Total syntheses of (−)-Borrelidin and (−)-Doliculide and the development of the catalytic asymmetric addition of Grignard reagents to ketones
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Catalytic Asymmetric Synthesis of (−)-Doliculide

In this chapter the catalytic asymmetric synthesis of (−)-Doliculide is described. Iterative copper-catalyzed asymmetric conjugate addition reactions and asymmetric hydrogenation are key strategic elements in the synthesis. Furthermore, the synthesis of two analogues of Doliculide is described, that should reveal its close relationship to other natural depsipeptides.*

* The experiments described in this chapter were carried out jointly by Dr. K. Matcha and me.
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3.1 Introduction

Natural products with potent cytotoxic effects are considered to be potential molecular probes in cancer research.\textsuperscript{1-4} As one of the biological targets in this exciting field, perturbation of actin receives wide-spread attention. Actin, an abundant protein in most eukaryotic cells, exists in equilibrium between its monomeric form, G-actin, and its polymeric form, F-actin (Figure 1).\textsuperscript{1,5} Actin participates in many important cellular processes including muscle contraction, cell motility, cell division and cytokinesis, cell signaling, and the establishment and maintenance of cell junctions and cell shape. Any perturbation of this equilibrium results in malfunctioning of the cell, which in turn causes cell death.\textsuperscript{6} Organic compounds that are capable of interacting and disrupting actin aggregation can be viewed as potential anticancer agents.

Figure 1: G-actin (left) and F-actin (right)\textsuperscript{7}

It is therefore not surprising that both in chemical biology and in drug design there is a great need for small molecules that can interfere with the assembly and disassembly of actin fibers. In this context, macrocyclic depsipeptide natural products such as Jasplakinolide 1,\textsuperscript{8,9} Chondramide C 2,\textsuperscript{10} Sergamide A 3,\textsuperscript{11} and Doliculide 4\textsuperscript{12-14} (Figure 2) have shown to stabilize F-actin in a way similar to Phalloidin,\textsuperscript{15,16} the first known F-actin stabilizing natural product. Moreover, higher membrane permeability of these depsipeptides over Phalloidin render them useful molecular probes in studying actin behavior.\textsuperscript{17-19}
The structural similarity between the cyclodepsipeptides, comprising a complex hybrid of a peptide and a polyketide, is striking. A recent study by Arndt, Waldmann and co-workers, compared several cyclodepsipeptides together with a series of synthetic analogues, in their cytotoxicity toward MCF-7 and HT-29 cancer cells. This study confirmed earlier hypotheses that, whereas the peptide region of the
compounds is most probably involved in actin binding, the polyketide region probably holds this peptide region in the appropriate conformation. Simplifications of the polyketide region were therefore to some extent allowed, leaving the actin-binding activity intact. Doliculide, not included in the above-mentioned study, possesses a smaller ring size but shows a prominent structural similarity with the other cyclodepsipeptides. It displays strong actin binding activity but has hardly been used in cell biology because of its limited availability. Biochemical data and pharmacophore analysis strongly suggest that the binding mode of Doliculide is similar to that of Jasplakinolide. Nevertheless, due to its activity, its low cytotoxicity compared to the other cyclodepsipeptides, and its high cell permeability, Doliculide is potentially a more effective molecular probe for chemical biology than the afore-mentioned compounds.

(−)-Doliculide 4, a 16-membered depsipeptide was isolated by Yamada et al. in 1994 from the Japanese sea hare Dolabella auricularia and had established its absolute configuration by means of extensive spectral analysis. Doliculide exhibits exceedingly potent cytotoxicity against HeLa-S3 cells with an IC50 value of 0.005 μg/mL. It is structurally somewhat distinct from other depsipeptides in both the peptide and polyketide regions. Recently, Hamel and co-workers found that Doliculide arrests cells at G2/M phase of the cell cycle by interfering with the actin assembly in a way similar to Jasplakinolide. Limited structure activity relationship studies on Doliculide are known, and no efforts towards the synthesis of more potent and less complex Doliculide analogues have been made.

The distinct molecular complexity of Doliculide coupled with its remarkable biological activity profile has elicited considerable interest among synthetic chemists. Only three syntheses of Doliculide have been reported to date and are centered mainly on late-stage coupling of independently synthesized polyketide and peptide parts (Scheme 1). A major challenge is the efficient synthesis of the stereochemically complex polyketide part, in particular the syn deoxypropionate unit, whereas the synthesis of the peptide part is relatively straightforward. In these modular syntheses, the groups of Ghosh and Hanessian relied on chiral pool-based starting materials whereas Yamada used chiral auxiliaries. As reported approaches installed the required stereocenters through substrate controlled stereoselectivity, there is a severe setback in the perspective of synthesizing analogues with opposite diastereomers to study the conformational effects on the 16-membered ring closure and bioactivity. Moreover, synthesis of the all-syn deoxypropionate motif is challenging; a fine tuning of selectivity is only possible using a catalyst. So, we were interested in developing a catalytic asymmetric route to Doliculide in which the stereochemical outcome of
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Each chiral center would be controlled by the catalyst. This catalytic approach should be considerably more efficient and result in excellent selectivities so that separation of diastereomers is avoided.

Scheme 1: Retrosynthetic analysis of Doliculide (4)

3.2 Results and Discussion

In our disconnection we concluded, like our predecessors, that 4 would be best obtained from the union of polyketide 5 and peptide 6. In our approach, the 1,3-diol unit in 5 would be installed through asymmetric hydrogenation and CBS reduction of the corresponding 1,3-dicarbonyl precursor derived from ketone 7. The syn-trimethyl deoxypropionate unit in 7, in turn, should be available from unsaturated thioester 8, like in the previous chapter by iterative conjugate addition.25,26 The protected tyrosine-glycine dipeptide 6 can be readily accessed from commercial D-tyrosine.
Scheme 2: Synthesis of the polyketide part of 4; the deoxypropionate unit

The synthesis of the polyketide part 5 was started with the preparation of methyl ketone 7 from readily available thioester 8 (Scheme 2). Earlier work by our group and the work described in the previous chapter has shown that the Cu/Josiphos-catalyzed iterative asymmetric conjugate addition of MeMgBr leads to excellent stereochemical control in the synthesis of 1,3-methyl arrays.27-29 With this knowledge, we proceeded with the conjugate addition of methylmagnesium bromide to unsaturated thioester 8 in presence of 1 mol% of CuBr/11. Thioester 10 obtained in 94% yield showed an excellent enantioselectivity (98%) and complete
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dioselectivity. Reduction of thioester 10 to the corresponding aldehyde with DIBAL-H followed by Horner-Wadsworth-Emmons (HWE) reaction with \((\text{EtO})_2\text{P(O)CH}_2\text{C(O)SEt}\) provided the unsaturated ester 12 in excellent yield. Thioester 12, upon treatment with methylmagnesium bromide and 1 mol% of CuBr furnished the syn-1,3-dimethyl thioester 13 in high yield and selectivity. Thioester 13 was subsequently transformed into \(\alpha,\beta\)-unsaturated methyl ketone 14 by a sequence of DIBAL-H reduction and HWE reaction with \((\text{EtO})_2\text{P(O)CH}_2\text{COMe}\) in 92% yield over two steps. Under identical conjugate addition conditions as used previously, 14 showed nearly exclusive syn-selectivity in towards the desired methyl ketone 15. The stereochemistry at the newly formed chiral centers was unambiguously assigned by comparing with our previous results. Methyl ketone 15 was transformed into alcohol 16 by a two-step protocol involving a Baeyer-Villiger oxidation with mCPBA and subsequent hydrolysis in 89% yield over two steps. Protection of the hydroxyl group as its corresponding benzyl ether followed by deprotection of the TBDPS group furnished alcohol 17 in very good overall yield (we didn’t start synthesis with the benzyl protecting group because the 1,4-addition reaction with TBDPS protected 8 gave considerably high enantioselectivities than with benzyl protected 8). This bifunctional building block 17, in fact a desymmetrised diol, is a good starting point to polyketide 5 as one carbinol can be considered carboxyl equivalent and the other one can be extended to the 1,3-diol.
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Scheme 3: Synthesis of the polyketide part of 4; the 1,3-diol unit

To this end, 17 was oxidized to its corresponding aldehyde with TPAP and NMO followed by treatment with ethyl diazoacetate and NbCl₅ to furnish ω-keto ester 18 in 86% yield (Scheme 3). The anticipated catalytic asymmetric hydrogenation of 18 with 1 mol% of (R)-[(RuCl(Tol-BINAP))₂(μ-Cl)]₂[NH₂Me₂]₃ affored hydroxyester 19 in excellent yield 90% and diastereoselectivity (de 97%). Initial attempts towards the synthesis of isopropyl ketone 21 by the addition of isopropylithium to the TBS protected Weinreb amide prepared from 19 resulted in low yields, probably due to the steric bulk of the TBS group. However, addition of isopropylithium to the Weinreb amide generated from hydroxy ester 19 in 95%
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yield, provided under optimized conditions hydroxy-isopropyl ketone 20 in 81% yield. The hydroxy group in 20 was subsequently protected as its TBS ether to give isopropyl ketone 21. Stereoselective borane reduction of 21 with the Corey-Bakshi-Shibata (CBS) method was the next step.36-38 The use of (R)-CBS oxazaborolidine catalyst furnished exclusively the desired (S)-alcohol 22 in 95% yield, whereas its enantiomer gave exclusively the corresponding (R)-alcohol. The stereochemistry of the newly formed chiral center was assigned by comparing the $^{13}$C chemical shifts of C3 in both alcohols with that present in polyketide 5.39 Carbon C3 in the desired (S)-alcohol 22 appeared at δ 75.9 which is identical with the corresponding carbon in polyketide 5, while the same carbon in the (R)-alcohol appeared at δ 77.8.

