Supplementary Materials for

A domino 10-step total synthesis of FR252921 and its analogues, complex macrocyclic immunosuppressants.

Yong Chen,1 Guilhem Coussanes,1 Caroline Souris,1 Paul Aillard,1 Dainis Kaldre,1 Kathrin Runggatscher,2 Stefan Kubicek,2 Giovanni Di Mauro,1 Boris Maryasin1,3 and Nuno Maulide1,2,*

1 Institute of Organic Chemistry, University of Vienna, Währinger Strasse 38, 1090 Vienna, Austria
2 CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Lazarettgasse 14, AKH B1 25.3, 1090 Vienna, Austria
3 Institute of Theoretical Chemistry, University of Vienna, Währinger Strasse 17, 1090 Vienna, Austria

Correspondence to: nuno.maulide@univie.ac.at
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1. General information

Unless otherwise stated, all glassware was oven dried before use and all reactions were carried out under an argon atmosphere using standard Schlenk-techniques. Dry solvents were purchased from Acros Organics or Sigma-Aldrich and used without further purification. All reagents were purchased from commercial sources and were used without further purification unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with Kieselgel F254 with 0.2 mm thickness. Visualization was achieved by ultraviolet light (254 nm) or by staining with potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck ans co.). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Mass spectra were obtained using a Finnigan MAT 8200 (70 eV), an Agilent 5973 (70 eV), using electrospray ionization (ESI) or electron impact ionization (EI). All \(^1\)H NMR, \(^13\)C NMR NMR were recorded on a BrukerAV-400, AV-500, AV-600 or AV-700 spectrometer in Chloroform-\(d\)1 or DMSO-\(d\)6. Chemical shifts are given in parts per million (ppm), referenced to tetramethylsilane using the solvent peak as internal standard (CDCl\(_3\): \(^1\)H = 7.26 ppm, \(^13\)C = 77.16 ppm; CD\(_3\)SOCD\(_3\): \(^1\)H = 2.50 ppm, \(^13\)C = 39.52 ppm). Coupling constants were quoted in Hz. \(^1\)H NMR splitting patterns were designated as singlet (s), broad (brd), doublet (d), triplet (t), quartet (q), pentet (p), sextet (se), septet (sep), octet (o) or combinations thereof. Splitting patterns that could not be interpreted were designated as multiplet (m).
2. Synthesis and characterizations

2.1. Synthesis of compound 6

To a flame-dried 100 mL Schlenk tube was added Schwartz reagent Cp₂ZrHCl (1.04 g, 4.03 mmol, 0.1 equiv.) under argon, then CH₂Cl₂ (30 mL) was added. The resulted white suspension was then charged with 1-nonyne (6.6 mL, 40.3 mmol, 1.0 equiv.) and gradually a yellowish solution was formed. To this solution, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin) (6.4 mL, 44.3 mmol, 1.1 equiv.) was added, followed by trimethylamine (Et₃N) (0.56 mL, 4.03 mmol, 0.1 equiv.). The mixture was then heated to reflux for 16 h. ¹H NMR was used to monitor the reaction. Once the alkyne was fully consumed, then the mixture was concentrated under vacuum. Purification by column chromatography (silica gel, Heptane/EtOAc = 15:1) afforded 9.62 g (79%) of the product 3 as a colorless oil. The spectra data is in accordance with the literature.

The acid (rac)-7 has been synthesized before by our group. We describe herein an improved synthesis of (rac)-7 through modification of the purification conditions.

The bicyclobutene lactone (0.3 M, 34 mL, Et₂O) was stirred with activated 3 Å molecular sieves (10 g) at -20 °C for 15 min. Then dry HCl (2 M in Et₂O, 20 mL) was added. The solution was then stirred vigorously at -20 °C for another 24 h. The mixture was then allowed to warm to room temperature, concentrated. Purification by column chromatography (silica gel,
Heptane/EtOAc = 4:1, 3% AcOH as additive) afforded 1.10 g (83%) of acid (rac)-7 as a colorless powder.

Typical yield obtained using the non-improved purification or crystallization: 44%3.

**NB:** The addition of acetic acid in the eluent is crucial for a facile isolation of acid (rac)-7 by column chromatography.

In a schlenck tube, cis-chloro cyclobutene methyl ester 44 (15 mg, 0.10 mmol, 1.0 equiv.), Pd(OAc)2 (2.3 mg, 0.01 mmol, 10 mol%), SPhos (8.4 mg, 0.02 mmol, 20 mol%) and K3PO4 (65.0 mg, 0.30 mmol, 3.0 equiv.) were charged. Then a solution of (E)-4,4,5,5-tetramethyl-2-(non-1-en-1-yl)-1,3,2-dioxaborolane 3 (28.3 mg, 0.11 mmol, 1.5 equiv.) in THF (3.0 mL) was added. Finally degassed H2O (1.0 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 3 h. Once the starting material disappeared on TLC, EtOAc (1 mL) and 1 M HCl (0.5 mL) was added. The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine, dried over Na2SO4, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc: 9/1) afforded 19.4 mg (82%) of the desired product 6 as a colorless oil. **FTIR (CHCl3, cm⁻¹):** 2924, 2854, 1717, 1617, 1434, 1360, 1302, 1260, 1135, 1004, 632. **1H NMR (500 MHz, CDCl3):** δ 7.30 (dd, J = 15.1, 10.9 Hz, 1H), 6.52 (dd, J = 15.1, 10.9 Hz, 1H), 6.20 (dd, J = 14.9, 11.4 Hz, 1H), 6.12 (dd, J = 14.9, 10.9 Hz, 1H), 5.96-5.90 (m, 1H), 5.84 (d, J = 18.3 Hz, 1H), 3.74 (s, 3H), 2.13 (q, J = 7.6 Hz, 2H), 1.43-1.37 (m, 2H), 1.31-1.24 (m, 8H), 0.87 (t, J = 7.6 Hz, 3H) ppm. **13C NMR (126 MHz, CDCl3):** δ 167.8, 145.3, 141.6, 141.0, 129.9, 127.8, 119.6, 51.6,
33.1, 31.9, 29.3, 29.2, 29.1, 22.8, 14.2 ppm. **HRMS (ESI) (m/z):** calculated for [M]$^+$ (C$_{15}$H$_{24}$O$_2$) requires 236.1774, found 236.1776.

### 2.2. Synthesis of compound 11

![Reaction Scheme]

To a two-necked 250 mL round bottom flask was added 10 g 3 Å molecular sieves, pent-4-ynoic acid 8 (4.80 g, 48.9 mmol, 1.0 equiv.) and tBuOH (150 mL). The solution was stirred at room temperature for 30 min. Then diphenyl phosphoryl azide (DPPA) (11.6 mL, 54 mmol, 1.1 equiv.) and Et$_3$N (7.5 mL, 54 mmol, 1.1 equiv.) were added. The resulted mixture was heated to reflux for 12 h. Then the mixture were concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 3:1) afforded 5.38 g (65%) of the desired product 9 as a colorless oil. The spectral data is in accordance with the literature$^5$.

![Reaction Scheme]

In a dry flask, tert-butyl but-3-yne-1-ylcarbamate 9 (8.40 g, 49.7 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (80 mL) was charged. Then HBpin (8.6 mL, 59.6 mmol, 1.2 equiv.) was added, followed by Cp$_2$ZrHCl (Schwarz reagent) (1.28 g, 4.97 mmol, 10 mol%) and Et$_3$N (0.70 mL, 4.97 mmol, 10 mol%). The mixture was stirred at 60°C for 16 h. Then the reaction mixture was cooled down to room temperature. The mixture was concentrated under reduced pressure. Purification by column chromatography (silica gel, Pentane/EtOAc: 7/3) afforded 12.6 g (85%) of the desired hydroborated product 10 as a white solid upon storage in the fridge. **FTIR (CHCl$_3$, cm$^{-1}$):** 3339, 2978, 1714, 1639, 1359, 1144, 850. **$^1$H NMR (500 MHz, CDCl$_3$):** δ 6.53 (dt, $J = 17.9, 6.7$ Hz,
1H) 5.49 (d, $J = 17.9$ Hz, 1H), 4.56 (brd, 1H), 3.24-3.17 (m, 2H), 2.33 (app. q, $J = 6.6$ Hz, 2H), 1.41 (s, 9H), 1.25 (s, 12H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 156.0, 150.7, 121.5, 83.4, 79.3, 39.3, 36.3, 28.7, 25.1 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{15}$H$_{28}$BNO$_4$Na) requires 320.2002, found 320.2003.

To a stirred solution of tert-butyl (E)-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)carbamate 10 (8.30 g, 27.9 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (50 mL) was added trifluoroacetic acid (TFA) (21.3 mL, 115 mmol, 10 equiv.). The resulting mixture was vigorously stirred at room temperature for 1 h. Then CH$_2$Cl$_2$ and TFA was removed under vacuum to give the crude amine salt 11 (8.60 g) as a yellowish oil which was used in the next step without further purification.

2.3. Synthesis of compound 16

Compound 13 was prepared as described in the literature$^6$. NaN$_3$ (4.32 g, 66.4 mmol, 2.0 equiv.) was added to the stirred solution of ethyl (R)-(γ)-4-chloro-3-hydroxybutanoate 12 (5.54 g, 33.2 mmol, 1.0 equiv.) in DMF (80 mL), then the mixture was heated to 100 ºC for 3 h. Once peaks of compound 12 disappeared on crude $^1$H NMR, the mixture was cooled to room temperature and the salt was filtered. The remaining salt was washed wish EtOAc (30 mL). The collected organic phase was concentrated to give a crude oil. Purification by column chromatography
(silica gel, Heptane/EtOAc = 2:1) afforded 4.66 g (81%) of the product 13 as a light yellowish oil. The spectral data is in accordance with the literature.\(^6\) \(\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\):} \(\delta\) 4.24-4.16 (m, 3H), 3.40-3.31 (m, 2H), 3.16 (d, \(J = 4.2\) Hz, 1H), 2.55 (d, \(J = 4.4\) Hz, 1H), 2.53 (d, \(J = 1.6\) Hz, 1H), 1.28 (t, \(J = 7.1\) Hz, 3H) ppm. \([\alpha]_D^{20} = +4.4\) (C = 1.2, MeOH). Lit.\(^6\) \([\alpha]_D^{28} = +7.5\) (c = 3.65, MeOH).

The solution of ethyl (\(R\))-4-azido-3-hydroxybutanoate 13 (3.10 g, 17.9 mmol, 1.0 equiv.) in THF (10 mL) was dropwise added to the solution of LHMDS (1.0 M in THF, 36.7 mL, 2.05 equiv.) at -60 °C, and the resulting mixture was stirred vigorously for 30 min. Then the temperature was increased to -35 °C and the mixture was stirred for another 30 min. The temperature was cooled down to -60 °C again, then MeI (2.2 mL, 35.8 mmol, 2.0 equiv.) was added. The mixture was stirred at -60 °C for 2 h, then -40 °C for 2 h and -20 °C for another 2 h. Then the mixture was quenched by 15% citric acid (aq.) (50 mL) to adjust the pH around 3-4. The aqueous layer was extracted with EtOAc (3 x 40 mL) and the combined organic layers were washed by brine, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1) afforded 2.38 g (71%, d.r. = 18:1) of the desired product 14 as a colorless oil. In addition, 260 mg (8%) of starting material 13 was also recovered. \(\text{FTIR (CHCl}_3, \text{cm}^{-1}\):} 2101, 1724, 1459, 1262, 1186. \(\text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3\):} \(\delta\) 4.19 (q, \(J = 7.1\)Hz, 2H), 3.89-3.85 (m, 1H), 3.43 (dd, \(J = 12.7, 3.8\) Hz, 1H), 3.35 (dd, \(J = 12.7, 6.2\) Hz, 1H), 3.16 (d, \(J = 6.1\) Hz, 1H), 2.71 – 2.62 (m, 1H), 1.29 (t, \(J = 7.1\) Hz, 3H), 1.22 (d, \(J = 7.2\) Hz, 3H). \(\text{\textsuperscript{13}C NMR (151 MHz, CDCl}_3\):} \(\delta\) 175.5, 72.8, 61.2, 54.5, 42.6, 14.3 ppm. HRMS
(ESI) (m/z): calculated for [M+Na]$^+$ (C$_7$H$_{13}$N$_3$O$_3$Na) requires 210.0849, found 210.0848. $[\alpha]_D^{20}$ = +2.45 (c = 1.02, CHCl$_3$).

