 220.31, 136.12, 133.95, 129.92, 128.10, 63.04, 51.04, 39.29, 26.79, 26.73, 21.19, 19.55. HRMS, calcd for C22H28O2Si (M+Na+) 375.17453, found 375.17451.

(1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-vinylcyclopentanol (39):

Anhydrous cerium trichloride (730 mg, 2.95 mmol) was taken up in a dry 50 ml base-washed flask charged with a stir bar. The flask was evacuated to 0.1 mm Hg and heated to 140 °C for 10 h. After cooling to rt under vacuum, N2 followed by dry THF (10 ml), was introduced and the mixture was stirred for 10 h at rt, followed by cooling to –78 °C. Vinylmagnesium chloride (2.94 ml, 1 M solution in THF, 2.94 mmol) was added and the cream-colored suspension was stirred at –78 °C for 2 h before a solution of 38 (400 mg, 1.05 mmol) in THF (5 ml) was added. The reaction mixture was stirred for an additional 3 h before it was diluted with ether (20 ml) and washed with 1 M aq. HCl (2 x 5 ml) and brine (5 ml). The organic phase was dried (MgSO4), concentrated at reduced pressure and subjected to chromatography on silica gel (pentane/ether, 5:1) to give 39 (371 mg, 93% yield) as a single isomer. 1H NMR (400 MHz, CDCl3) δ 7.76 – 7.57 (m, 4H), 7.51 – 7.31 (m, 6H), 5.93 (dd, J = 17.1, 10.6, 1H), 5.50 (dd, J = 17.1, 1.9, 1H), 5.18 (dd, J = 10.6, 1.9, 1H), 3.96 (dd, J = 10.8, 3.5, 2H), 3.77 (dd, J = 10.6, 4.0, 1H), 2.20 – 2.03 (m, 1H), 1.97 (m, 1H), 1.89 – 1.64 (m, 5H), 1.13 – 1.02 (m, 9H). 13C NMR (101 MHz, CDCl3) δ 144.33, 135.89, 132.96, 130.12, 128.03, 112.87, 83.49, 63.35, 49.35, 41.03, 27.09, 26.09, 21.95, 19.39. HRMS, calcd for C24H32O2Si (M-H) 379.2093, found 379.2093.

(1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-vinylcyclopentyl acetate (40):

To 39 (381 mg, 1 mmol) in 3 ml pyridine, acetic anhydride (0.12 ml, 1.18 mmol) and DMAP (12.5 mg, 0.10 mmol) was added at 0 °C and the reaction mixture was stirred at 50 °C for 5 h. After addition of water, the reaction mixture was extracted with ether. The combined organic extracts were dried over MgSO4, and concentrated in vacuo. Flash chromatography (50:5 pentane/ether) afforded 40 (376 mg, 89% yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 7.86 – 7.57 (m, 4H), 7.58 – 7.31 (m, 6H), 6.10 (ddd, J = 17.6, 11.1, 5.2, 1H), 5.19 – 4.96 (m, 2H), 3.94 (m, 1H), 3.70 (ddd, J = 10.2, 7.4, 5.1, 1H), 2.57 – 2.37 (m, 1H), 2.25 – 2.06 (m, 2H), 2.06 – 1.84 (m, 4H), 1.82 – 1.51 (m, 3H), 1.08 (dd, J = 5.2, 2.6, 9H). 13C NMR (101 MHz, CDCl3) δ 170.23, 140.56, 136.00, 134.08, 129.80, 127.84.
(R)-dimethyl 2-[(2-[[((R)-dimethyl]diphenylsilyl)oxy)methyl]cyclopentylidene)ethyl]malonate (41): A mixture of Pd(dba)$_2$ (11.5 mg, 0.02 mmol) and (+)-BINAP (12.5 mg, 0.02 mmol) was stirred for 15 min in 0.5 ml of THF. 40 (113 mg, 0.50 mmol) in THF (2 mL) was subsequently added by syringe. After being stirred for 15 min, the solution was added to a stirred suspension of sodium dimethyl malonate (160 mg, 1.04 mmol) in THF (1 ml). The reaction mixture was stirred at rt overnight, diluted with ether (10 ml) and the organic phase washed with 2x10 ml of saturated aqueous NH$_4$Cl. The aqueous phases were backextracted with ether (3x10 ml) and the combined ethereal phases were dried (MgSO$_4$) and concentrated. The crude product was purified by flash chromatography (silica, pentane/ether 50/5) to give a 1:1 mixture of E and Z (41) 131 mg, 88% yield.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.81 – 7.57 (m, 4H), 7.53 – 7.30 (m, 6H), 5.13 (d, $J$ = 8.0, 0H), 3.87 – 3.21 (m, 9H), 2.74 – 2.04 (m, 4H), 1.66 (ddd, $J$ = 24.3, 17.4, 9.4, 4H), 1.27 (s, 2H), 1.11 – 1.04 (m, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 169.82, 147.54, 147.14, 135.84, 134.16, 129.75, 127.83, 117.70, 116.74, 67.22, 65.50, 52.64, 46.97, 43.31, 33.80, 29.93, 29.38, 28.94, 27.09, 24.32, 23.86, 19.47.