After having established the stereochemistry at all chiral centers, hydrogenolysis of benzyl ether 22 over 10% Pd/C under a H$_2$ atmosphere resulted in smooth debenzylolation to give the corresponding alcohol. Finally, oxidation with TEMPO and bis(acetoxy)iodobenzene (BAIB) produced aldehyde 23 in excellent overall yield. Aldehyde 23 was subsequently transformed to polyketide unit 5 by NaClO$_2$ oxidation followed by esterification with Boc$_2$O. The spectral data and optical rotation value of compound 5 are in agreement with that reported in the literature.39 Overall, polyketide unit 5 was synthesized in 23 steps starting from 8 with an overall yield of 17.36% which is a considerable improvement compared to Ghosh’s approach.22 (30 steps and 1.28% overall yield).

With polyketide part 5 in hand, we next focused our attention on the synthesis of the peptide unit 6. As this synthesis, developed by Ghosh and Liu,22 is relatively straightforward and the subsequent combination of 5 and 6 rather efficient, we decided to adapt this existing method from Ghosh (Scheme 4).22 Synthesis starts from commercially available D-tyrosine, which was iodinated with iodine in a mixture of ethanol and aqueous ammonia. Esterification of the resulting meta-iodo tyrosine derivative with dry HCl in methanol was followed by Boc protection. Protection of the phenolic group as a TIPS ether followed by N-methylation with sodium hydride and methyl iodide furnished the N-methylated tyrosine. This reaction was performed exactly with Ghosh reported conditions at 60 °C, we observed a 25% racemization product, this was overlooked by Ghosh et al. and to overcome this problem we performed the same reaction at room temperature, the racemization of the product is decreased to less than 5%). Removal of the Boc group by treatment with trifluoroacetic acid and coupling of the resulting amine with N- Boc-glycine in the presence of EDC and HOBT under standard conditions afforded the dipeptide 5a. Selective hydrolysis of the methyl ester with LiOH gave the crude acid 6. Esterification of the alcohol of 5 with acid 6 followed by
intramolecular cycloamidation to give (-)-Doliculide with excellent reproducible yields as reported by Gosh (Scheme 4).  

The spectroscopic data of Doliculide synthesized by this route are in excellent agreement with the literature.  

The present approach provides Doliculide in an overall yield of 13.25%, which is the best reported to date.

Scheme 4: Synthesis of the peptide part 6 and the final steps in the synthesis of Doliculide
Besides the intriguing structural similarity of Doliculide to other cyclodepsipeptides, the developed convergent catalytic asymmetric synthesis encouraged us towards the synthesis of Doliculide analogues in order to evaluate its structure-activity relationship. Although it is known that the peptide unit of the cyclodepsipeptides plays a crucial role in actin binding activity, we first decided to vary in this part. The presence of a glycine residue in Doliculide, compared to an alanine residue in the other depsipeptides sticks out. Are these residues interchangeable in doliculide or is a glycine essential for activity or successful ringclosure? So, we embarked on the formal replacement of the glycine with either an (S)-alanine (coined Ala(Gly) Doliculide) or an (R)-alanine residue in Doliculide to investigate the effect of the C-13 methyl group.

Scheme 5: Synthesis of 13C-(S)-methyl Doliculide
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The synthesis again started from tyrosine derivative 24, used in the synthesis of Doliculide (Scheme 5). Coupling of amine 24 with N-Boc-(S)-alanine 25a and N-Boc-(R)-alanine 25b in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), and hydroxybenzotriazole (HOBT) provided the dipeptides 26a and 26b respectively. Selective hydrolysis of the esters 26a and 26b with aqueous LiOH delivered the corresponding acids which were subsequently coupled to polyketide 5 to provide the corresponding diesters 27a and 27b. To our surprise, coupling of the acid generated from 26b with 5 resulted in very low conversion to give 27b (15% yield), whereas the acid prepared from 26a provided, under identical reaction conditions, 27a in 96% yield with full conversion. We accepted this result, as ester 27a will lead to Ala(Gly) doliculide 29 with the desired (S)-C13 methyl group present in the other depsipeptides. Deprotection of the TBS and both the Boc groups in 27a with trifluoroacetic acid, followed by intramolecular cycloamidation with benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent) provided cycloamide 28a in 80% yield over two steps. On the contrary, 27b failed to give the desired cycloamide 28b. Finally, removal of the TIPS group in 28a afforded C13-(S)-methyl doliculide 29 in 95% yield.

Recently, Hamel and co-workers compared Doliculide with Jasplakinolide, Phalloidin and Chondramide C in their computer-aided shape descriptor analysis program. This study reveals that every atom of Doliculide closely matches with an atom in at least one of the other three depsipeptides. This holds in particular for the dipeptide unit. The overlap of the phenol fragment of Doliculide with the indole fragment of Jasplakinolide and Chondramide C, including their halogen substituents, suggests that these dipeptide segments form the same pharmacophore. This study encouraged us to replace the iodo-tyrosine in Doliculide with a tryptophan, in order to prove similar binding modes of these units to actin. This envisaged Doliculide analogue 34, coined Trp(iodoTyr) Doliculide is expected not only to show similar actin binding activity but also to provide considerable advantages over Doliculide itself such as a reduced number of synthetic steps and the absence of the labile iodide substituent in the tyrosine. Moreover, the fluorescence properties of tryptophan might be used to obtain information on the Doliculide-actin interactions.
The synthesis of the required tryptophan-glycine dipeptide 32 started from commercially available D-tryptophan methylester 30. Sequential reductive aminations with benzaldehyde and paraformaldehyde, respectively, followed by hydrogenolysis with Pd(OH)$_2$/H$_2$ gave amine 31 as described in the literature.\textsuperscript{39} Coupling of 31 with N-Boc glycine in the presence of EDC, and HOBT afforded the desired dipeptide 32 in 82% yield. Steglich esterification of the acid, generated from selective hydrolysis of the ester function in 32, with the hydroxy group of polyketide unit 5 furnished the coupling product 33 in excellent yield (93%). Removal of the TBS and Boc groups in 33 with TFA, followed by intramolecular cycloamidation with BOP reagent provided the hybrid Doliculide analogue 34 in 82% yield and the spectral data were coincident with the natural compound. At the moment of writing, the prepared new analogues are subjected to biological activity.
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tests in collaboration with the Waldmann group at the Max Planck Institute of Molecular Physiology in Dortmund, Germany.

3.3 Summary and concluding remarks

In this chapter, the first efficient catalytic asymmetric total synthesis of Doliculide 4 is described. The synthesis is significantly shorter and produces 4 in much higher yield (13%) than the previously reported syntheses. 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. Although the total number of steps is still considerable, we are convinced that the current route has arrived at, or is approaching, the status of a preparation that can be carried out conveniently to provide researchers in chemical biology with sufficient amounts of Doliculide. In addition, this catalytic approach paves the way for the preparation of Doliculide analogues, as is convincingly demonstrated by the preparation of two Doliculide analogues, dubbed Ala(Gly) Doliculide and Trp(iodoTyr) Doliculide. The biological activity of these analogues is under investigation.

3.4 Experimental Section

General

See experimental section of Chapter 2.