The d.r. of compound 14 was determined by the reduction of the ester to the corresponding alcohol 14'.

Fig. S1. $^1$H NMR of reduced ester 14 to determine the d.r.

To a stirred solution of ethyl (2S,3R)-4-azido-3-hydroxy-2-methylbutanoate 14 (2.11 g, 11.3 mmol, 1.0 equiv.) and 2,6-lutidine (2.6 mL, 22.5 mmol, 2.0 equiv.) in CH$_2$Cl$_2$ (22 mL) at 0 °C
was added TBSOTf (3.4 mL, 14.7 mmol, 1.3 equiv.). The mixture was stirred vigorously for 30 min at 0 °C, then quenched by sat. NH₄Cl (aq.) (15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers were washed by brine, dried over MgSO₄, filtered and concentration under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 15:1) afforded 3.33 g (98%) of the desired product 15 as a colorless oil. **FTIR (CHCl₃, cm⁻¹):** 2165, 2029, 1960, 1900, 1217, 773. **¹H NMR (400 MHz, CDCl₃):** δ 4.13 (q, J = 7.1 Hz, 2H), 4.06-4.00 (m, 1H), 3.40 (dd, J = 12.8, 3.8 Hz, 1H), 3.23 (dd, J = 12.8, 5.5 Hz, 1H), 2.78-2.71 (m, 1H) 1.27 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 174.1, 73.2, 60.7, 54.3, 44.3, 25.8, 18.0, 14.3, 12.6, -4.2, -5.0 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]⁺ (C₁₃H₂₇O₃N₃SiNa) requires 324.1714, found 324.1707. [α]D²⁰ = +26.8 (c = 0.91, CHCl₃).

Ethyl (2S,3R)-4-azido-3-((tert-butyldimethylsilyl)oxy)-2-methylbutanoate 15 (3.00 g, 9.95 mmol, 1.0 equiv.) was dissolved in THF/MeOH/H₂O (20 mL/20 mL/10 mL), then LiOH•H₂O (2.09 g, 49.8 mmol, 5.0 equiv.) was added. The resulting mixture was stirred at room temperature for 4 h. Then MeOH was removed under vacuum, the mixture was acidified by 1 N HCl (aq.) to pH = 2-3. The aqueous phase was extracted with EtOAc (5 x 10 mL), the combined organic layers were washed by brine, dried over MgSO₄, filtered and concentration under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 5:1 to 2:1) afforded 2.62 g (96%) of the desired product 16 as a colorless oil. **FTIR (CHCl₃, cm⁻¹):** 2930, 2858, 2101, 1709, 1256, 1104, 837, 777. **¹H NMR (400 MHz, CDCl₃):** δ 4.02 (td, J = 5.6,
4.0 Hz, 1H), 3.44 (dd, J = 12.8, 4.0 Hz, 1H), 3.26 (dd, J = 12.8, 5.4 Hz, 1H), 2.85-2.74 (m, 1H),
1.17 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H) ppm. ¹³C NMR (100 MHz,
CDCl₃): δ 179.5, 73.2, 54.2, 44.0, 25.8, 18.1, 12.7, -4.2, -5.0 ppm. HRMS (ESI) (m/z):
calculated for [M+Na]+ (C₁₁H₂₃O₃N₃SiNa) requires 296.1401, found 296.1403. [α]D²⁰ = +22.1 (c
= 1.10, CHCl₃). Lit.⁸ [α]D²⁰ = +22.5 (c = 1.7, CHCl₃).

2.4. Synthesis of compound 18

To a stirred solution of ethyl (R)-4-azido-3-hydroxybutanoate 13 (485 mg, 2.8 mmol, 1.0 equiv.)
and 2,6-lutidine (0.65 mL, 5.6 mmol, 2.0 equiv.) in CH₂Cl₂ (5 mL) at 0 °C was added TBSOTf
(1.0 mL, 4.2 mmol, 1.5 equiv.). The mixture was stirred vigorously for 30 min at 0 °C, then
quenched by sat. NH₄Cl (aq.) (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL),
the combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated
under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc =
15:1) afforded 710 mg (88%) of the desired product 17 as a colorless oil. The spectral data is in
accordance with the literature⁶. ¹H NMR (400 MHz, CDCl₃): δ 4.28-4.22 (m, 1H), 4.19-4.07
(m, 2H), 3.37 (dd, J = 12.5, 4.4 Hz, 1H), 3.23 (dd, J = 12.5, 5.3 Hz, 1H), 2.53 (dd, J = 6.3, 3.8
Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm. [α]D²⁰ = -2.7 (c
= 0.82, CHCl₃). Lit.⁶ [α]D²⁵ = +2.2 (c = 0.33, CHCl₃). (We believed the reported value by the
literature⁶ was wrong. We synthesized compound 17 starting from two different batches of the
starting material (R)-(γ)-4-chloro-3-hydroxybutanoate 12 and both gave the optical rotation
values minus sign. For instance, another measured value of compound 17: \([\alpha]_D^{20} = -1.0 \) (c = 1.0, CHCl₃).

To a stirred solution of ethyl (R)-4-azido-3-((tert-butyldimethylsilyl)oxy)butanoate 17 (645 mg, 2.24 mmol, 1.0 equiv.) in THF/MeOH/H₂O (2/2/1, 11 mL) at 0 °C was added LiOH•H₂O (471 mg, 11.2 mmol, 5.0 equiv.). The resulting mixture was stirred vigorously for 4 h at room temperature. Then MeOH was removed under vacuum, and the mixture was acidified by 1 N HCl (aq.) to pH = 2-3. The aqueous phase was extracted with EtOAc (5 x 10 mL), the combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 3:1) afforded 500 mg (86%) of the desired product 18 as a colorless oil. FTIR \((\text{CHCl}_3, \text{cm}^{-1})\): 2930, 2858, 2104, 1712, 1285, 1256, 1110, 837, 778. \(\text{¹H NMR (400 MHz, CDCl}_3\):} \delta 4.32-4.19 \text{(m, 1H)}, 3.38(dd, \text{J} = 12.6, 4.5 \text{Hz, 1H)}, 3.26 \text{(dd, J = 12.6, 5.2 Hz, 1H)}, 2.60 \text{(qd, J = 15.7, 6.1 Hz, 2H)} \text{0.89 (s, 9H)}, 0.13 \text{(s, 3H)}, 0.10 \text{(s, 3H)} \text{ppm.} \text{¹³C NMR (100 MHz, CDCl}_3\):} \delta 175.9, 68.6, 56.4, 39.8, 25.8, 18.0, -4.6, -4.9 ppm. HRMS \((\text{ESI}) \text{(m/z):} \text{calculated for [M+Na]⁺ (C₁₀H₂₀O₃N₃Si) requires 258.1279, found 258.1277.} \ [\alpha]_D^{20} = +3.03 \) (c = 1.22, CHCl₃).

2.5. Synthesis of amine 21, 23 and 25

\[ \text{TBSO} \quad \text{OS} \quad \text{N} \quad \text{Me} \quad \text{HATU} \quad \text{BF₄}^- \quad \text{TBSO} \quad \text{OS} \quad \text{N} \quad \text{Me} \quad \text{BH₃} \quad \text{BF₄}^- \quad \text{92%} \]

S12
The crude amine salt 11 (3.58 g, 11.5 mmol, 1.2 equiv.) and the acid 16 (2.62 g, 9.55 mmol, 1.0 equiv.) were dissolved in CH₂Cl₂ (50 mL). At 0 °C, Et₃N (13.3 mL, 95.5 mmol, 10 equiv.) was added, followed by O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (4.36 g, 11.5 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature overnight. Then the reaction was quenched by 1 N HCl (aq.) (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 1:1) afforded 4.00 g (92%) of the product 20 as a colorless oil. FTIR (CHCl₃, cm⁻¹): 2977, 2932, 2102, 1643, 1361, 1101. ¹H NMR (400 MHz, CDCl₃): δ 6.54 (dt, J = 17.9, 6.5 Hz, 1H), 5.93 (t, J = 4.8 Hz 1H), 5.50 (dd, J = 18.0, 0.9 Hz, 1H), 3.97-3.85 (m, 1H), 3.45 (ddd, J = 13.1, 9.8, 5.1 Hz, 2H), 3.28-3.15 (m, 2H), 2.51-2.39 (m, 1H), 2.35 (ap q, J = 6.7 Hz, 2H), 1.25 (s, 12H), 1.10 (d, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 174.0, 150.3, 83.3, 73.6, 54.8, 45.6, 38.0, 35.7, 25.9, 24.9, 18.1, 15.0, -4.3, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₁H₄₁O₄N₄BSiNa) requires 475.2882, found 475.2886. [α]D²⁰ = +6.56 (c = 0.90, CHCl₃).

To a solution of amide 20 (4.00 g, 8.84 mmol, 1.0 equiv.) in THF/MeOH/H₂O (30 mL/30 mL/ 30 mL) was added activated zinc (2.32 g, 35.4 mmol, 4.0 equiv.) and NH₄Cl (3.79 g, 70.8 mmol, 8.0 equiv.). The mixture was stirred vigorously at room temperature for 3 h. Then the organic solvents were removed under vacuum. The remaining aqueous phase was basified by sat.
Na₂CO₃ (aq.) (10 mL) to pH around 9, and extracted with CH₂Cl₂ (5 x 15 mL). The combined organic layers were washed by brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product 21 (3.77 g) was used in the next step without further purification.

The crude amine salt 11 (675 mg, 2.17 mmol, 1.2 equiv.) and the acid 18 (470 mg, 1.8 mmol, 1.0 equiv.) were dissolved in CH₂Cl₂ (10 mL). At 0 °C, Et₃N (2.5 mL, 18 mmol, 10 equiv.) was added, followed by HATU (961 mg, 2.53 mmol, 1.4 equiv.). The resulting mixture was allowed to warm to room temperature overnight. Then the reaction was quenched by 1 N HCl (aq.) (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 1:1) afforded 561 mg (71%) of the product 22 as a colorless oil. FTIR (CHCl₃, cm⁻¹): 3309, 2930, 2858, 2102, 1642, 1552, 1454, 1360, 1322, 1256, 1145, 1096, 971, 838, 778. ¹H NMR (600 MHz, CDCl₃): δ 6.54 (dt, J = 17.8, 6.4 Hz, 1H), 5.79 (s, 1H), 5.52 (d, J = 18.0 Hz, 1H), 4.33-4.21 (m, 1H), 3.45-3.40 (m, 1H), 3.38 (dd, J = 12.7, 3.5 Hz, 1H), 3.31-3.26 (m, 1H), 3.18 (dd, J = 12.6, 4.8 Hz, 1H), 2.41 (dd, J = 14.4, 5.4 Hz, 1H), 2.38-2.35 (m, 2H), 2.34 (dd, J = 14.2, 6.1 Hz, 1H), (1.27 (s, 12H), 0.89 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 170.0, 150.2, 121.7, 83.4, 69.3, 56.4, 42.2, 38.1, 35.6, 25.9, 24.9, 18.1, -4.6, -4.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₀H₃₉O₄N₄BSiNa) requires 461.2726, found 461.2701. [α]D₂₀ = -9.71 (c = 1.03, CHCl₃).
To a solution of amide 22 (561 mg, 1.28 mmol, 1.0 equiv.) in THF/MeOH/H₂O (3 mL/3 mL/3 mL) was added activated zinc (167 mg, 2.56 mmol, 4.0 equiv.) and NH₄Cl (274 mg, 5.12 mmol, 8.0 equiv.). The mixture was stirred vigorously at room temperature for 3 h. Then the organic solvents were removed under vacuum. The remaining aqueous phase was basified by sat. Na₂CO₃ (aq.) (10 mL) to pH around 9, and extracted with CH₂Cl₂ (5 x 15 mL). The combined organic layers were washed by brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product 23 was used in the next step without further purification.