HRMS, calcd for C$_{26}$H$_{34}$O$_3$Si (M+Na$^+$) 445.21639, 445.21639.

(R,E)-methyl4-(2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentylidene)butanoate (42):

To 41 (53 mg, 0.1 mmol) in 2 ml DMSO, NaCN (8 mg, 0.3 mmol) was added at rt and the reaction mixture was stirred at 150 °C for 20 h. After addition of water, the reaction mixture was extracted with ether. The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo. Flash chromatography (50:5 pentane/ether) afforded 42 (35 mg, 80% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.67 (d, $J$ = 5.0, 4H), 7.39 (d, $J$ = 6.7, 6H), 5.18 (s, 0H), 3.74 – 3.29 (m, 5H), 2.22 (dd, $J$ = 63.3, 29.6, 7H), 1.90 – 1.45

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\[(\text{m, 4H}), 1.40 - 1.16 (\text{m, 3H}), 1.05 (\text{s, 9H}).\]

\[^{13}\text{C} \text{NMR (75 MHz, CDCl}_3) \delta 173.88, 145.44, 134.14, 129.72, 127.80, 120.47, 119.53, 67.27, 65.58, 46.84, 43.47, 34.68, 33.74, 33.65, 32.54, 31.73, 29.52, 27.09, 24.95, 24.37, 19.50.\] HRMS, calcd for \(\text{C}_{27}\text{H}_{36}\text{O}_3\text{Si} (M+Na}^+) 459.23204, 459.23203.

\((\text{R})\text{-tert-butyl}(2\text{-methylene cyclopentyl})\text{methoxy)diphenylsilane (44):}\]

To 38 (200 mg, 0.56 mmol) in 10 ml THF, Tebbe reagent (0.5 M in toluene, 2.27 ml, 1.13 mmol) was added at rt and the reaction mixture was stirred for 5 h. After addition of water, the reaction mixture was extracted with ether. The combined organic extracts were dried over MgSO\(_4\) and concentrated in vacuo. Flash chromatography (50:5 pentane/ether) afforded 44 (161 mg, 82% yield) as a colorless oil.

\[^{1}H \text{NMR (400 MHz, CDCl}_3) \delta 7.86 - 7.56 (\text{m, 4H}), 7.55 - 7.30 (\text{m, 6H}), 4.87 (\text{dd, } J = 40.1, 1.4, 2\text{H}), 3.64 (\text{ddd, } J = 17.9, 9.9, 6.9, 2\text{H}), 2.68 (\text{s, 1H}), 2.44 - 2.16 (\text{m, 2H}), 1.92 (\text{s, 1H}), 1.78 - 1.50 (\text{m, 3H}), 1.07 (\text{d, } J = 16.7, 9\text{H}).\]

\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3) \delta 154.02, 135.91, 134.27, 129.75, 127.82, 106.02, 67.33, 46.50, 34.13, 30.43, 27.13, 24.76, 19.55.\] HRMS, calcd for \(\text{C}_{23}\text{H}_{30}\text{OSi} (M+Na}^+) 373.19526, 373.19523.

Compounds 23, 24, 25, 51, 52 and 53:

Spectral data 23, 24, 25, 51, 52 and 53 were coincident with those reported by Omura et al.\(^{19,30}\)

2.7 References