(+)-(4S,6R,8R)-9-((tert-butyldiphenylsilyl)oxy)-4,6,8-trimethylnonan-2-one (15)

(S,RFe)-Josiphos (11).CuBr complex (141 mg, 0.019 mmol, 1 mol%) was dissolved in tBuOMe (135 mL). The mixture was cooled to ~80 °C and methylmagnesium bromide (6.9 mL, 20.6 mmol, 3.0 M in diethyl ether) was added dropwise over 15 min. The reaction mixture was stirred for 15 min at the same temperature and subsequently a solution of enone 14 (7.9 g, 18.7 mmol, for the synthesis of fragment 14 see Chapter 2) in tBuOMe (22 mL) was added with a syringe pump over 2.5 h. The reaction mixture was stirred at ~80 °C for 18 h, quenched by the addition of MeOH (8 mL) and aq. NH₄Cl (30 mL), and allowed to reach rt. 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.
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(pentane:diethyl ether, 40:1) to afford 15 as a colorless oil (7.2 g, 88% yield). [α]D25 = +2.5 (c=1.85, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.68 (d, J = 4 Hz, 4H), 7.45-7.37 (m, 6H), 3.53 (dd, J = 8.2, 4.3 Hz, 1H), 3.43 (dd, J = 8.2, 4.3 Hz, 1H), 2.38 (dd, J = 14.4, 3.2 Hz, 1H), 2.14-2.08 (m, 2H), 2.11 (s, 3H), 1.74 (m, 1H), 1.48 (m, 1H), 1.38 (quin, J = 6.4 Hz, 1H), 1.20-1.15 (m, 1H), 1.07 (s, 9H), 0.99-0.90 (m, 1H), 0.95 (d, J = 6.4, 3H), 0.87 (d, J = 6.4, 3H). 13C NMR (101 MHz, CDCl3) δ 209.0, 135.6, 135.6, 134.06, 134.03, 129.5, 127.5, 68.7, 50.8, 45.0, 41.2, 33.1, 30.4, 27.6, 26.7, 20.7, 20.6, 19.3, 18.0. HRMS calcd for C28H42O2SiNa (M+Na+) 461.2846 found 461.2845.

(+)-(2S,4R,6R)-7-((tert-butyldiphenylsilyl)oxy)-2,4,6-trimethylheptyl acetate (15a)

To a stirred mixture of 15 (2.5 g, 5.69 mmol) in CHCl3 (40 mL) was added mCPBA (2.92 g, 17.1 mmol) at rt. After stirring for 16 h at 60 °C, the reaction mixture was cooled to rt. The solvent was evaporated and the crude reaction mixture was purified by flash chromatography (eluent pentane/ether 40:1) to afford 15a as colorless oil (1.95 g, 75% yield + 500 mg recovered starting material). Repeating the above procedure for the recovered starting material afforded 15a (2.2 g) in an overall yield of 86% yield. 1H NMR (400 MHz, CDCl3) δ 7.69 (d, J = 7.6, 1.6 Hz, 4H), 7.45-7.37 (m, 6H), 3.97 (dd, J = 10.4, 4.6 Hz, 1H), 3.82 (dd, J = 10.8, 6.4 Hz, 1H), 3.53 (dd, J = 10.0, 5.4 Hz, 1H), 3.44 (dd, J = 10.0, 6.4 Hz, 1H), 2.04 (s, 3H), 1.89-1.74 (m, 2H), 1.55 (m, 1H), 1.42-1.24 (m, 2H), 1.11-1.04 (m, 2H), 1.08 (s, 9H), 0.95 (d, J = 6.4, 3H), 0.92 (d, J = 6.4, 3H), 0.87 (d, J = 6.4, 3H). 13C NMR (101 MHz, CDCl3) δ 171.2, 135.6, 135.6, 134.05, 134.0, 129.5, 127.5, 69.2, 68.7, 41.3, 41.2, 33.1, 29.9, 27.6, 26.9, 20.9, 20.6, 19.3, 18.0, 17.8.

(+)-(2S,4R,6R)-7-((tert-butyldiphenylsilyl)oxy)-2,4,6-trimethylheptan-1-ol (16)

To a stirred solution of 15a (2.2 g, 4.85 mmol) in 8 mL of methanol was added potassium carbonate (804 mg, 5.82 mmol). The reaction was stirred at rt for 3 h and the diluted with water. 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 (pentane:EtOAc 10:1) to afford 16 as a colourless oil (1.93 g, 96% yield). [α]D25 = +1.4 (c=1.05, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.69 (d, J = 7.2 Hz, 4H), 7.46-7.38 (m, 6H), 4.54 (dd, J = 4.9, 2.5 Hz, 2H), 3.45 (dd, J = 9.6, 6.4 Hz, 1H), 3.34 (dd, J = 10.4, 6.4 Hz, 1H), 1.80-1.68 (m, 2H), 1.55 (m, 1H), 1.43-1.36 (m, 2H), 1.29 (m, 1H), 1.09 (s, 9H), 0.96 (d, J = 6.8, 3H), 0.92 (d, J = 6.8, 3H), 0.93-0.90 (m, 1H), 0.87 (d, J = 6.8, 3H). 13C NMR (101 MHz, CDCl3) δ 135.6, 135.6, 134.1, 134.0, 129.5, 127.5, 68.7, 68.1, 68.1, 41.3, 41.2, 33.2, 33.1, 27.8, 26.9, 26.9, 20.9, 20.6, 19.3, 18.0, 17.8.
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26.9, 21.0, 19.3, 18.1, 17.6. HRMS calcd for C_{33}H_{46}O_{2}SiNa (M+Na^+) 525.3159 found 525.3154.

(+)-(2R,4R,6S,7-(benzyloxy)-2,4,6-trimethylheptyl)oxy)(tert-butyldiphenylsilane (16a)

To a magnetically stirred suspension of NaH (300 mg, 12.4 mmol, 60% in oil), freed from adhering oil by repeated washing with petroleum ether, in dry THF (20 mL) at 0 °C was added dropwise a solution of alcohol 16 (1.9 g, 4.61 mmol) in dry THF (12 mL) under N2 atmosphere. The mixture was allowed to reflux for 0.5 h, and then HMPA (0.8 mL) was added dropwise, followed by benzyl bromide (0.65 mL, 5.53 mmol). After refluxing for an additional 3 h, the reaction mixture was cooled to 0 °C and quenched by adding saturated aqueous NH4Cl (8 mL). 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 (pentane/EtOAc 40:1) to furnish benzyl ether 16a (2.14 g, 92%) as colorless oil. [δ]D25 = +4.4 (c=1.55, CHCl3).

1H NMR (400 MHz, CDCl3) 4.55-4.50 (m, 2H), 3.55 (dd, J=9.6, 4.8 Hz, 1H), 3.44 (dd, J=10.0, 6.4 Hz, 1H), 3.37 (dd, J=8.8, 5.4 Hz, 1H), 3.20 (t, J=7.2 Hz, 1H), 1.89-1.78 (m, 2H), 1.57 (m, 1H), 1.42-1.31 (m, 2H), 1.09 (s, 9H), 0.96 (d, J=6.8, 6H), 0.94-0.90 (m, 2H), 0.87 (d, J=6.8, 3H).

13C NMR (101 MHz, CDCl3) 138.8, 135.8, 135.8, 134.1, 134.0, 129.4, 128.4, 127.5, 127.4, 127.3, 75.9, 73.1, 69.0, 41.7, 41.5, 33.4, 31.1, 27.9, 27.1, 21.1, 19.5, 18.6, 18.2. HRMS calcd for C_{33}H_{46}O_{2}SiNa (M+Na^+) 525.3159 found 525.3154.