The crude amine salt 11 (1.00 g, 5.07 mmol, 1.3 equiv.) and carboxylic acid 19 (0.793 g, 3.9 mmol, 1.0 equiv.) were dissolved in CH₂Cl₂ (20 mL) and cooled down to 0 °C. Diisopropyl ethyl amine (DIPEA) (5.4 mL, 31.2 mmol, 8.0 equiv.) was added, followed by EDCI (1.12 g, 5.85 mmol, 1.4 equiv.) and HOBt (88% w/w, 0.90 g, 5.85 mmol, 1.4 equiv.). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was then diluted with water. The aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL), washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH₂Cl₂/EtOAc = 20:1 to 9:1) to afford the desired product.
24 (861 mg, 58%). **FTIR (CHCl₃, cm⁻¹):** 3177, 2978, 2932, 1692, 1641, 1532, 1363, 1322, 1271, 1167, 1145. **¹H NMR (600 MHz, CDCl₃):** δ 6.55 (dt, J = 18.0, 6.5 Hz, 1H), 5.99 (brd, 1H), 5.51 (d, J = 18.0 Hz, 1H), 4.76 (brd, 1H), 3.35 (q, J = 6.6 Hz, 2H), 3.15 (q, J = 6.6 Hz, 2H), 2.37 (q, J = 6.6 Hz, 2H), 2.18 (t, J = 6.2 Hz, 2H), 1.79 (p, J = 6.8 Hz, 2H), 1.43 (s, 9H), 1.26 (s, 12H) ppm. **¹³C NMR (151 MHz, CDCl₃):** δ 172.5, 156.4, 150.3, 83.2, 39.72 38.6, 38.0, 35.6, 33.7, 31.0, 28.4, 26.3, 24.8 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]⁺ (C₁₉H₃₅B₉NaO₅) requires 405.2531, found 405.2531.

To a solution of carbamate 24 (861 mg, 1.90 mmol, 1.0 equiv.) in CH₂Cl₂ (20 mL) at 0 °C was carefully charged TFA (1.61 mL, 22.5 mmol, 12 equiv.) and the mixture was stirred for 1 h at room temperature. TFA and CH₂Cl₂ were removed under vacuum to afford 1.26 g of the crude salt 25 which was used as such in the next step.
2.6. Numbering of the compounds

For more clarity, the following numbering of the compounds will be used. The compounds within the same series will be classified by a same letter. Therefore the compound name is composed of a number and a letter.

**Table S1. Numbering of the compounds**

| Series     | Letter |
|------------|--------|
| FR252921   | a      |
| FR252922   | b      |
| FR256523   | c      |
| FR1        | d      |
| FR2        | e      |
| FR3        | f      |
| FR4        | g      |
| FR5        | h      |
| FR6        | i      |
| FR7        | j      |
| FR8        | k      |
| FR9        | l      |
| FR10       | m      |
| FR11       | n      |
2.7. Synthesis of aldehydes

General method A

![Chemical structure](image)

**Fig. S2.** Synthesis aldehyde *via* method A

1) At room temperature, to the solution of the aldehyde (1.0 equiv.) in toluene was added the Wittig reagent (1.1 equiv.). Reaction was stirred at 80 °C for 12 h, then cooled to room temperature and the solvent was removed *in vacuo*. Crude product was purified by column chromatography on silica gel to give the pure ester or directly used in the next step after simple filtration over silica.

2) The ester obtained was then dissolved in CH₂Cl₂. At 0 °C, diisobutylaluminium hydride (DIBAL-H) (2.5 equiv.) was dropwise added. After 1 h, the mixture was first carefully quenched by sat. Rochelle salt solution. The resulting mixture was allowed to stir vigorously till the organic and aqueous phases separated. Then the mixture was extracted with CH₂Cl₂ 3 times. The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

3) To the solution of the crude alcohol (1.0 equiv.) in CH₂Cl₂ was added activated MnO₂ (15 equiv.). The mixture was stirred vigorously for 5 h. Then the mixture was filtrated, and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel delivered the desired aldehyde.
General method B

Fig. S3. Synthesis aldehyde via method B

1) At 0 °C, to the solution of the phosphonate (1.2 equiv.) in THF, was added portion wise NaH (1.3 equiv.). The mixture was stirred for 30 min. The aldehyde (1.0 equiv.) in THF solution was added, and the mixture was stirred for another 2 h. The reaction was carefully quenched by sat. NH₄Cl. The aqueous phase was extracted with EtOAc 3 times. The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel to give the pure ester.

2) The ester obtained was then dissolved in CH₂Cl₂. At 0 °C, diisobutylaluimnum hydride (DIBAL-H) (2.5 equiv.) was dropwise added. After 1 h, the mixture was first carefully quenched by sat. Rochelle salt solution. The resulting mixture was allowed to stir vigorously till the organic and aqueous phases separated. Then the mixture was extracted with CH₂Cl₂ 3 times. The combined organic layers were washed by brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

3) To the solution of the crude alcohol (1.0 equiv.) in CH₂Cl₂ was added activated MnO₂ (15 equiv.). The mixture was stirred vigorously for 5 h. Then the mixture was filtrated, and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel delivered the desired aldehyde.
Yield: 63% over 3 steps (method B). The spectra data is in accordance with the literature⁹.
Yield: 92% (method B). FTIR (CHCl₃, cm⁻¹): 2925, 1706, 1234. ¹H NMR (400 MHz, CDCl₃): δ 6.25 (ddt, J = 14.9, 10.8, 1.3 Hz, 1H), 6.02 (d, J = 10.8 Hz, 1H), 5.78-5.64 (m, 1H), 4.05 (s, 2H), 2.11 (q, J = 7.0 Hz, 2H), 1.78 (s, 3H), 1.46-1.34 (m, 2H), 1.28 (d, J = 13.8 Hz, 12H), 0.88 (t, J = 6.9 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 157.7, 135.5, 134.8, 125.9, 125.6, 68.9, 33.1, 32.1, 29.7, 29.7, 29.6, 29.5, 29.4, 22.8, 14.2, 14.2 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₁₇H₃₀O₂Na) requires 289.2138, found 289.2135.

Yield: 76% over 2 steps (method A). FTIR (CHCl₃, cm⁻¹): 2924, 2854, 1682, 1635, 1463, 1206, 966. ¹H NMR (400 MHz, CDCl₃): δ 9.42 (s, 1H), 6.81 (d, J = 11.1 Hz, 1H), 6.51 (ddt, J = 15.1, 11.1, 1.4 Hz, 1H), 6.27-6.20 (m, 1H), 2.26-2.21 (m, 2H), 1.83 (d, J = 0.7 Hz, 3H), 1.50-1.43 (m, 2H), 1.30-1.27 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H) ppm. ¹³C NMR (100 MHz; CDCl₃): δ 195.2, 149.4, 146.1, 136.1, 126.0, 33.6, 32.0, 29.7, 29.6, 29.4, 29.4, 28.9, 22.8, 14.2, 9.5 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₁₅H₂₆ONa) requires 245.1876, found m/z 245.1876.

Yield: 91% (method A). FTIR (CHCl₃, cm⁻¹): 2926, 2855, 1708, 1614, 1435, 1249, 1225, 1098, 990, 750. ¹H NMR (400 MHz, CDCl₃): δ 7.22-7.20 (m, 1H), 6.50 (dd, J = 14.8, 10.6 Hz, 1H), 6.38 (dd, J = 14.8, 11.4 Hz, 1H), 6.18 (dd, J = 15.1, 10.5 Hz, 1H), 5.94-5.86 (m, 1H), 3.75 (s, 3H), 2.14 (dd, J = 14.3, 7.1 Hz, 2H), 1.95 (d, J = 1.1 Hz, 1H), 1.43-1.40 (m, 2H), 1.29-1.28 (m, 8H), 0.88 (t, J = 6.0 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 169.1, 140.2, 139.9, 138.9, 130.4, 126.0, 125.7, 51.9, 33.1, 32.0,
29.3, 29.3, 29.2, 22.8, 14.2, 12.8 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$

($C_{16}H_{26}O_2Na$) requires 273.1831, found: 273.1820.
Yield: 62% over 2 steps (method A). FTIR (CHCl$_3$, cm$^{-1}$): 2926, 2855, 1678, 1611, 1195, 998, 837. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.43(s, 1H), 6.85 (dd, $J$ = 10.9, 1.3 Hz, 1H), 6.66-6.51 (m, 2H), 6.23 (ddt, $J$ = 15.1, 10.0, 1.3 Hz, 1H), 6.04-5.97 (m, 1H), 2.20-2.14 (m, 2H), 1.85 (d, $J$ = 1.0 Hz, 3H), 1.46-1.39 (m, 2H), 1.33-1.26 (m, 8H), 0.88 (t, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.8, 149.1, 142.1, 142.0, 137.0, 130.3, 125.3, 33.2, 31.9, 29.3, 29.1, 22.8, 14.2, 9.6 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{15}$H$_{24}$ONa) requires 243.1719, found 243.1715.

Yield: 53% over 3 steps (method A). (Volatile). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 9.55 (s, 1H), 7.21 (m, 1H), 6.84 (d, $J$ = 11.3 Hz, 1H), 6.13 (m, 1H), 1.94 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 194.1, 142.4, 131.55 (q, $J$ = 6.8 Hz), 125.5 (q, $J$ = 34.3 Hz), 9.9 ppm.

Yield: 54% over 3 steps (method A). The spectra data is in accordance with the literature.$^{10}$

Yield: 73% over 3 steps (method A). FTIR (CHCl$_3$, cm$^{-1}$): 1671, 1619, 1192, 1180, 1012, 965, 803. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 9.50 (s, 1H), 7.43 (d, $J$ = 8.1 Hz, 2H), 7.15-7.20 (m, 3H), 7.01 (d, $J$ = 11.2 Hz, 1H), 6.97 (d, $J$ = 15.4 Hz, 1H), 2.38 (s, 3H), 1.95 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 194.8, 149.0, 141.2, 139.7, 133.3, 129.6, 127.4, 122.5, 21.4, 9.7 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{13}$H$_{14}$NaO) requires 209.0937, found 209.0936.
Yield: 35% over 3 steps (method A). FTIR (CHCl₃, cm⁻¹): 1671, 1621, 1322, 1193, 1164, 1121, 1066, 966, 803. \( ^1 \text{H NMR (600 MHz, CDCl}_3 \text{)} \): \( \delta \) 9.53 (s, 1H), 7.61-7.64 (m, 3H), 7.30 (dd, \( J = 15.5, 11.2 \text{ Hz, 2H} \)), 6.99-7.04 (m, 2H), 1.97 (s, 3H) ppm. \( ^{13} \text{C NMR (151 MHz, CDCl}_3 \text{)} \): \( \delta \) 194.6, 147.4, 139.4, 138.9, 127.5, 125.8 (q, \( J = 3.8 \text{ Hz} \)), 125.6, 9.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]\(^+\) (C\(_{13}\)H\(_{11}\)F\(_3\)NaO) requires 263.0654, found m/z 263.0652.

The aldehyde was prepared as described in the literature\(^1\).
2.8. Synthesis of aldol adducts

To a flame-dried Schlenk tube was added activated 3 Å MS, acetylthiazolidinethione (1.0 equiv.) and CH₂Cl₂. At -78 °C, TiCl₄ (1 M in CH₂Cl₂, 1.1 equiv.) was added and the mixture was stirred for 10 min. Then DIPEA (1.1 equiv.) was added slowly and the solution was stirred for 30 min at -78 °C. Then the aldehyde (1.1 equiv.) dissolved in CH₂Cl₂ was added dropwise to the mixture. The solution was stirred at -78 °C for 3 h. Then the reaction was quenched with sat. NH₄Cl (aq.) at -78 °C and allowed to reach room temperature. The aqueous layer was extracted 3 times with CH₂Cl₂. The combined organic layers were washed by brine, dried over Na₂SO₄, filtered and concentrated in vacuum. The crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 9:1 to 7:3). Note: This reaction is very sensitive to moisture.

**Yield:** 3.40 g, 74%, d.r. = 11:1. **FTIR (CHCl₃, cm⁻¹):** 2924, 2854, 1693, 1343, 1163, 1137, 1044, 965. **¹H NMR (600 MHz, CDCl₃):** δ 7.36-7.34 (m, 2H), 7.30-7.27 (m, 3H), 6.25 (ddt, J = 14.9, 10.8, 1.3 Hz, 1H), 6.11 (d, J = 10.9 Hz, 1H), 5.75-5.70 (m, 1H), 5.39-5.36 (m, 1H), 4.64 (d, J = 9.6 Hz, 1H), 3.55 (dd, J = 17.4, 2.5 Hz, 1H), 3.44-3.39 (m, 2H), 3.24 (dd, J = 13.2, 3.8 Hz, 1H), 3.05 (dd, J = 13.2, 10.6 Hz, 1H), 2.90 (d, J = 11.5 Hz, 1H), 2.54 (d, J = 3.3 Hz, 1H), 2.12-2.01 (m, 2H), 1.78 (s, 3H), 1.39-1.36 (m, 2H), 1.31-1.25 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H) ppm. **¹³C NMR (151 MHz, CDCl₃):** δ 201.5, 173.0, 136.6, 136.3, 135.1, 129.6, 129.1, 127.4, 125.9, 125.8, 72.8, 68.6, 44.5, 36.9, 33.2,
32.3, 32.0, 29.5, 29.33, 29.31, 22.8, 14.3, 13.0 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{25}$H$_{35}$NO$_2$S$_2$Na) requires m/z 468.2001, found m/z 468.1988. $[\alpha]_D^{20} = +155$ (c = 0.94, CHCl$_3$).

**Yield:** 360 mg, 62%, d.r = 9:1:1. **FTIR (CHCl$_3$, cm$^{-1}$):** 2924, 2853, 1696, 1343, 1164, 1137, 1045, 966. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.36-7.34 (m, 2H), 7.30-7.27 (m, 3H), 6.24 (dd, $J$ = 15.0, 10.8 Hz, 1H), 6.11 (d, $J$ = 10.9 Hz, 1H), 5.75-5.70 (m, 1H), 5.39-5.36 (m, 1H), 4.64 (d, $J$ = 9.6 Hz, 1H), 3.55 (dd, $J$ = 17.4, 2.5 Hz, 1H), 3.44-3.39 (m, 2H), 3.24 (dd, $J$ = 13.2, 3.8 Hz, 1H), 3.05 (dd, $J$ = 13.2, 10.6 Hz, 1H), 2.90 (d, $J$ = 11.5 Hz, 1H), 2.54 (d, $J$ = 3.6 Hz, 1H), 2.12-2.09 (m, 2H), 1.78 (s, 3H), 1.39-1.37 (m, 2H), 1.26 (brd, 12H), 0.88 (t, $J$ = 7.1 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 201.5, 173.0, 136.6, 136.3, 135.1, 129.6, 129.1, 127.4, 125.9, 125.7, 72.8, 68.6, 44.5, 36.9, 33.1, 32.3, 32.0, 29.70, 29.7, 29.5, 29.4, 22.8, 14.3, 13.0 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{27}$H$_{39}$NO$_2$S$_2$Na) requires 496.2314, found 496.2316. $[\alpha]_D^{20} = +153$ (c = 1.09, CHCl$_3$).

**Yield:** 170 mg, 62%, d.r. = 11:1. **FTIR (CHCl$_3$, cm$^{-1}$):** 2924, 2854, 1739, 1695, 1345, 1164, 1137, 1045, 987. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.37-7.33 (m, 2H), 7.30-7.26 (m, 3H), 6.33 (dd, $J$ = 14.4, 10.8 Hz, 1H), 6.25-6.08 (m, 3H), 5.76-5.68 (m, 1H), 5.40-5.35 (m, 1H), 4.65 (d, $J$ = 9.4 Hz, 1H), 3.57 (dd, $J$ = 17.4, 2.8 Hz, 1H), 3.46-3.38 (m, 2H), 3.24 (dd, $J$ = 13.2, 3.8 Hz, 1H), 3.05 (dd, $J$ = 13.2, 10.5 Hz, 1H), 2.90 (d, $J$ = 11.6 Hz, 1H), 2.59 (d, $J$ = 3.5 Hz, 1H), 2.12-2.07 (m, 2H), 1.80 (d, $J$ = 0.6 Hz, 3H), 1.40-1.37 (m, 2H), 1.32-1.27 (m, 8H), 0.88 (t, $J$ = 7.1 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 201.5, 172.9, 137.1, 136.6, 135.9, 134.0, 130.6, 129.6,
129.1, 127.4, 126.03, 125.97, 72.9, 68.6, 44.5, 37.0, 33.0, 32.3, 32.0, 29.4, 29.3, 22.8, 14.2, 13.2 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]⁺ (C_{27}H_{37}NO_{2}S_{2}Na) requires 494.2158, found 494.2163. \([a]_D^{20} = +106\) (c = 1.00, CHCl₃).

**Yield:** 678 mg, 60%, d.r. = >20:1. **FTIR (CHCl₃, cm⁻¹):** 2924, 2852, 1741, 1697, 1455, 1363, 1342, 1262, 1164, 1044, 701. **¹H NMR (400 MHz, CDCl₃):** δ 7.39-7.26 (m, 5H), 5.41 (ddd, \(J = 10.6, 6.9, 4.1\) Hz, 1H), 4.14 (brd, 1H), 3.65 (dd, \(J = 17.8, 2.4\) Hz, 1H), 3.49-3.35 (m, 1H), 3.23 (dd, \(J = 13.2, 3.9\) Hz, 1H), 3.13 (dd, \(J = 17.8, 9.4\) Hz, 1H), 3.05 (dd, \(J = 13.2, 10.4\) Hz, 1H), 2.90 (d, \(J = 11.6\) Hz, 1H), 2.68 (d, \(J = 3.8\) Hz, 1H), 1.63-1.18 (m, 20H), 0.88 (t, \(J = 6.9\) Hz, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ 201.6, 173.5, 136.6, 129.6, 129.1, 127.4, 68.5, 68.0, 46.1, 37.0, 36.6, 32.2, 32.1, 29.81, 29.78, 29.8, 29.7, 29.7, 29.5, 25.7, 22.8, 14.3 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]⁺ (C_{24}H_{37}NO_{2}S_{2}Na) requires 458.2158, found 458.2159. \([a]_D^{20} = +176\) (c = 1.12, CHCl₃).

**Yield:** 175 mg, 50%, d.r. = 1:1. The spectra data is in accordance with the literature. **Lit.:** \([a]_D^{20} = +167\) (c = 1.14, CHCl₃), found \([a]_D^{20} = +212\) (c = 1.00, CHCl₃).

**Yield:** 82 mg, 25%, d.r. = 4:1. **FTIR (CHCl₃, cm⁻¹):** 2925, 1691, 1660, 1344, 1295, 1263, 1166, 1106, 1045, 969, 893. **¹H NMR (700 MHz, CDCl₃):** δ 7.34-7.37 (m, 2H), 7.27-7.30 (m, 3H), 7.00-7.05 (m, 1H), 6.11 (d, \(J = 11.9\) Hz, 1H), 5.72 (dq, \(J = 13.3, 6.3\) Hz, 1H), 5.39-5.42 (m, 1H), 4.66 (d, \(J = 9.1\) Hz, 1H), 3.72 (dd, \(J = 17.5, 2.1\) Hz, 1H), 3.42 (dd, \(J = 11.9, 7.0\) Hz, 1H), 3.27 (dd, \(J = 17.5, 9.8\) Hz, 1H), 1.63-1.18 (m, 20H), 0.88 (t, \(J = 6.9\) Hz, 3H) ppm.
1H), 3.24 (dd, \( J = 12.6, 3.5 \) Hz, 1H), 3.06 (dd, \( J = 13.3, 10.5 \) Hz, 1H), 2.92 (d, \( J = 11.9 \) Hz, 1H), 2.05 (s, 1H), 1.87 (s, 3H) ppm. \(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \( \delta \) 201.5, 172.5, 145.8, 136.2, 132.6 (q, \( J = 6.7 \) Hz), 129.4, 129.0, 127.3, 121.6, 125.0 (q, \( J = 268.4 \) Hz), 118.8 (q, \( J = 33.4 \) Hz), 71.8, 68.3, 44.2, 36.8, 32.2, 13.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]\(^+\) (C\(_{19}\)H\(_{20}\)F\(_3\)NNaO\(_2\)S\(_2\)) requires 438.0780, found 438.0779. \([\alpha]D^{20} = +113 \) (c = 1.00, CHCl\(_3\)).

Yield: 189 mg, 56%, d.r. = 9:1. FTIR (CHCl\(_3\), cm\(^{-1}\)): 2884, 2856, 1639, 1537, 1467, 1357, 1320, 1254, 1142, 965, 909, 834, 777, 729.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.42 (d, \( J = 7.7 \) Hz, 2H), 7.26-7.37 (m, 7H), 7.23 (t, \( J = 7.2 \) Hz, 1H), 7.00 (dd, \( J = 15.0, 10.8 \) Hz, 1H), 6.57 (d, \( J = 15.0 \) Hz, 1H), 6.33 (d, \( J = 10.8 \) Hz, 1H), 5.37-5.42 (m, 1H), 4.70 (d, \( J = 10.8 \) Hz, 1H), 3.63 (d, \( J = 17.4 \) Hz, 1H), 3.40-3.46 (m, 2H), 3.25 (dd, \( J = 11.4 \) Hz, 1H), 3.06 (app t, \( J = 10.8 \) Hz, 1H), 2.92 (d, \( J = 11.4 \) Hz, 1H), 2.68 (s, 1H), 1.91 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 201.4, 172.7, 138.4, 137.5, 136.4, 132.9, 129.4, 128.9, 128.6, 127.5, 127.3, 126.3, 125.7, 124.4, 72.6, 68.5, 44.3, 36.8, 32.1, 13.4 ppm. HRMS (ESI) (m/z): calculated for [M+Na]\(^+\) (C\(_{24}\)H\(_{25}\)NNaO\(_2\)S\(_2\)) requires 446.1219, found 446.1211. \([\alpha]D^{20} = +179 \) (c = 1.00, CHCl\(_3\)).

Yield: 163 mg, 55%, d.r. = 9:1. FTIR (CHCl\(_3\), cm\(^{-1}\)): 2920, 1694, 1510, 1453, 1343, 1292, 1258, 1192, 1163, 1137, 1043, 966, 801, 746, 702. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.28-7.37 (m, 7H), 7.13 (d, \( J = 7.8 \) Hz, 2H), 7.00 (dd, \( J = 15.6, 10.8 \) Hz, 1H), 6.55 (d, \( J = 15.0 \) Hz, 1H), 6.31 (d, \( J = 10.8 \) Hz, 1H), 5.37-5.42 (m, 1H), 4.70 (d, \( J = 9.6 \) Hz, 1H), 3.62 (d, \( J = 17.4 \) Hz, 1H), 3.39-3.47 (m, 2H), 3.25 (dd, \( J = 13.2, 3.0 \) Hz, 1H), 3.04-3.08 (m, 1H), 2.91 (d, \( J = 11.4 \) Hz, 1H), 2.05 (s, 1H), 1.87 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 201.5, 172.5, 145.8, 136.2, 132.6 (q, \( J = 6.7 \) Hz), 129.4, 129.0, 127.3, 121.6, 125.0 (q, \( J = 268.4 \) Hz), 118.8 (q, \( J = 33.4 \) Hz), 71.8, 68.3, 44.2, 36.8, 32.2, 13.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]\(^+\) (C\(_{19}\)H\(_{20}\)F\(_3\)NNaO\(_2\)S\(_2\)) requires 438.0780, found 438.0779. \([\alpha]D^{20} = +113 \) (c = 1.00, CHCl\(_3\)).
2.66 (s, 1H), 2.34 (s, 3H), 1.90 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 201.3, 172.7, 137.7, 137.4, 136.4, 134.7, 132.9, 129.4, 129.3, 128.9, 127.3, 126.3, 125.9, 123.5, 72.6, 68.5, 44.3, 36.8, 32.1, 21.2, 13.3 ppm. HRMS (ESI) ($m/z$): calculated for [M+Na]$^+$ (C$_{25}$H$_{27}$NNaO$_2$S$_2$) requires 460.1365, found 460.1370. $[\alpha]_D^{20} = +152$ (c = 0.50, CHCl$_3$).