(+)-(2R,4S,6S)-7-(benzyloxy)-2,4,6-trimethylheptan-1-ol (17)

To a stirred mixture of 16a (2.0 g, 3.98 mmol) in THF (20 mL) at 0 °C was added TBAF (1.0 M solution in THF, 4.8 mL, 4.78 mmol). The resulting solution was stirred for 5 h at rt and quenched with sat. aq. NH4Cl. 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 (pentane/EtOAc 4:1) to afford 17 as a colourless oil (1.01 g, 96% yield), [δ]D25 = +8.2 (c=1.75, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.34 (d, J=4.4 Hz, 4H), 3.37-3.33 (m, 2H), 3.22 (dd, J=8.6, 6.8 Hz, 1H), 1.88-1.67 (m, 3H), 1.59 (m, 1H), 1.40-1.27 (m, 2H), 0.96 (d, J=6.8, 3H), 0.91 (d, J=6.8, 3H), 0.92-0.87 (m, 1H), 0.90 (d, J=7.2, 3H). 13C NMR (101 MHz, CDCl3) δ 138.7, 129.2, 127.48, 127.4, 75.8, 73.0, 68.0, 41.6, 41.1, 33.0, 30.9, 27.7, 21.0, 18.3, 17.5. HRMS calcd for C_{17}H_{29}O_{2} (M+H^+) 265.2160 found 265.2160.
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(−)-(4R,6R,8S)-ethyl 9-(benzyloxy)-4,6,8-trimethyl-3-oxononanoate (18)

To a stirred mixture of 17 (950 mg, 3.59 mmol) in CH₂Cl₂ (25 mL) were added molecular sieves 4 Å (1.5 g), NMO (843 mg, 7.18 mmol) and TPAP (38 mg, 0.11 mmol). The reaction was stirred at rt for 1 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (pentane:ether 40:1) to afford 17a as a colourless oil (832 mg, 88% yield). To the mixture of above aldehyde (800 mg, 3.05 mmol) and ethyl diazoacetate (0.38 mL, 3.66 mmol) in dichloromethane (20 mL) was added portionwise NbCl₅ (41.2 mg, 0.15 mol%) over 15 min at 0 °C, and the mixture was stirred at rt for 4 h. The reaction mixture was subsequently concentrated under reduced pressure and the crude was purified by flash chromatography (pentane:EtOAc 40:1) to give keto-ester 18 as a colourless oil (932 mg, 88% yield).

[Δ]D₂⁵ = −1.8 (c=1.20, CHCl₃).

1H NMR (400 MHz, CDCl₃)
δ 7.38-7.34 (m, 4H), 7.29-7.24 (m, 1H), 4.97 (s, 1H, for enol form), 4.52-4.45 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.45 (d, J = 1.6 Hz, 1H), 3.32-3.29 (m, 1H), 3.26-3.19 (m, 1H), 2.78-2.71 (m, 1H), 2.39-2.30 (m, 1H, for enol form), 1.91-1.83 (m, 1H), 1.77-1.70 (m, 1H), 1.54-1.45 (m, 1H), 1.38-1.30 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H, for enol form), 1.09 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H, for enol form), 0.88 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H, for enol form).

13C NMR (101 MHz, CDCl₃)
δ 206.7, 182.7 (for enol), 173.0 (for enol), 167.4, 138.9, 128.4, 127.6, 127.5, 88.4, 76.2 (for enol), 75.9, 73.16, 73.13 (for enol), 64.1, 60.0 (for enol), 47.8, 44.4, 41.9 (for enol), 41.7, 41.2 (for enol), 39.4, 37.5 (for enol), 30.9, 28.1, 28.0 (for enol), 20.7, 20.6 (for enol), 18.1, 17.8 (for enol), 17.3, 14.4 (for enol). HRMS calcd for C₂₁H₃₂O₄Na (M+Na⁺) 371.2193 found 371.2199.

(−)-(35,4R,6R,8S)-ethyl 9-(benzyloxy)-3-hydroxy-4,6,8-trimethylnonanoate (19)

A solution of 18 (800 mg, 2.29 mmol) and (R)-[RuCl₂(Tol-BINAP)]₂(μ-Cl)₂[NH₄][MeCN] (41 mg, 0.023 mmol) in EtOH (20 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 18 h. After the hydrogen pressure was released, the solution was concentrated under reduced pressure and purified by flash chromatography (pentane:EtOAc, 50:10) to afford 19 (728 mg, 91%, anti/syn >99:1). [Δ]D₂⁵ = −1.2 (c=1.25, CHCl₃).

1H NMR (400 MHz, CDCl₃)
δ 7.34 (d, J = 5.4 Hz, 4H), 7.28-7.25 (m, 1H), 4.48 (dd, J = 16.2, 12.4 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.87 (m, 1H), 3.35 (dd, J = 6.0, 5.4 Hz, 1H), 3.20 (dd, J = 8.8, 6.8 Hz, 2H), 2.00 (s, 3H), 1.96-1.91 (m, 1H), 1.86-1.81 (m, 2H), 1.75-1.70 (m, 2H), 1.49-1.41 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H), 0.76 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 6.4 Hz, 3H). HRMS calcd for C₂₃H₃₄O₅Na (M+Na⁺) 385.2424 found 385.2428.
1H), 2.94 (brs, 1H), 2.45-2.39 (m, 2H), 1.85 (m, 1H), 1.76-1.70 (m, 1H), 1.57 (m, 1H), 1.40-1.30 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.90-0.84 (m, 2H), 0.87 (d, J = 6.8, 3H), 0.91 (d, J = 6.8, 3H), 0.91 (d, J = 6.8, 3H), 0.90 (d, J = 6.8, 3H), 0.87 (d, J = 6.8, 3H), 0.89 (d, J = 6.8, 3H), 0.89-0.84 (m, 2H), 0.87 (d, J = 6.8, 3H).

**13C NMR (101 MHz, CDCl₃)**

173.6, 138.7, 128.2, 127.4, 127.3, 75.6, 73.0, 71.6, 60.7, 41.4, 40.5, 37.3, 35.4, 30.9, 27.9, 21.2, 18.6, 15.3, 14.1. HRMS calcd for C₂₁H₃₄O₄Na (M+Na⁺) 373.2350 found 373.2357.

**(3S,4R,6R,8S)-9-(benzyloxy)-3-hydroxy-N-methoxy-N,4,6,8-tetramethylnonanamide (19a)**

To a suspension of MeONHMe·HCl (585 mg, 6.0 mmol) in CH₂Cl₂ (18 mL) at –10 °C was added AlMe₃ (2.0 M solution in toluene, 3.1 mL, 6.2 mmol). An evolution of gas ensued and the resulting mixture was stirred at 0 °C for 30 min before being treated with a solution of ester 19 (700 mg, 2.0 mmol) in CH₂Cl₂ (8 mL). The resulting mixture was stirred at rt for 3 h. The reaction was again cooled to 0 °C and quenched with saturated aqueous potassium sodium tartrate (4 mL). The resulting mixture was diluted with diethyl ether (50 mL), water (4 mL) and then stirred at rt for 30 min. The insoluble materials were filtered off, and the filtrate was washed with brine, dried (MgSO₄), and concentrated under reduced pressure followed by flash chromatography (pentane:EtOAc, 4:1) to furnish 19a (698 mg, 95%) as a colorless oil.

**1H NMR (400 MHz, CDCl₃)**

7.33 (d, J = 5.4 Hz, 4H), 7.29-7.25 (m, 1H), 4.48 (dd, J = 16.2, 12.4 Hz, 2H), 3.90-3.86 (m, 1H), 3.75 (d, J = 2.0 Hz, 1H), 3.66 (s, 3H), 3.35 (dd, J = 8.0, 5.4 Hz, 1H), 3.20 (dd, J = 12.0, 7.2 Hz, 1H), 3.18 (s, 3H), 2.58 (d, J = 16.4 Hz, 1H), 2.41 (dd, J = 16.4, 10.0 Hz, 1H), 1.54 (m, 1H), 1.77 (quint, J = 6.8 Hz, 1H), 1.59 (m, 1H), 1.41-1.34 (m, 2H), 0.99-0.82 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8, 3H), 0.89 (d, J = 6.8, 3H), 0.87 (d, J = 6.8, 3H), 0.89 (d, J = 6.8, 3H), 0.87 (d, J = 6.8, 3H), 0.89 (d, J = 6.8, 3H), 0.87 (d, J = 6.8, 3H), 0.89 (d, J = 6.8, 3H).

**13C NMR (101 MHz, CDCl₃)**

174.3, 138.8, 128.2, 127.4, 127.3, 75.6, 73.0, 71.4, 61.2, 41.1, 40.5, 35.3, 33.8, 31.8, 30.9, 27.9, 21.2, 18.6, 15.4. HRMS, calcd for C₂₁H₃₅NO₄Na (M+Na⁺) 388.2464 found 388.2470.

**(-)-(5S,6R,8R,10S)-11-(benzyloxy)-5-hydroxy-2,6,8,10-tetramethylundecan-3-one (20)**

To a solution of Weinreb amide 19a (650 mg, 1.78 mmol) in THF (40 mL) at –78 °C was added dropwise a solution of isopropyl lithium (0.7 M in THF, 5.5 mL, 3.83 mmol). After stirring at –78 °C for 3 h, the reaction
mixture was quenched with methanol (3 mL) and saturated aqueous NH₄Cl (5 mL), and subsequently warmed to room temperature and extracted with ELo. The combined organic layers were dried with MgSO₄ and concentrated. Purification of the residue by flash chromatography (pentane:EtOAc, 90:10) afforded the pure β-hydroxy ketone 20 (502 mg, 81%) as a colorless oil. [α]D²⁰ = -17.3 (c=1.48, CHCl₃). 

1H NMR (400 MHz, CDCl₃) δ 7.32 (d, J = 5.4 Hz, 4H), 7.29-7.24 (m, 1H), 4.48 (dd, J = 16.2, 12.4 Hz, 2H), 3.90-3.88 (m, 1H), 3.34 (dd, J = 8.8, 4.8 Hz, 1H), 3.20 (dd, J = 8.8, 7.2 Hz, 1H), 3.16 (brs, 1H), 2.62-2.44 (m, 3H), 1.85 (quint, J = 6.4 Hz, 1H), 1.71 (quint, J = 6.8 Hz, 1H), 1.56 (quint, J = 6.8 Hz, 1H), 1.39-1.29 (m, 2H), 1.09 (d, J = 6.8 Hz, 6H), 0.97-0.84 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8, 3H), 1.39-1.29 (m, 2H), 0.97-0.84 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8, 3H).

13C NMR (101 MHz, CDCl₃) δ 16.5, 138.7, 128.2, 127.4, 127.3, 75.6, 73.0, 71.0, 42.3, 41.5, 41.1, 40.5, 35.2, 30.9, 27.8, 21.2, 18.5, 18.0, 15.4. HRMS, calcd for C₂₂H₃₆O₃Na (M+Na)⁺ 371.2562 found 371.2569.

Catalytic asymmetric synthesis of (–)-Doliculide

To a solution of alcohol 20 (400 mg, 1.15 mmol) in CH₂Cl₂ (15 mL) were added 2,6-lutidine (0.18 mL, 1.61 mmol) and TBSOTf (0.3 mL, 1.32 mmol) at 0 °C. After stirring at the same temperature for 1 h, the mixture was quenched with saturated aqueous NH₄Cl (3 mL), and then warmed to rt and extracted with Et₂O. The combined organic layers were dried with MgSO₄ and concentrated. Purification of the residue by flash chromatography (pentane:ether, 47:3) afforded the pure ketone 21 (505 mg, 95%) as a colorless oil. To a stirred solution of this ketone 21 (320 mg, 0.69 mmol) and (R)-Me-CBS reagent (39 mg, 0.14 mmol) in dry THF (10 mL) was added BH₃.SMe₂ (0.51 mL, 1.03 mmol, 2.0 M in THF) at –20 °C under Ar atmosphere. After stirring at 0 °C for 5 h, the reaction was quenched by adding MeOH (3 mL) at 0 °C and stirred at the same temperature for 30 min. The mixture was quenched by adding saturated aqueous NH₄Cl and extracted with ether. After separation of the two layers, the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (pentane:ether, 43:7) to afford 22 (308 mg, 95%) as a clear oil. [α]D²⁰ = -7.2 (c=1.50, CHCl₃). 1H NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 5.4 Hz, 4H), 7.30-7.24 (m, 1H), 4.50 (dd, J = 16.2, 12.4 Hz, 2H), 3.82-3.78 (m, 1H), 3.36 (dd, J = 9.4, 5.4 Hz, 1H), 2.35 (brs, 1H), 1.89-1.79 (m, 2H), 1.66-1.52 (m, 3H), 1.40-1.26 (m, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.90 (s, 3H), 0.91-0.88 (m, 2H), 0.89 (d, J = 6.8 Hz, 6H), 0.83 (d, J = 6.8 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H). 13C NMR (101 MHz, CDCl₃) δ 138.8, 128.4, 127.6, 127.5, 75.9, 73.8, 73.5, 73.1, 41.8, 41.5, 35.8, 34.7.
A solution of the benzyl ether 22 (270 mg, 0.58 mmol) in dry methanol (5 mL) containing Pd/C (10%, 40 mg) was stirred under hydrogen atmosphere (balloon) at rt for 15 h. The catalyst was filtered off, and the solvent removed in vacuo to afford alcohol 22a (187 mg, 86%) as colorless liquid. 

\[\text{[\text{IH}] D} = -14.5 \text{ (c=1.47, CHCl}_3\text{)}\].

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)}: \delta 3.81 (t, J = 5.6 Hz, 1H), 3.54 (dd, J = 8.8, 5.8 Hz, 1H), 3.47 (dd, J = 10.4, 5.4 Hz, 1H), 3.36 (dd, J = 10.4, 6.4 Hz, 1H), 2.30 (br s, 1H), 1.79 (quint, J = 6.4 Hz, 1H), 1.67 (sex, J = 6.4 Hz, 1H), 1.62-1.53 (m, 2H), 1.48 (dd, J = 13.2, 9.2 Hz, 1H), 1.36-1.22 (m, 3H), 0.91-0.85 (m, 23H), 0.81 (d, J = 6.8 Hz, 3H), 0.05 (d, J = 6.4 Hz, 6H). \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{)}: \delta 73.4, 73.0, 67.5, 41.7, 41.0, 35.6, 34.3, 34.0, 33.0, 27.7, 25.00, 25.86, 21.0, 16.4, 17.9, 17.7, 14.6, -4.3, -4.5. \text{HRMS, calcd for C}_{21}H_{46}O_3SiNa (M+Na)\textsuperscript{+} 397.3114, found 397.3120.\]

(2S,4R,6R,7S,9S)-7-((tert-butyldimethylsilyl)oxy)-9-hydroxy-2,4,6,10-tetramethylundecanoic acid (23)

TEMPO (7.2 mg, 0.045 mmol) was added to a solution of alcohol 22a (170 mg, 0.45 mmol) and bis(acetoxy)iodobenzene (585 mg, 1.8 mmol) in 10 mL of CH₂Cl₂. The reaction mixture was stirred at rt for 5 h and then concentrated under reduced pressure. Flash chromatography (pentane:ether, 47:3) provided pure aldehyde (160 mg, 94%) as a colorless oil. To this aldehyde (160 mg, 0.43 mmol) in a 5:1 mixture of t-BuOH-water (10 mL) were added 2-methyl-2-butene (0.45 ml, 4.3 mmol), NaClO₂ (230 mg, 2.6 mmol) and NaH₂PO₄ (116 mg, 0.85 mmol). After stirring for 6 h at 23 °C, the reaction mixture was quenched with phosphate buffer solution (pH 3.5, 10 mL) and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude acid 23, which was used in the next reaction without further purification. \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{):} \delta 3.81 (l, J = 5.8 Hz, 1H), 3.58 (dd, J = 9.2, 5.2 Hz, 1H), 3.58 (dd, J = 9.2, 5.2 Hz, 1H), 2.57 (m, 1H), 1.82 (quint, J = 6.4 Hz, 1H), 1.71-1.63 (m, 2H), 1.52 (dd, J = 14.4, 7.2 Hz, 1H), 1.48 (s, 1H).
Catalytic asymmetric synthesis of (–)-Doliculide

1.43-1.25 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.08-1.04 (m, 1H), 0.92-0.87 (m, 19H), 1.81 (d, J = 6.8 Hz, 3H), 0.07 (d, J = 6.8 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 181.8, 73.6, 73.0, 42.0, 37.5, 35.4, 34.5, 34.1, 29.6, 28.2, 25.8, 20.4, 18.4, 18.3, 18.0, 17.6, 14.4, –4.36, –4.56

(+)-(2S,4S,6S,7S,9S)-tert-butyl 7-((tert-butyldimethylsilyl)oxy)-9-hydroxy-2,4,6,10-tetramethylundecanoate (5)

To a solution of acid 23 in t-BuOH (8 mL) were added Boc₂O (185 mg, 0.85 mmol) and DMAP (15.6 mg, 0.12 mmol). The resulting solution was stirred at 30 °C for 4 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (pentane/ether, 47:3) to provide 5 (158 mg, 82% over 2 steps) as a colorless oil. 

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1H NMR (400 MHz, CDCl₃) δ 3.79 (m, 1H), 3.61 (dd, J = 8.8, 5.6 Hz, 1H), 2.49 (brs, 1H), 2.42 (m, 1H), 1.82 (m, 1H), 1.74-1.67 (m, 1H), 1.64-1.53 (m, 3H), 1.42 (s, 10H), 1.39-1.24 (m, 2H), 1.08 (d, J = 8.2 Hz, 3H), 0.95-0.88 (m, 21H), 0.83 (d, J = 8.0 Hz, 3H), 0.083 (d, J = 11.2 Hz, 6H). 13C NMR (101 MHz, CDCl₃) δ 176.6, 80.1, 74.5, 73.7, 42.2, 41.4, 38.9, 35.8, 35.2, 34.5, 28.7, 28.5, 26.3, 21.1, 19.0, 18.9, 18.4, 18.1, 14.9, –3.9, –4.0. HRMS, calcd for C₂₅H₃₅O₄SiNa (M+Na)⁺ 467.3527 found 467.3526.