Yield: 275 mg, 70%, d.r. = 9:1. FTIR (CHCl$_3$, cm$^{-1}$): 2923, 1691, 1611, 1324, 1257, 1189, 1163, 1121, 1066, 1044, 966, 817, 750, 703. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.56 (d, $J$ = 7.8 Hz, 2H), 7.50 (d, $J$ = 8.4 Hz, 2H), 7.34-7.38 (m, 2H), 7.28-7.31 (m, 3H), 7.10 (dd, $J$ = 15.0, 10.8 Hz, 1H), 6.58 (d, $J$ = 15.6 Hz, 1H), 6.37 (d, $J$ = 10.8 Hz, 1H), 5.37-5.42 (m, 1H), 4.70 (d, $J$ = 9.6 Hz, 1H), 3.68 (dd, $J$ = 17.4, 2.4 Hz, 1H), 3.36-3.44 (m, 2H), 3.25 (dd, $J$ = 13.2, 3.6 Hz, 1H), 3.06 (dd, $J$ = 13.2, 10.2 Hz, 1H), 2.92 (d, $J$ = 12.0 Hz, 1H), 2.75 (d, $J$ = 3.6 Hz, 1H), 1.93 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 201.4, 172.7, 141.0, 140.3, 136.3, 131.2, 129.4, 129.0, 127.3, 126.8, 126.4, 125.5 (q, $J$ = 3.8 Hz), 125.1, 72.4, 68.4, 44.3, 36.8, 32.1, 13.6 ppm. HRMS (ESI) ($m/z$): calculated for [M+Na]$^+$ (C$_{25}$H$_{24}$F$_3$NNaO$_3$S$_2$) requires 514.1093, found 514.1094. $[\alpha]_D^{20} = +155$ (c = 0.49, CHCl$_3$).

Yield: 480 mg, 75%, d.r. = 15:1. FTIR (CHCl$_3$, cm$^{-1}$): 1689, 1488, 1342, 1258, 1163, 1044, 749. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.53-7.46 (m, 2H), 7.38-7.34 (m, 2H), 7.31-7.28 (m, 5H), 5.40 (ddd, $J$ = 10.8, 7.0, 4.1 Hz, 1H), 5.29-5.19 (m, 1H), 3.82 (dd, $J$ = 17.6, 2.6 Hz, 1H), 3.49 (dd, $J$ = 17.6, 9.4 Hz, 1H), 3.40 (dd, $J$ = 11.6, 7.2 Hz, 1H), 3.25 (dd, $J$ = 13.2, 4.0 Hz, 1H), 3.11 (d, $J$ = 4.0 Hz, 1H), 3.06 (dd, $J$ = 13.2, 10.4 Hz, 1H), 2.92 (d, $J$ = 11.6 Hz, 1H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 201.5,
172.6, 141.5, 136.4, 131.8, 129.6, 127.6, 127.5 121.7, 69.5, 68.4, 47.4, 37.0, 32.3 ppm. 

**HRMS (ESI) (m/z):** calculated for [M+Na]\(^+\) (C\(_{19}\)H\(_{18}\)NO\(_2\)BrS\(_2\)Na) requires 459.9834, found 459.9831. \([\alpha]_D^{20} = +177\) (c = 1.15, CHCl\(_3\)).

**Yield:** 2.88 g, 89%, d.r. = 14:1. **FTIR (CHCl\(_3\), cm\(^{-1}\)):** 1689, 1342, 1294, 1257, 1164, 1137, 1044. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.41-7.26 (m, 5H), 6.43-6.34 (m, 1H), 5.39 (ap ddd, \(J = 10.6, 6.8, 4.2\) Hz, 1H), 4.68 (dt, \(J = 9.6, 2.7\) Hz, 1H), 3.66 (dd, \(J = 17.5, 2.5\) Hz, 1H), 3.43 (dd, \(J = 11.6, 7.2, 0.8\) Hz, 1H), 3.36 (dd, \(J = 17.5, 9.6\) Hz, 1H), 3.23 (dd, \(J = 13.2, 4.0\) Hz, 1H), 3.05 (dd, \(J = 13.2, 10.4\) Hz, 1H), 2.92 (d, \(J = 11.6\) Hz, 1H), 2.84 (d, \(J = 3.9\) Hz, 1H), 1.84 (d, \(J = 1.1\) Hz, 3H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 201.6, 172.4, 141.9, 136.4, 129.6, 129.1, 127.5, 105.7, 71.7, 68.5, 44.2, 37.0, 32.4, 16.1 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]\(^+\) (C\(_{16}\)H\(_{18}\)NO\(_2\)BrS\(_2\)Na) requires 423.9834, found 423.9834. \([\alpha]_D^{20} = +143\) (c = 1.20, CHCl\(_3\)).

**Yield:** 378 mg, 73%, d.r. = >20:1. **FTIR (CHCl\(_3\), cm\(^{-1}\)):** 1690, 1343, 1258, 1165, 1137, 1044, 747, 702. \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 7.85 (ddd, \(J = 12.9, 10.0, 4.7\) Hz, 4H), 7.49 (tdd, \(J = 8.7, 7.7, 3.4\) Hz, 3H), 7.36 (dd, \(J = 9.4, 5.5\) Hz, 2H), 7.33-7.27 (m, 3H), 5.46 (dt, \(J = 9.3, 2.8\) Hz, 1H), 5.39 (dd, \(J = 10.8, 7.1, 4.0\) Hz, 1H), 3.89 (dd, \(J = 17.6, 2.6\) Hz, 1H), 3.67 (dd, \(J = 17.6, 9.5\) Hz, 1H), 3.36 (dd, \(J = 11.6, 7.2\) Hz, 1H), 3.27 (dd, \(J = 13.1, 3.9\) Hz, 1H), 3.20 (d, \(J = 3.9\) Hz, 1H), 3.06 (dd, \(J = 13.1, 10.5\) Hz, 1H), 2.89 (d, \(J = 11.6\) Hz, 1H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 201.5, 172.8, 139.9, 136.5, 133.4, 133.1, 129.6, 129.1, 128.6, 128.2, 127.8, 127.4, 126.4, 126.1, 124.6, 124.0,
70.3, 68.5, 47.5, 36.9, 32.3 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]⁺ (C₂₃H₂₁NO₂S₂Na) requires 430.0906, found 430.0908. \([\alpha]D^{20} = +157\ (c = 1.23, \text{CHCl}_3)\).
2.9. Synthesis of amide products

Aldol adduct (1.0 equiv.) and the crude amine (1.3 equiv.) were dissolved in CH₂Cl₂ (0.1 M). DMAP (0.5 equiv.) was then charged and the reaction mixture was vigorously stirred overnight at room temperature. The reaction was quenched with water and extracted 3 times with CH₂Cl₂. The resulting organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1, then Heptane/Isopropanol = 20:1 to 3:1).

**Fig. S5.** Synthesis of amide products.

Yield: 1.02 g, 57%. FTIR (CHCl₃, cm⁻¹): 2926, 2855, 1642, 1537, 1360, 1144, 836. ¹H NMR (600 MHz, CDCl₃): δ 6.55 (dt, J = 18.0, 6.5 Hz, 1H), 6.38 (brd, 1H), 6.22 (dd, J = 15.0, 10.9 Hz, 1H), 6.11 (brd, 1H), 6.08 (d, J = 10.9 Hz, 1H), 5.76-5.66 (m, 1H), 5.52 (d, J = 18.0 Hz, 1H), 4.43 (d, J = 8.4 Hz, 1H), 3.90-3.87 (m, 1H), 3.74-3.69 (m, 1H), 3.49 (brd, 1H), 3.47-3.41 (m, 1H), 3.30-3.24 (m, 1H), 2.96-2.92 (m, 1H), 2.44-2.34 (m, 5H), 2.09 (q, J = 7.2 Hz, 2H), 1.74 (s, 3H), 1.38-1.36 (m, 2H), 1.30-1.25 (m, 20H), 1.13 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.88 (t, J = 7.1 Hz, 3H), 0.15 (s, 3H), 0.08 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 174.5, 172.3, 150.4, 136.1, 135.4, 125.8, 125.7, 121.7 (deduced from HSQC), 83.4, 73.7, 72.1, 44.8, 42.9, 41.6, 37.9, 35.8, 33.2, 32.0, 29.6, 29.3, 26.0, 24.9, 22.8, 18.1, 15.3,
14.3, 12.8, -4.4, -4.8 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{36}$H$_{67}$N$_2$O$_6$BNa) requires 685.4754, found 685.4759. [a]$_D^{20}$ = +12.3 (c = 0.50, CHCl$_3$).

Yield: 240 mg, 60%. **FTIR (CHCl$_3$, cm$^{-1}$):** 2927, 2854, 1643, 1548, 1361, 1324, 1145, 837. **$^1$H NMR (600 MHz, CDCl$_3$):** $\delta$ 6.55 (dt, $J$ = 18.0, 6.5 Hz, 1H), 6.48-6.44 (m, 1H), 6.23-6.15 (m, 2H), 6.07 (d, $J$ = 10.9 Hz, 1H), 5.72-5.67 (m, 1H), 5.51 (d, $J$ = 18.0 Hz, 1H), 4.43 (d, $J$ = 8.7 Hz, 1H), 3.89-3.86 (m, 1H), 3.74-3.69 (m, 1H), 3.47-3.42 (m, 1H), 3.29-3.24 (m, 1H), 2.94-2.89 (m, 1H), 2.45-2.34 (m, 5H), 2.11-2.07 (m, 2H), 1.74 (s, 3H), 1.37-1.36 (m, 2H), 1.25 (brd, 24H), 1.13 (d, $J$ = 7.2 Hz, 3H), 0.89 (s, 9H), 0.87 (t, $J$ = 7.1 Hz, 3H), 0.15 (s, 3H), 0.08 (s, 3H) ppm. **$^{13}$C NMR (151 MHz, CDCl$_3$):** $\delta$ 174.6, 172.3, 150.4, 136.0, 135.4, 125.8, 125.7, 121.7 (deduced from HSQC), 117.4, 83.4, 73.7, 72.1, 44.7, 42.9, 41.6, 37.9, 35.8, 33.2, 32.0, 29.71, 29.66, 29.55, 29.48, 29.38, 26.0, 24.9, 22.8, 18.1, 15.4, 14.3, 12.8, -4.4, -4.8 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{38}$H$_{71}$N$_2$O$_6$BNa) requires 713.5067, found 713.5072. [a]$_D^{20}$ = +31.5 (c = 0.55, CHCl$_3$).