(+)-(2S,4S,6S,7S,9S)-tert-butyl 9-(((R)-2-(2-(tert-butoxycarbonyl)amino)-N-methylacetamido)-3-(3-iodo-4-((triisopropylsilyl)oxy)phenyl)propanoyl)oxy)-7-((tert-butyldimethylsilyl)oxy)-2,4,6,10-tetramethylundecanoate (5b)

To a stirred solution of acid 5a (125 mg, 0.2 mmol) in CH₂Cl₂ (16 ml) at –20 °C were added DCC (41.7 mg, 0.2 mmol) and DMAP (6.6 mg, 0.05 mmol). The resulting mixture was stirred at –20 °C for 16 h, filtered through a short plug of silica gel and concentrated. The residue was purified by flash chromatography (pentane:EtOAc, 47:3) to give 5b (46.4 mg, 98%) as a colorless oil. [γ]D² = +3.8 (c=0.74, CHCl₃).
(−)-(3R,9S,11R,13R,14S,16S)-14-hydroxy-3-(3-iodo-4-((triisopropylsilyl)oxy)benzyl)-16-isopropyl-4,9,11,13-tetramethyl-1-oxa-4,7-diazacyclohexadecane-2,5,8-trione (5c)

To a stirred solution of ester 5b (45 mg, 0.042 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added trifluoroacetic acid (1 mL). The temperature was raised to rt over 1 h, the solution was stirred for an additional 2 h and then concentrated, coevaporated three times with benzene, and dried under reduced pressure. To the above crude in anhydrous CH₂Cl₂ (90 ml) were added N,N-bis(2-oxo-3-oxazolidinyl)-phosphinic reagent (BOP) (90 mg, 0.2 mmol) and DMAP (45 mg, 0.37 mmol) at 0 °C. The temperature was allowed to rise to rt overnight, and the reaction mixture was washed with dilute aq. HCl and brine. The organic layers were dried over MgSO₄ and concentrated to give a residue which was purified by flash chromatography (pentane/EtOAc, 40:10) to provide cyclic amide 5c (25 mg, 81%) as a colorless oil. \[^1\]H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 1.6 Hz, 1H), 7.01 (dd, J = 8.4, 1.8 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.18 (d, J = 12.3, 4.4 Hz, 1H), 5.05 (dd J = 5.2, 1.8, 1H), 4.80 (dd, J = 16.6, 8.8 Hz, 1H), 3.58 (d, J = 10.6, Hz, 1H), 3.44 (dd, J = 15.4, 4.6 Hz, 1H), 3.20 (d, J = 18.4, 1H), 2.92 (a, 3H), 2.88 (dd, J = 15.5, 12.5 Hz, 1H), 2.93-2.80 (m, 1H), 2.60 (m, 1H), 2.41 (m, 1H), 2.03 (m, 1H), 1.87 (m, 1H), 1.54-1.41 (m, 3H), 1.39-1.28 (m, 7H), 1.13 (d, J = 7.5 Hz, 24H), 1.12-1.04 (m, 4H), 0.98 (d, J = 5.6 Hz, 3H), 0.95 (d, J = 7.2 Hz, 6H), 0.84 (d, J = 8.6 Hz, 3H). ^{13}C NMR (101 MHz, CDCl₃) δ 178.1, 172.4, 172.0, 155.0, 139.5, 130.9, 129.2, 118.6, 90.9, 66.0, 58.6, 45.4, 43.5, 40.2, 39.6, 34.7, 33.2, 31.1, 30.8, 27.4, 19.3, 18.7, 18.5, 18.3, 18.2, 17.9, 13.9, 13.5, -3.5, -4.2. HRMS, calcd for C₅₁H₉₄IN₂O₇Si₂ (M+H)⁺ 1061.564 found 1061.560.
Catalytic asymmetric synthesis of (–)-Doliculide

(–)-Doliculide (4)

To TIPS ether 5c (20 mg, 0.027 mmol) in THF (1.5 ml) was added TBAF (41 μl, 0.041 mmol, 1 M in THF) at 0 °C. The resulting solution was stirred for 15 min at this temperature. The reaction mixture was quenched by addition of saturated aq. NH₄Cl (500 μl) and diluted with EtOAc (10 ml). The aqueous phase was extracted with EtOAc (3 × 6 ml), and the organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography (pentane:EtOAc, 1:1) to give doliculide 4 (16.0 mg, 95%) as a white solid. mp 171-173 °C. [Į]₂₅ = –25.9 (c=2.81, MeOH).

1H NMR (500 MHz, CDCl₃) δ 7.51 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.3, 2.0 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1H), 6.14 (brs, 1H), 5.50 (dd, J = 12.4, 4.4 Hz, 1H), 5.08 (dd, J = 5.2, 1.8, 1H), 4.83 (dd, J = 16.8, 8.8 Hz, 1H), 3.60 (d, J = 9.5 Hz, 1H), 3.47 (dd, J = 15.7, 4.4 Hz, 1H), 3.29 (dd, J = 16.8, 1.8, 1H), 2.96 (s, 3H), 2.91 (dd, J = 15.5, 12.5 Hz, 1H), 2.57 (d, J = 3.5, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.89 (m, 1H), 1.63 (brs, 1H), 1.55 (t, J = 12.8 Hz, 1H), 1.45 (dd, J = 13.9, 11.8, 1.9 Hz, 1H), 1.34 (ddd, J = 13.9, 11.8, 2.4 Hz, 1H), 1.19 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.10-1.03 (m, 3H), 0.98 (d, J = 6.3 Hz, 3H), 0.97 (d, J = 7.2 Hz, 6H), 0.95 (d, J = 6.9 Hz, 3H). 13C NMR (125 MHz, CDCl₃) δ 178.2, 172.3, 172.0, 154.5, 138.4, 130.5, 130.0, 115.6, 85.9, 77.7, 66.1, 58.5, 45.2, 43.4, 40.1, 39.5, 34.6, 33.1, 32.7, 31.1, 30.5, 27.3, 19.2, 18.7, 18.4, 18.0, 14.8. HRMS, calcd for C₂₇H₄₀N₂O₅(M-H)⁺ 599.1976 found 599.1973. The spectral data correspond to those reported in the literature.

Synthesis of Ala(Gly) Doliculide (29)

(+)-(R)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-N-methylpropanamido)-3-((3-iodo-4-(triisopropylsilyl)oxy)phenyl)propanoate (26a)

To amine 24 (0.3 g, 0.66 mmol) and Boc-(S)-alanine 25a (0.15 g, 0.85 mmol) in DMF at 0 °C were added EDC (0.17 g, 0.85 mmol) and HOBT (0.13 g, 1.0 mmol). The resulting solution was warmed to rt and stirred for 5 h. The solution was quenched with saturated aq. NH₄Cl, diluted with dichloromethane and washed with water. The organic layer was separated, dried and concentrated to give dipeptide 26a (0.31 g, 90%) after column chromatography.
(pentane:EtOAc, 75:25). [$\beta$]$^25_D$ = +18.4 (c=3.32, MeOH). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, $J$ = 7.1 Hz, 1H), 6.96 (dd, $J$ = 8.2, 1.8 Hz, 1H), 6.70 (d, $J$ = 8.3 Hz, 1H), 5.43 (d, $J$ = 7.9 Hz, 1H), 5.27 (dd, $J$ = 11.4, 4.9 Hz, 1H), 4.52 – 4.45 (m, 1H), 3.70 (s, 3H), 3.26 (dd, $J$ = 14.9, 5.1 Hz, 1H), 3.00 – 2.73 (m, 1H), 2.84 (s, 3H), 1.40 (s, 9H), 1.34 – 1.21 (m, 4H), 1.08 (d, $J$ = 7.6 Hz, 18H), 0.92 (d, $J$ = 6.4 Hz, 3H). 

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.8, 170.9, 155.1, 154.5, 139.6, 130.6, 129.6, 117.9, 90.3, 79.5, 57.8, 52.5, 46.6, 33.4, 32.4, 28.5, 18.9, 18.2, 13.1. HRMS, calcd for C$_{28}$H$_{48}$IN$_2$O$_6$Si (M+H)$^+$ 663.2320 found 663.2320.

(–)-(25,45,6R,7S,9S)-tert-butyl 9-(((R)-2-((S)-2-((tert-butoxycarbonyl)amino)-N-methylpropanamido)-3-(3-iodo-4-((triisopropylsilyl)oxy)phenyl)propanoyl)oxy)-7-((tert-butyldimethylsilyl)oxy)-2,4,6,10-tetramethylundecanoate (27a)

To dipeptide 26a (0.23 g, 0.34 mmol) in a 2:1 mixture of THF:water (9 mL) was added LiOH (36.6 mg, 0.87 mmol) at 0 °C. The resulting mixture was stirred for 1 h and then acidified to pH=3.5 with aqueous NaHSO$_4$. The mixture was extracted with ether. The combined organic layers were dried over MgSO$_4$ and concentrated to give the acid (170 mg) after column chromatography (CH$_2$Cl$_2$:MeOH 20:1). To a stirred solution of alcohol 5 (20 mg, 0.045 mmol) and acid (127 mg, 0.2 mmol) in CH$_2$Cl$_2$ (16 ml) at –20 °C were added DCC (41.1 mg, 0.2 mmol) and DMAP (6.6 mg, 0.05 mmol). The resulting mixture was stirred at –20 °C for 16 h and then filtered through a short plug of silica gel and concentrated. The residue was purified by flash chromatography (pentane:EtOAc, 47:3) to give 27a (45.2 mg, 96%) as a colorless oil. [$\beta$]$^25_D$ = –0.9 (c=2.05, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, $J$ = 1.6 Hz, 1H), 6.99 (dd, $J$ = 6.4, 2.2 Hz, 1H), 6.71 (d, $J$ = 8.4 Hz, 1H), 5.45 (d, $J$ = 8.0 Hz, 1H), 5.32 (d, $J$ = 7.6 Hz, 1H), 4.94 (m, 1H), 4.49 (quint, $J$ = 7.8 Hz, 1H), 3.51 (m, 1H), 3.28 (dd, $J$ = 15.2, 5.2 Hz, 1H), 2.90 (m, 1H), 2.87 (s, 3H), 2.41 (m, 1H), 1.93-1.86 (m, 1H), 1.70-1.62 (m, 1H), 1.42 (m, 19H), 1.31 (m, 4H), 1.10 (m, 23H), 0.84-0.79 (m, 27H), 0.03 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.3, 173.6, 170.1, 155.1, 154.5, 139.6, 130.8, 129.6, 118.0, 90.3, 79.5, 78.1, 72.8, 57.7, 52.9, 46.7, 41.3, 41.1, 38.6, 36.4, 33.5, 32.5, 31.9, 20.0, 28.7, 28.5, 28.1, 20.9, 19.0, 18.7, 18.2, 17.9, 17.8, 13.7, 13.3, -3.7, -4.5. HRMS, calcd for C$_{52}$H$_{96}$IN$_2$O$_9$Si (M+H)$^+$ 1075.569 found 1075.568.
Catalytic asymmetric synthesis of (–)-Doliculide

(–)-(3R,6S,9S,11S,13R,14S,16S)-14-hydroxy-3-(3-iodo-4-((triisopropylsilyl)oxy)benzyl)-16-isopropyl-4,6,9,11,13-pentamethyl-1-oxa-4,7-diazacyclohexadecane-2,5,8-trione (28a)

To a stirred solution of ester 27a (23 mg, 0.021 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added trifluoroacetic acid (0.5 mL). The temperature was raised to rt over 1 h, the solution was stirred for an additional 2 h and then concentrated, co-evaporated three times with benzene, and dried under reduced pressure. To the above crude material in anhydrous CH$_2$Cl$_2$ (90 ml) were added N,N-bis(2-oxo-3-oxazolidinyl)-phosphinic reagent (BOP) (45 mg, 0.1 mmol) and DMAP (23 mg, 0.19 mmol) at 0 °C. The temperature was allowed to rise to rt overnight, and the reaction mixture was washed with dilute aq. HCl and brine. The organic layers were dried over MgSO$_4$ and concentrated to give a residue which was purified by flash chromatography (pentane:EtOAc, 40:10) to provide cyclic amide 28a (12 mg, 80%) as a colorless oil. $\Delta^{25}D = -21.4$ (c=0.38, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, $J = 1.6$ Hz, 1H), 7.00 (dd, $J = 8.2$, 1.8 Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.03 (dd, $J = 12.8$, 4.8 Hz, 1H), 5.09 (m, 1H), 4.97 (dd, $J = 9.2$, 7.2 Hz, 1H), 3.55 (m, 1H), 3.45 (dd, $J = 12.8$, 4.8 Hz, 1H), 2.97 (s, 3H), 2.82 (dd, $J = 15.6$, 12.5 Hz, 1H), 2.35-2.29 (m, 1H), 2.22 (d, $J = 4.4$ Hz, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.54-1.39 (m, 3H), 1.35-1.25 (m, 6H), 1.12 (d, $J = 7.5$ Hz, 23H), 1.12-1.06 (m, 4H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 7.2$ Hz, 3H), 0.92 (d, $J = 5.2$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.8, 175.6, 171.9, 154.6, 139.2, 130.6, 129.1, 118.1, 90.3, 77.1, 65.9, 56.7, 45.0, 44.0, 43.3, 39.1, 34.4, 32.5, 31.3, 29.8, 26.9, 18.8, 18.7, 18.5, 18.3, 18.1, 17.6, 14.4, 13.2. HRMS, calcd for C$_{37}$H$_{64}$IN$_2$O$_6$ (M+H)$^+$ 787.3572 found 787.3563.

(–)-Ala(Gly)-Doliculide (29)

To TIPS ether 28a (10 mg, 0.012 mmol) in THF (1.5 ml) was added TBAF (21 μl, 0.021 mmol, 1 M in THF) at 0 °C. The resulting solution was stirred for 15 min at this temperature. The reaction mixture was quenched by addition of saturated aq. NH$_4$Cl (300 μl) and diluted with EtOAc.
The aqueous phase was extracted with EtOAc (3×6 ml), and the organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography (pentane:EtOAc, 1:1) to give Ala(Gly)doliculide 29 (7.8 mg, 95%) as a white solid. [Į]D = –29.6 (c=0.23, MeOH). 1H NMR (500 MHz, CDCl₃) δ 7.55 (brs, 1H), 7.44 (d, J = 1.5 Hz, 1H), 7.09 (dd, J = 8.5, 2.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.30 (d, J = 9.5 Hz, 1H), 5.76 (dd, J = 12.5, 4.0 Hz, 1H), 5.11 (dd, d, J = 5.2, 1.8, 1H), 4.94 (dd, J = 8.5, 7.0 Hz, 1H), 3.58 (m, 1H), 3.49 (dd, J = 15.0, 4.5 Hz, 1H), 3.00 (s, 3H), 2.82 (dd, J = 15.0, 12.5 Hz, 1H), 2.40 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.73 (bbrs, 1H), 1.53 (t, J = 12.0 Hz, 1H), 1.40 (m, 1H), 1.25 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.07-1.00 (m, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H). 13C NMR (125 MHz, CDCl₃) δ 177.1, 176.5, 171.1, 154.4, 138.4, 130.3, 129.7, 115.3, 84.9, 77.4, 66.1, 57.0, 44.8, 43.9, 43.5, 39.0, 34.5, 33.4, 32.4, 31.6, 29.3, 26.9, 18.9, 18.68, 16.59, 17.6, 17.3, 14.4. HRMS calcd for C₂₈H₄₄N₂O₆ (M+H)+ 631.2238 found 631.2229.