Yield: 86 mg, 57%. **FTIR (CHCl$_3$, cm$^{-1}$):** 2927, 1642, 1542, 1360, 1322, 1144, 988, 837, 778. **$^1$H NMR (600 MHz, CDCl$_3$):** $\delta$ 6.54 (dt, $J$ = 17.9, 6.6 Hz, 1H), 6.45 (brd, 1H), 6.29 (dd, $J$ = 14.6, 11.1 Hz, 1H), 6.21-6.03 (m, 4H), 5.73-5.68 (m, 1H), 5.51 (d, $J$ = 18.0 Hz, 1H), 4.46 (brd, 1H), 3.87 (brd, 1H), 3.74-3.69 (m, 1H), 3.64 (d, $J$ = 10.7 Hz, 1H), 3.46-3.40 (m, 1H), 3.28-3.24 (m, 1H), 2.91 (brd, 1H), 2.44-2.33 (m, 5H), 2.10-2.06 (m, 2H), 1.76 (s, 3H), 1.37-1.36 (m, 2H), 1.25 (brd, 20H), 1.12 (d, $J$ = 7.2 Hz,
\( ^1^H \text{NMR (600 MHz, CDCl}_3\)): \( \delta \) 6.54 (dt, \( J = 18.0, 6.4 \text{ Hz, 1H} \)), 6.45-6.37 (m, 1H), 6.24-6.22 (m, 1H), 5.51 (d, \( J = 18.0 \text{ Hz, 1H} \)), 3.96 (brd, 1H), 3.88-3.86 (m, 1H), 3.83-3.81 (m, 1H), 3.71-3.67 (m, 1H), 3.48-3.42 (m, 1H), 3.28-3.23 (m, 1H), 2.95-2.90 (m, 1H), 2.45-2.41 (m, 1H), 2.37-2.32 (m, 1H), 2.23 (dd, \( J = 15.3, 9.3 \text{ Hz, 1H} \)), 1.53-1.48 (m, 1H), 1.44-1.37 (m, 2H), 1.30-1.23 (m, 29H), 1.14 (d, \( J = 7.2 \text{ Hz, 3H} \)), 0.89 (s, 9H), 0.87 (t, \( J = 6.9 \text{ Hz, 3H} \)), 0.15 (s, 3H), 0.09 (s, 3H) ppm. 

\( ^{13}C \text{NMR (151 MHz, CDCl}_3\)): \( \delta \) 174.7, 172.9, 150.4, 121.4 (deduced from HSQC), 83.4, 72.1, 68.7, 44.7, 42.9, 42.6, 37.9, 37.0, 35.8, 32.0, 29.80, 29.77, 29.74, 29.73, 29.71, 29.5, 26.0, 25.7, 24.91, 24.88, 22.8, 18.1, 15.5, 14.3, -4.4, -4.8 ppm. 

HRMS (ESI) (m/z): calculated for [M+Na\(^{+}\)] \((C_{35}H_{69}N_2O_6BSiNa)\) requires 675.4910, found 675.4910. \([\alpha]^D_{20} = +25.9 \text{ (c = 0.59, CHCl}_3\)].

**Yield:** 37 mg, 51%. 
**FTIR (CHCl\(_3\), cm\(^{-1}\)):** 3315, 2975, 2902, 2858, 1643, 1547, 1463, 1360, 1254, 1144, 837, 778. 

\( ^1^H \text{NMR (600 MHz, CDCl}_3\)): \( \delta \) 6.50-6.56 (m, 2H), 6.25 (t, \( J = 5.4 \text{ Hz, 1H} \)), 5.51 (d, \( J = 18.0 \text{ Hz, 1H} \)), 4.16 (m, 1H), 4.02 (brd, 1H), 3.84-3.89 (m, 1H), 3.66-3.71 (m,
\begin{align*}
\text{1H NMR (600 MHz, CDCl\textsubscript{3})}: & \delta 6.55 (dt, J = 18.0, 6.4 Hz, 1H), 6.45 (brd, 1H), 6.33 (brd, 1H), 6.21 (dd, J = 14.5, 11.0 Hz, 1H), 6.07 (d, J = 10.8 Hz, 1H), 5.72-5.67 (m, 1H), 5.51 (d, J = 18.0 Hz, 1H), 4.43 (d, J = 8.9 Hz, 1H), 4.18-4.15 (m, 1H), 3.59-3.55 (m, 1H), 3.43-3.38 (m, 2H), 3.30 -3.25 (m, 1H), 3.11-3.07 (m, 1H), 2.44 (dd, J = 15.1, 9.2 Hz, 1H), 2.40-2.31 (m, 4H), 2.26 (dd, J = 14.0, 5.0 Hz, 1H), 2.09 (q, J = 7.1 Hz, 2H), 1.73 (s, 3H), 1.38-1.35 (m, 2H), 1.25 (brd, 20H), 0.88-0.86 (m, 12H), 0.10 (s, 3H), 0.08 (s, 3H) ppm. \\
\text{13C NMR (151 MHz, CDCl\textsubscript{3})}: & \delta 172.6, 170.4, 150.4, 143.7, 136.1, 135.4, 125.8, 125.7, 121.6 (deduced from HSQC), 83.4, 73.8, 68.4, 44.2, 42.4, 41.7, 38.2, 35.6, 33.1, 32.0, 29.6, 29.3, 25.9, 24.9, 22.8, 18.1, 14.2, 12.7, -4.7, -4.8 ppm. \\
\text{HRMS (ESI) (m/z): calculated for [M+Na]\textsuperscript{+} (C\textsubscript{35}H\textsubscript{65}N\textsubscript{2}O\textsubscript{6}BNa) requires 671.4597, found 671.4603.}\end{align*}
6.08 (d, J = 10.8 Hz, 1H), 6.13 (brd, 1H), 5.66-5.73 (m, 1H), 5.52 (d, J = 18.0 Hz, 1H), 4.43 (d, J = 8.8 Hz, 1H), 3.24-3.38 (m, 4H), 2.34-2.40 (m, 4H), 2.21 (t, J = 6.6 Hz, 2H), 2.09 (q, J = 7.2 Hz, 2H), 1.80-1.86 (m, 2H), 1.73 (s, 3H), 1.33-1.40 (m, 2H), 1.21-1.31 (m, 22H), 0.88 (t, J = 7.0 Hz, 3H) ppm. \(^{13}C\) NMR (151 MHz; CDCl\(_3\)): \(\delta\) 172.7, 172.5, 150.2, 135.9, 135.4, 125.6, 125.5, 83.3, 73.6, 41.4, 38.9, 38.0, 35.5, 33.9, 33.0, 31.8, 29.4, 29.2, 25.1, 24.8, 24.7, 22.7, 14.1, 12.6 ppm. HRMS (ESI) (m/z): calculated for [M+Na]\(^{+}\) (C\(_{29}\)H\(_{51}\)BN\(_2\)NaO\(_5\)) requires 541.3783, found 541.3783. \([\alpha]D^{20}_20 = +5.2\) (c = 1.00, CHCl\(_3\)).

Yield: 41 mg, 40%. FTIR (CHCl\(_3\), cm\(^{-1}\)): 3339, 2930, 2858, 1642, 1543, 1467, 1360, 1319, 1295, 1260, 1144, 1108, 837, 779.

\(^1H\) NMR (600 MHz, CDCl\(_3\)): \(\delta\) 6.99 (t, J = 13.5 Hz, 1H), 6.60 (brd, 1H), 6.55 (dt, J = 17.8, 6.4 Hz, 1H), 6.20-6.27 (m, 2H), 5.66-5.71 (m, 1H), 5.52 (d, J = 18.0 Hz, 1H), 4.48 (d, J = 8.9 Hz, 1H), 4.36 (s, 1H), 3.82-3.88 (m, 1H), 3.63-3.71 (m, 1H), 3.38-3.46 (m, 1H), 3.23-3.33 (m, 1H), 2.88-2.96 (m, 1H), 2.32-2.46 (m, 4H), 2.20 (brd, 1H), 2.03 (brd, 1H), 1.83 (s, 3H), 1.25 (s, 12H), 1.14 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H) ppm. \(^{13}C\) NMR (151 MHz, CDCl\(_3\)): \(\delta\) 174.6, 171.7, 150.1, 146.5, 132.7 (q, J = 6.8 Hz), 123.5 (d, J = 268.6 Hz), 121.2, 118.9 (q, J = 33.4 Hz), 117.3, 83.2, 72.6, 71.8, 44.5, 42.9, 41.0, 37.8, 35.6, 25.8, 24.8, 24.7, 15.3, 13.6, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]\(^{+}\) (C\(_{30}\)H\(_{52}\)BF\(_3\)N\(_2\)NaO\(_6\)Si) requires 655.3532, found 655.3560. \([\alpha]D^{20}_20 = +22.1\) (c = 1.00, CHCl\(_3\)).
Yield: 96 mg, 58%. FTIR (CHCl₃, cm⁻¹): 3339, 3029, 1692, 1493, 1319, 1192, 1044, 963, 909, 748. ¹H NMR (500 MHz, CDCl₃): δ 7.40 (d, J = 7.3 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.99 (dd, J = 15.5, 11.0 Hz, 1H), 6.50-6.57 (m, 2H), 6.46 (brd, 1H), 6.31 (dd, J = 11.0, 0.9 Hz, 1H), 6.12 (brd, 1H), 5.49 (dt, J = 17.9, 1.4 Hz, 1H), 4.51 (t, J = 6.1 Hz, 1H), 3.87-3.92 (m, 1H), 3.76-3.76 (m, 1H), 3.35-3.43 (m, 1H), 3.21-3.30 (m, 1H), 2.89-2.98 (m, 1H), 2.30-2.46 (m, 5H), 1.86 (s, 3H), 1.25 (s, 12H), 1.13 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 174.4, 172.0, 150.2, 138.8, 137.5, 132.7, 128.6, 127.4, 126.3, 125.4, 124.5, 83.2, 73.4, 72.0, 44.7, 42.8, 41.4, 37.8, 35.6, 25.8, 25.7, 24.7, 15.2, 13.1, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₃₅H₅₇BN₂NaO₆Si) requires 663.3979, found 663.3979. [α]D²⁰ = +26.3 (c = 1.00, CHCl₃).

Yield: 163 mg, 67%. FTIR (CHCl₃, cm⁻¹): 3339, 3029, 1692, 1493, 1319, 1192, 1044, 963, 909, 748, 778, 732; ¹H NMR (500 MHz, CDCl₃): δ 7.30 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.94 (dd, J = 15.5, 11.0 Hz, 1H), 6.50-6.57 (m, 2H), 6.48 (brd, 1H), 6.29 (dd, J = 11.0, 0.9 Hz, 1H), 6.12 (brd, 1H), 5.49 (dt, J = 18.0, 1.4 Hz, 1H), 4.51 (t, J = 6.1 Hz, 1H), 3.85-3.95 (m, 1H), 3.69-3.75 (m, 1H), 3.37-3.43 (m, 1H), 3.18-3.27 (m, 1H), 2.89-2.95 (m, 1H), 2.30-2.46 (m, 5H), 2.30 (s, 3H), 1.86 (s, 3H), 1.25 (s, 12H), 1.13 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 174.4, 172.0, 150.2, 138.2, 137.4, 134.7, 132.7, 129.3, 126.2, 125.6, 123.5, 83.2, 73.5, 72.0, 44.7, 42.8, 41.5, 37.8, 35.6, 25.8, 24.7, 21.2, 15.2, 13.1, -4.5, -5.0 ppm. HRMS
(ESI) (m/z): calculated for [M+Na]+ (C_{36}H_{59}BN_{2}O_{6}Si) requires 677.4128, found 677.4135. 

[a]_{D}^{20} = +24.0 (c = 1.00, CHCl_{3}).

Yield: 238 mg, 42%. FTIR (CHCl_{3}, \text{cm}^{-1}): 3318, 2968, 2900, 1642, 1541, 1360, 1324, 1165, 1124, 1067, 910, 734; 1H NMR (500 MHz, CDCl_{3}): δ 7.55 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 6.85 (dd, J = 15.5, 11.0 Hz, 1H), 6.52-6.59 (m, 2H), 6.34 (m, 2H), 6.08 (t, J = 5.6 Hz, 1H), 5.52 (d, J = 18.0, 1H), 4.50-4.55 (m, 1H), 3.87-3.93 (m, 1H), 3.85 (d, J = 3.0 Hz, 1H), 3.69-3.76 (m, 1H), 3.40-3.47 (m, 1H), 3.23-3.31 (m, 1H), 2.94-2.99 (m, 1H), 2.33-2.45 (m, 5H), 1.89 (s, 3H), 1.25 (s, 12H), 1.14 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H) ppm. 13C NMR (126 MHz, CDCl_{3}): δ 174.3, 171.9, 150.2, 141.0, 140.8, 131.1, 126.9, 126.3, 125.5, 124.9, 73.2, 71.9, 44.8, 42.9, 41.3, 37.8, 35.6, 25.8, 24.8, 15.1, 13.4, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]^+ (C_{36}H_{56}BF_{3}N_{2}O_{6}Si) requires 731.3845, found 731.3850. [a]_{D}^{20} = +23.6 (c = 1.00, CHCl_{3}).