Synthesis of Trp(iodoTyr) doliculide (34)

(+)-(R)-methyl 2-(benzyl(methyl)amino)-3-(1H-indol-3-yl)propanoate (30a)

To D-tryptophan methyl ester 30 (500 mg, 1.96 mmol) in MeOH (19 mL) was added benzaldehyde (209 µL, 2.06 mmol) in one portion. After 1 h of stirring at rt, NaBH₃CN (129 mg, 2.06 mmol) was added. After stirring for 18 h, paraformaldehyde (184 mg, 1.96 mmol (for MW = 90.1)), was added as a solid powder and allowed to dissolve. Following full dissolution, additional NaBH₃CN (129 mg, 2.06 mmol) was added and the reaction was allowed to stir at rt for 18 h. The reaction mixture was concentrated in vacuo. Ethyl acetate was added and the resulting slurry was filtered through celite and concentrated in vacuo. Flash chromatography, (EtOAc:hexanes 1:3) on neutralized silica gel (NEt₃) afforded 30a (550 mg, 89%) as a clear oil. [Į]D = +66.2 (c=0.93, CHCl₃). 1H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 7.46 (d, 1H, J = 7.8Hz), 7.26-7.20 (m, 6H), 7.13 (t, 1H, J = 7.2 Hz), 7.04 (t, 1H, J = 7.64 Hz), 6.93 (d, 1H, J = 2.0 Hz), 3.84 (d, 1H, J = 13.6 Hz), 3.71 (dd, 1H, J = 5.8, 9.0 Hz), 3.62 (d, 1H, J = 12.5 Hz), 3.60 (s, 3H), 3.33 (dd, 1H, J = 9.1,14.4 Hz), 3.08 (dd, 1H, J = 5.8, 14.4 Hz), 2.34 (s, 3H). 13C NMR (101 MHz, CDCl₃) δ 172.8, 139.4, 136.2, 128.9, 128.3, 127.6, 127.1, 122.8, 121.9, 119.3, 118.8, 112.3, 111.2, 66.4, 58.9, 51.1, 38.3, 25.8. [Į]D = –21.4 (c = 0.025 in MeOH). HRMS calcd for C₂₀H₂₃N₂O₂ [M+H]+ 323.1754, found 323.1776.
Catalytic asymmetric synthesis of (−)-Doliculide

(+)-(R)-methyl 2-[(2-((tert-butoxycarbonyl)amino)-N-methylacetamido)-3-(1H-indol-3-yl)propanoyl] (32)

The N-benzyl-N-methyl amino ester 30a (633 mg, 1.96 mmol), was dissolved in methanol (19.6 mL). After degassing, Pd(OH)$_2$ (20% Pd, 317 mg), was added, the solution was placed on an autoclave and treated with 55 psi of H$_2$ for 18 h. Filtration through celite and concentration in vacuo afforded the N-methyl amino ester 31 (449 mg, 99%). To this amine 31 (325 mg, 1.40 mmol) and Boc-glycine (294 mg, 1.68 mmol) in a 3:1 mixture of CH$_2$Cl$_2$:DMF (8 mL) at 0 °C were added EDC (249 mg, 1.61 mmol) and HOBT (227 mg, 1.68 mmol). The resulting solution was warmed to room temperature and stirred for 5 h. The solution was quenched with saturated aq. NH$_4$Cl, diluted with dichloromethane and washed with water. The organic layer was separated, dried, and concentrated to give dipeptide 32 (462 mg, 85%) after column chromatography (pentane:EtOAc, 60:40).

$[\alpha]_D^{25} = +32.9$ (c=6.38, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.41 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.95 (s, 1H), 5.48 (br s, 1H), 5.29 (dd, J = 10.4, 5.6 Hz, 1H), 3.92 (dd, J = 17.6, 4.4 Hz, 1H), 3.80 (br d, J = 17.6, 4.4 Hz, 1H), 3.72 (s, 3H), 3.45 (dd, J = 15.2, 5.2 Hz, 1H), 3.26 (dd, J = 15.2, 10.4 Hz, 1H), 2.73 (s, 3H), 1.44 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.3, 169.2, 155.9, 136.3, 127.3, 122.4, 122.2, 119.6, 118.3, 111.5, 110.8, 79.8, 58.4, 52.5, 42.6, 31.8, 28.4, 24.4. HRMS calcld for C$_{20}$H$_{27}$N$_3$O$_5$Na [M+Na]$^+$, 412.1842, found 412.1871.

(+)-(2R,4S,6R,7S,9S)-tert-butyl 9-(((R)-2-((tert-butoxycarbonyl)amino)-N-methylacetlamido)-3-(1H-indol-3-yl)propanoyl)oxy)-7-((tert-butylidimethylsilyl)oxy)-2,4,6,10-tetramethylundecanoate (33)

To dipeptide 31 (250 mg, 0.64 mmol) in a 2:1 mixture of THF:water (7 mL) was added LiOH (94 mg, 2.24 mmol) at 0 °C. The resulting mixture was stirred for 1 h and then acidified to pH=3.5 with aqueous NaHSO$_3$. The mixture was extracted with ether. The combined organic layers were dried over MgSO$_4$ and concentrated to give the acid (190 mg) after column chromatography (CH$_2$Cl$_2$: MeOH, 10:1). To a stirred solution of alcohol 5 (16 mg, 0.036 mmol) and the acid (67 mg, 0.18 mmol) in CH$_2$Cl$_2$ (14 mL) at –20 °C, were
added DCC (37 mg, 0.18 mmol) and DMAP (5.3 mg, 0.043 mmol). The resulting mixture was stirred at –20°C for 16 h and then filtered through a short plug of silica gel and concentrated. The residue was purified by flash chromatography (pentane:EtOAc, 10:1) to give 33 (26.5 mg, 93%) as a colorless oil. 

1H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 5.50 (brs, 1H), 5.43 (dd, J = 10.4, 4.8 Hz, 1H), 4.96 (m, 1H), 3.86 (d, J = 3.6 Hz, 1H), 3.49-3.44 (m, 2H), 3.24 (dd, J = 15.2, 10.4 Hz, 1H), 2.80 (s, 3H), 2.42 (m, 1H), 1.93 (m, 1H), 1.71-1.64 (m, 4H), 1.43 (s, 1H), 1.25 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.89-0.81 (m, 24H), 0.04 (d, J = 4.0 Hz, 6H).

13C NMR (101 MHz, CDCl₃) δ 176.5, 170.6, 169.1, 155.8, 136.3, 127.4, 122.4, 122.1, 119.7, 118.4, 111.4, 111.1, 80.0, 79.7, 77.9, 72.8, 57.7, 42.7, 41.3, 41.0, 38.6, 36.4, 32.5, 31.9, 28.7, 28.5, 28.2, 26.1, 24.5, 20.8, 18.6, 18.2, 17.9, 17.8, 13.6, -3.8, -4.5. HRMS calcd for C₄₄H₇₅N₃O₈SiNa [M+Na]⁺, 824.5215, found 824.5188.

(1S,2R)-Trp(iodoTyr) doliculide (34)

To a stirred solution of ester 20 (12.5 mg, 0.016 mmol) in CH₂Cl₂ (1 mL) at 0°C was added trifluoroacetic acid (0.4 mL). The temperature was raised to rt over 1 h, the solution was stirred for an additional 2 h and then concentrated, co-evaporated three times with benzene, and dried under reduced pressure. To the above crude in anhydrous CH₂Cl₂ (40 ml) were added N,N-bis(2-oxo-3-oxazolidinyl)-phosphinic reagent (BOP) (34 mg, 0.07 mmol) and DMAP (15 mg, 0.12 mmol) at 0 °C. The temperature was allowed to rise to rt overnight, and the reaction mixture was washed with dilute aq. HCl and brine. The organic layers were dried over MgSO₄ and concentrated to give a residue which was purified by flash chromatography (pentane:EtOAc, 2:1) to provide Trp(iodoTyr) doliculide 34 (6.4 mg, 82%) as a colorless oil. [α]D²⁵ = +2.26 (c=1.41, CHCl₃) 

1H NMR (400 MHz, CDCl₃:CD₃OD 10:1) δ 8.86 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.44-7.35 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H), 5.44 (dd, J = 12.4, 5.4 Hz, 1H), 5.01 (dd, J = 11.2, 4.8 Hz, 1H), 4.71 (dd, J = 16.4, 6.0 Hz, 1H), 3.54 (dd, J = 9.6, 4.2 Hz, 1H), 3.51 (dd, J = 15.6, 4.0 Hz, 1H), 3.35 (br s, 1H), 3.24-3.15 (m, 2H), 2.92 (s, 3H), 2.38 (m, 1H), 1.96 (sextet, J = 5.6, 1H), 1.85 (sextet, J = 5.6, 1H), 1.43 (m, 1H), 1.29 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H), 1.04-0.98 (m, 3H), 0.93 (d, J = 7.6 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H). 

13C NMR (101 MHz, CDCl₃:CD₃OD 10:1) δ 178.1, 172.6, 171.7, 136.3, 127.4, 122.4, 122.1, 119.7, 118.3, 80.0, 79.7, 77.9, 72.8, 111.4, 110.5, 77.4, 65.8, 58.1, 45.0, 43.1, 39.8, 39.1, 34.5, 32.5, 30.8, 30.3, 27.2,
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24.7, 18.9, 18.0, 17.7, 14.5. HRMS calcd for C_{29}H_{43}N_{3}O_{5}Na [M+Na]^+ 536.3094, found 536.3135.

3.5 References