Yield: 120 mg, 40%. FTIR (CHCl_{3}, \text{cm}^{-1}): 1739, 1641, 1535, 1361, 1321, 1143, 849, 778. 1H NMR (600 MHz, CDCl_{3}): δ 7.46 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 6.54 (dt, J = 18.0, 6.4 Hz, 1H), 6.42 (brd, 1H), 6.13 (brd, 1H), 5.51 (d, J = 18.0 Hz, 1H), 5.08-5.06 (m, 1H), 4.47 (d, J = 3.2 Hz, 1H), 3.86-3.83 (m, 1H), 3.70-3.66 (m, 1H), 3.45-3.40 (m, 1H), 3.29-3.23 (m, 1H), 2.95-2.90 (m, 1H), 2.53-2.52 (m, 2H), 2.37-2.32 (m, 3H), 1.24 (s, 12H), 1.12 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H) ppm. 13C NMR (151 MHz, CDCl_{3}): δ 174.6, 171.8, 150.4, 142.2, 131.7, 127.6, 121.5 (deduced from HSQC), 121.4, 83.4, 72.0, 70.3,
44.8, 44.7, 42.9, 37.9, 35.8, 26.0, 24.91, 24.89, 18.1, 15.4, -4.4, -4.8 ppm. **HRMS (ESI) (m/z):** calculated for \([\text{M+Na}]^+\) (C_{30}H_{50}N_2O_6BBrSiNa) requires 677.2586, found 677.2566. \([\alpha]_D^{20} = +40.3\) (c = 1.10, CHCl_3).

Yield: 349 mg, 51%. **FTIR (CHCl_3, cm\(^{-1}\)):** 3337, 2927, 2856, 1643, 1543, 1465, 1360, 1322, 1144, 837, 778. \(^1\)H NMR (600 MHz, CDCl_3): \(\delta\) 6.55 (dt, \(J = 18.0\), 6.5 Hz, 1H), 6.38 (m, 1H), 6.35 (s, 1H), 6.11 (t, \(J = 5.5\) Hz 1H), 5.52 (d, \(J = 18.0\) Hz, 1H), 4.49-4.54 (m, 1H), 4.08 (d, \(J = 3.1\) Hz, 1H), 3.86-3.90 (m, 1H), 3.67-3.72 (m, 1H), 3.42-3.49 (m, 1H), 3.24-3.31 (m, 1H), 2.93-2.99 (m, 1H), 2.35-2.43 (m, 4H), 2.25 (dd, \(J = 15.3, 9.1\) Hz, 1H), 1.80 (s, 3H), 1.26 (s, 12H), 1.15 (d, \(J = 7.2\) Hz, 3H), 0.89 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl_3): \(\delta\) 174.4, 171.5, 150.2, 142.0, 105.3, 83.3, 72.3, 71.9, 44.7, 42.7, 40.9, 37.8, 35.6, 25.8, 24.8, 15.8, 15.1, -4.5, -5.0 ppm. **HRMS (ESI) (m/z):** calculated for \([\text{M+Na}]^+\) (C_{27}H_{50}BBrN_2NaO_6Si) requires 639.2607, found 639.2605. \([\alpha]_D^{20} = +25.5\) (c = 1.00, CHCl_3).

Yield: 164 mg, 43%. **FTIR (CHCl_3, cm\(^{-1}\)):** 2952, 1642, 1545, 1360, 1322, 1143, 836, 778. \(^1\)H NMR (600 MHz, CDCl_3): \(\delta\) 7.85-7.82 (m, 4H), 7.49-7.46 (m, 3H), 6.54 (dt, \(J = 18.1, 6.5\) Hz), 6.38-6.36 (m, 1H), 5.95-5.93 (t, \(J = 5.6\) Hz, 1H), 5.51 (d, \(J = 18.0\) Hz, 1H), 5.30-5.27 (m, 1H), 4.27 (d, \(J = 3.1\) Hz), 3.83-3.79 (m, 1H), 3.73-3.68 (m, 1H), 3.42-3.36 (m, 1H), 3.24-3.19 (m, 1H), 2.93-2.88 (m, 1H), 2.72-2.64 (m, 2H), 2.35-2.29 (m, 2H), 2.16-2.11 (m, 1H), 1.24 (s, 12H), 1.01 (d, \(J = 7.1\) Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl_3): \(\delta\) 174.5, 171.8, 150.4, 140.5, 133.4, 133.0, 128.5, 128.2, 127.8, 126.4, 126.1, 124.6, 123.9, 121.8
(deduced from HSQC), 83.4, 72.0, 71.1, 44.9, 44.6, 42.8, 37.9, 35.8, 26.0, 24.9, 18.1, 15.2, -4.4, -4.9 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ ($C_{34}H_{53}N_2O_6BSiNa$) requires 647.3658, found 647.3669. $[\alpha]_D^{10} = +38.4$ (c = 1.47, CHCl$_3$).

2.10. Esterification

**Condition of 1st generation**

| Entry | Conditions | Comments |
|-------|------------|----------|
| 1     | Shiina condition (MNBA, DMAP, Et$_3$N, CH$_2$Cl$_2$), rt | 30a/cis-31a/trans-31a = 0.4:1:5 |
| 2     | Sc(OTf)$_3$, p-nitrobenzoic anhydride, CH$_3$NO$_2$, rt | Messy |
| 3     | Mitsunobu condition (PPh$_3$, DEAD, THF or Toluene), rt | Eliminated product observed |
| 4     | PyBOP, DIPEA, CH$_2$Cl$_2$, rt | Messy |
| 5     | HATU, DBU, DMF, rt | Not obtained |
| 6     | HBTU, DBU, DMF, rt | Not obtained |
| 7     | DIC, DMAP, DIPEA, CH$_2$Cl$_2$, rt | cis-31a/trans-31a = 1:1.2 |
| 8     | EDCI, DMAP, DIPEA, CH$_2$Cl$_2$, rt | cis-31a (30%), trans-31a (36%) |

MNBA: 2-Methyl-6-nitrobenzoic anhydride; DMAP: 4-Dimethylaminopyridine; DEAD: Diethyl azodicarboxylate; EDCI: N-(3-Dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride.; PyBOP: (Benzotriazol-1-yl)tripyrrolidinophosphonium hexafluorophosphate; DIPEA: N,N-Diisopropylethylamine; HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; HBTU: N,N,N',N'-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate; DIC: N,N'-Diisopropylcarbodiimide.

Note: The cis/trans ratio of compound 31a was determined by $^1$H NMR.$^{13}$ While in cis-31a, Ha and Hb are doublet with a coupling constant about 4.3 Hz (for instance: $\delta$Hb (5.08 ppm, d, $J$ = 4.3 Hz), in trans-31a, Ha and Hb are doublet doublet with a smaller coupling constant around 2.2 Hz (for instance: $\delta$Hb (4.91 ppm, dd, $J$ = 2.2, 1.1 Hz).
Condition of 2\textsuperscript{nd} generation

**Table S3. Model Study**

| Base            | Pka (in water)\textsuperscript{14} | cis/trans |
|-----------------|-------------------------------------|-----------|
| Pyridine        | 5.17                                | 96:4      |
| 2,6-lutidine    | 6.77                                | 40:60     |
| Et\textsubscript{3}N | 10.78                           | 30:70     |
| DIPEA           | 11.02                               | 30:70     |
| Proton sponge   | 12.34                               | 15:85     |
| Without base    | -                                   | 96:4 (trace amount) |

Note: The above model study showed that the strength of the base played a crucial role in the selective formation of cis-ester product. However, further study showed that the cis-chloro cyclobutene acid (rac)-7 chloride was volatile, which rendered the reaction poorly reproducible. We therefore conducted another screening of bases featuring the carbodiimide activation of the acid. However, only a slightly better result was obtained (**Table S4**).
Table S4. Screening of bases

| Base                | Pka (in water) | Comments                         |
|---------------------|----------------|----------------------------------|
| Pyridine            | 5.17           | Low conversion                   |
| 4-Iodopyridine      | -              | Low conversion                   |
| 3-methylpyridine    | 5.68           | 70% conversion, cis-31a/trans-31a = 2.0:1 |
| 2-methylpyridine    | 5.97           | Low conversion                   |
| 4-methylpyridine    | 6.02           | 57% conversion, cis-31a/trans-31a = 3.5:1 |
| 3,5-dimethylpyridine| 6.14           | cis-31a (43%), trans-31a (21%)   |
| 4-methoxyldpyridine | 6.62           | Full conversion, cis-31a/trans-31a = 1.5:1 |
| DMAP                | 9.60           | Full conversion, cis-31a/trans-31a = 1.0 :1 |

Note: As these studies showed that the combination of pyridine and acyl chloride was key for the selective cis-ester formation (Table S3). We decided to focus on the optimization of this condition. To address the issue of volatility of (rac)-7, we tried to find mild and clean conditions for the in-situ synthesis of (rac)-7, which led us to the condition of 3rd generation.
Condition of 3\textsuperscript{rd} generation

1. No isomerization was observed for the acid chloride formation

\[ \text{Cl} \xrightarrow{\text{Ghosez's reagent}} \text{Cl} + \text{Cl} + \text{O} \]

\[ \text{ratio:} \quad 0.68 \quad \text{0.1} \quad \text{1.0} \]

\[ \text{Measured by } ^1\text{H NMR} \]

**Fig. S6.** $^1$H NMR study of the acyl chloride formation mediated by Ghosez’s reagent.

Note: To achieve a high cis/trans selectivity, the Ghosez’s reagent needed to be freshly distilled.

2. Excellent result was achieved through the combination of the Ghosez’s reagent\textsuperscript{15} and pyridine

\[ \text{Cl} \xrightarrow{\text{Ghosez's reagent}} \text{Cl} \]

\[ \text{OH} \quad \text{OTBSHN} \]

\[ \text{CHCl}_3 \quad \text{40 min} \]

\[ \text{pyridine} \]

\[ 30\text{a} \]

\[ \text{79\%, cis-31a/trans-31a = 8.8:1} \]

**Fig. S7.** Optimized 3\textsuperscript{rd} generation condition on 30\text{a}.

Stability of the product

\[ \text{Cl} \xrightarrow{\text{DIPEA (2.5 equiv.)}} \text{Cl} \]

\[ \text{OTBSHN} \]

\[ \text{CD}_2\text{Cl}_2, 24\text{h, rt} \]

\[ \text{no isomerization was observed} \]

**Fig. S8.** Stability of cis-cyclobutene ester in the presence of DIPEA
General procedures for the esterification

1\textsuperscript{st} generation of esterification (method A)

The acid 7 (2.0 equiv.), EDCI or DIC (2.0 equiv.) and DIPEA (2.5 equiv.) were dissolved in CH\textsubscript{2}Cl\textsubscript{2} at room temperature. Then amide alcohol dissolved in CH\textsubscript{2}Cl\textsubscript{2} was added, followed by DMAP (0.2 equiv.). The mixture was vigorously stirred at room temperature overnight. Then the reaction was quenched by sat. NH\textsubscript{4}Cl (aq.). The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 times). The combined organic layers were washed by brine, dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 1:1) afforded the cis-isomer as mixture of diastereomers.

2\textsuperscript{nd} generation of esterification (method B)

Oxalyl chloride (10 equiv.) was added to a solution of cyclobutene acid 7 (3.0 equiv.) and DMF (1.0 equiv.) in pentane (0.05 M) at 0°C. A white precipitate formed immediately. After 1 h at
room temperature, the mixture was filtered and carefully concentrated in vacuo. The crude acyl chloride was then dissolved in CH₂Cl₂ and added to a solution of amide alcohol (1.0 equiv.) in CH₂Cl₂ and pyridine (4.0 equiv.) at 0° C. The reaction was allowed to reach room temperature and stirred overnight. The reaction was quenched with water and extracted 3 times with CH₂Cl₂. The resulting organic layers were combined, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 7:3 to 1:1) afforded the cis-isomer as mixture of diastereomers.

3rd generation of esterification (method C)

Fig. S11. Esterification via method C

The acid 7 (3.0 equiv.) was dissolved in CHCl₃, then the freshly distilled Ghosez’s reagent (3.1 equiv.) was added. The solution was stirred vigorously at room temperature for 40 min. Then the amide alcohol (1.0 equiv.) dissolved in CHCl₃ was added, followed by pyridine (3.5 equiv.). The resulting solution was vigorously stirred for another 4 h at room temperature. The reaction was quenched with water and extracted 3 times with CH₂Cl₂. The resulting organic layers were combined, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 7:3 to 1:1) afforded the cis-isomer as mixture of diastereoisomers.
Yield: 20.4 mg, 79% as a mixture of diastereoisomers (method C). FTIR (CHCl₃, cm⁻¹): 2929, 2856, 1738, 1645, 1539, 1361.

¹H NMR (600 MHz, CDCl₃): δ 6.54 (dt, J = 17.9, 6.2 Hz, 1H), 6.27-6.24 (m, 2H), 6.21-6.18 (m, 1H), 6.16-6.11 (m, 3H), 5.74-5.69 (m, 1H), 5.63 (dd, J = 7.9, 5.4 Hz, 1H), 5.50 (d, J = 18.1 Hz, 1H), 5.08 (d, J = 4.3 Hz, 1H), 4.07 (d, J = 4.3 Hz, 1H), 3.82-3.79 (m, 1H), 3.78-3.73 (m, 1H), 3.43-3.40 (m, 1H), 3.29-3.23 (m, 1H), 2.66 (dd, J = 14.4, 7.9 Hz, 1H), 2.49 (dd, J = 14.4, 5.4 Hz, 1H), 2.38-2.33 (m, 3H), 2.07 (q, J = 7.2 Hz, 2H), 1.77 (s, 3H), 1.36-1.34 (m, 2H), 1.25 (brd, 20H), 1.09 (d, J = 7.2 Hz, 3H), 0.89-0.86 (m, 12H), 0.14 (s, 3H), 0.07 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 174.6, 169.3, 168.8, 150.4, 140.6, 137.2, 136.6, 130.7, 129.0, 125.4, 121.5 (deduced from HSQC), 83.3, 77.0, 72.0, 56.9, 54.0, 44.5, 43.0, 40.9, 38.0, 35.8, 33.2, 31.9, 29.42, 29.36, 29.30, 26.0, 24.9, 22.8, 18.1, 15.5, 14.3, 12.7, -4.4, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₄₁H₇₀N₂O₇BClSiNa) requires 799.4626, found 799.4620.

Yield: 15.4 mg, 75% as a mixture of diastereoisomers (method C). FTIR (CHCl₃, cm⁻¹): 2954, 1738, 1646, 1542, 1360, 1323, 1144, 837, 778. ¹H NMR (600 MHz, CDCl₃): δ 6.55 (dt, J = 17.9, 6.4 Hz, 1H), 6.27-6.25 (m, 2H), 6.21-6.18 (m, 1H), 6.17-6.11 (m, 3H), 5.75-5.70 (m, 1H), 5.63 (dd, J = 7.7, 5.4 Hz, 1H), 5.50 (d, J = 18.1 Hz, 1H), 5.08 (d, J = 4.2 Hz, 1H), 4.07 (d, J = 4.3 Hz, 1H), 3.82-3.79 (m, 1H), 3.78-3.73 (m, 1H), 3.46-3.40 (m, 1H), 3.29-3.23 (m, 1H), 2.81-2.77 (m, 1H), 2.66 (dd, J = 14.4, 7.9 Hz, 1H), 2.50 (dd, J = 14.4, 5.4 Hz, 1H), 2.37-2.34 (m, 3H), 2.09-2.05 (m, 2H), 1.77 (s, 3H), 1.37-1.34 (m, 2H), 1.25 (brd, 24H), 1.09 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.14 (s, 3H), 0.07 (s,
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.55 (dt, $J = 17.8, 6.4$ Hz, 1H), 6.27-6.16 (m, 7H), 6.08 (dd, $J = 15.0, 9.8$ Hz, 1H), 5.74-5.69 (m, 1H), 5.67-5.65 (m, 1H), 5.51 (d, $J = 17.9$ Hz, 1H), 5.08 (d, $J = 3.9$ Hz, 1H), 4.07 (d, $J = 4.0$ Hz, 1H), 3.81-3.76 (m, 2H), 3.44-3.40 (m, 1H), 3.26-3.23 (m, 1H), 2.79-2.76 (m, 1H), 2.67 (dd, $J = 14.4, 7.8$ Hz, 1H), 2.51 (dd, $J = 14.4, 5.7$ Hz, 1H), 2.35-2.31 (m, 3H), 2.10-2.06 (m, 2H), 1.80 (s, 3H), 1.38-1.36 (m, 2H), 1.25 (brd, 20H), 1.08 (d, $J = 7.1$ Hz, 3H), 0.89-0.86 (m, 12H), 0.14 (s, 3H), 0.06 (s, 3H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.7, 169.2, 168.8, 150.4, 140.6, 136.63, 136.58, 135.0, 132.6, 130.4, 128.9, 125.5, 121.5 (deduced from HSQC), 83.3, 76.8, 72.0, 56.4, 54.0, 44.6, 42.9, 40.9, 38.0, 35.9, 33.0, 32.0, 29.4, 29.30, 29.28, 26.0, 24.9, 22.8, 18.1, 15.5, 14.2, 12.9, -4.4, -4.9 ppm.

HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{43}$H$_{74}$N$_2$O$_7$BClSiNa) requires 827.4939, found 827.4946.

Yield: 32.5 mg, 57% as a mixture of diastereoisomers (method C). FTIR (CHCl$_3$, cm$^{-1}$): 2948, 1736, 1646, 1541, 1360, 1324, 1169, 1144, 989, 837, 776.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.55 (dt, $J = 17.8, 6.4$ Hz, 1H), 6.27-6.16 (m, 7H), 6.08 (dd, $J = 15.0, 9.8$ Hz, 1H), 5.74-5.69 (m, 1H), 5.67-5.65 (m, 1H), 5.51 (d, $J = 17.9$ Hz, 1H), 5.08 (d, $J = 3.9$ Hz, 1H), 4.07 (d, $J = 4.0$ Hz, 1H), 3.81-3.76 (m, 2H), 3.44-3.40 (m, 1H), 3.26-3.23 (m, 1H), 2.79-2.76 (m, 1H), 2.67 (dd, $J = 14.4, 7.8$ Hz, 1H), 2.51 (dd, $J = 14.4, 5.7$ Hz, 1H), 2.35-2.31 (m, 3H), 2.10-2.06 (m, 2H), 1.80 (s, 3H), 1.38-1.36 (m, 2H), 1.25 (brd, 20H), 1.08 (d, $J = 7.1$ Hz, 3H), 0.89-0.86 (m, 12H), 0.14 (s, 3H), 0.06 (s, 3H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.6, 169.3, 168.8, 150.4, 140.6, 137.3, 136.6, 130.8, 129.0, 125.4, 121.3 (deduced from HSQC), 83.3, 77.0, 72.0, 56.4, 54.0, 44.5, 43.0, 40.9, 38.0, 35.9, 33.2, 32.0, 31.1, 29.70, 29.65, 29.5, 29.44, 29.43, 26.0, 24.9, 22.8, 18.1, 15.5, 14.3, 12.7, -4.3, -4.9 ppm.

HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{43}$H$_{74}$N$_2$O$_7$BClSiNa) requires 827.4939, found 827.4946.

Yield: 38 mg, 34% as a mixture of diastereoisomers (method A). FTIR (CHCl$_3$, cm$^{-1}$): 2926, 2855, 1735, 1643, 1540, 1359, 1324, 1144, 837,
1H NMR (600 MHz, CDCl3): \( \delta \) 6.55 (dt, \( J = 18.0 \), 6.5 Hz, 1H), 6.27-6.21 (m, 4H), 5.51 (d, \( J = 18.0 \) Hz, 1H), 5.24-5.20 (m, 1H), 5.10 (d, \( J = 4.3 \) Hz, 1H), 4.10 (d, \( J = 4.3 \) Hz, 1H), 3.87-3.85 (m, 1H), 3.75-3.70 (m, 1H), 3.46-3.41 (m, 1H), 3.28-3.23 (m, 1H), 2.88-2.84 (m, 1H), 2.51 (dd, \( J = 14.4 \), 6.7 Hz, 1H), 2.47 (dd, \( J = 14.4 \), 5.0 Hz, 1H), 2.42 (dd, \( J = 7.1 \), 4.9 Hz, 1H), 2.37-2.34 (m, 2H), 1.64-1.59 (m, 1H), 1.37-1.33 (m, 2H), 1.25-1.24 (m, 29H), 1.13 (d, \( J = 7.1 \) Hz, 3H), 0.90 (s, 9H), 0.87 (t, \( J = 7.1 \) Hz, 3H), 0.15 (s, 3H), 0.09 (s, 3H) ppm. 13C NMR (151 MHz, CDCl3): \( \delta \) 174.5, 169.9, 169.5, 150.4, 140.6, 136.7, 121.7 (deduced from HSQC), 83.4, 72.7, 72.1, 56.5, 54.0, 44.6, 43.1, 41.5, 38.0, 35.8, 34.0, 32.0, 29.78, 29.77, 29.7, 29.6, 29.50, 29.49, 26.0, 24.92, 24.91, 22.8, 18.1, 15.5, 14.3, -4.3, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]+ (C40H72N2O7BClSiNa) requires 789.4783, found 789.4764.

Yield: 21.4 mg, 61% as a mixture of diastereoisomers, d.r.: 2:1 (method B). FTIR (CHCl3, cm\(^{-1}\)): 3316, 2952, 2857, 1733, 1643, 1538, 1463, 1359, 1324, 1250, 1143, 837, 776. 1H NMR (600 MHz, CDCl3): Major diastereoisomer \( \delta \) 6.55 (dt, \( J = 18.0 \), 6.5 Hz, 1H), 6.25 (brd, 2H), 6.17-6.22 (m, 2H), 5.52 (d, \( J = 18.0 \) Hz, 1H), 5.28-5.37 (m, 1H), 5.10 (d, \( J = 4.2 \) Hz, 1H), 4.10 (d, \( J = 4.2 \) Hz, 1H), 3.85-3.89 (m, 1H), 3.68-3.77 (m, 1H), 3.40-3.48 (m, 1H), 3.23-3.30 (m, 1H), 2.82-2.90 (m, 1H), 2.49-2.59 (m, 1H), 2.41-2.46 (m, 2H), 2.37 (q, \( J = 6.6 \) Hz, 2H), 1.36 (d, \( J = 6.6 \) Hz, 3H), 1.25 (s, 12H), 1.14 (d, \( J = 7.2 \) Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H); Minor diastereoisomer \( \delta \) 5.18 (d, \( J = 4.2 \) Hz, 1H), 4.08 (d, \( J = 4.2 \) Hz, 1H), 1.14 (d, \( J = 7.2 \) Hz, 3H) ppm. 13C NMR (151 MHz, CDCl3): Major diastereoisomer \( \delta \) 174.4, 169.5, 169.1, 150.2, 140.4, 136.5, 83.2, 71.9, 69.0, 56.4, 53.6, 44.5, 43.0, 42.9, 37.8, 35.7, 31.9, 25.9, 24.8, 24.7, 22.7, 19.9, 17.9, 15.3, 14.1, -4.5, -5.0; Minor diastereoisomer \( \delta \) 174.3, 56.5, 53.8, 43.0, 42.9, 15.5 ppm.
HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{30}$H$_{52}$BClN$_2$NaO$_7$Si) requires 649.3218, found 649.3205.

Yield: 23 mg, 25% as a mixture of diastereoisomers (method A). FTIR (CHCl$_3$, cm$^{-1}$): 2927, 1738, 1642, 1554, 1359, 1323, 1145, 835, 777. $^1$H NMR (600 MHz, CDCl$_3$): δ 6.55 (dt, $J$ = 17.9, 6.5 Hz, 1H), 6.34 (t, $J$ = 5.5 Hz, 1H), 6.26-6.25 (m, 2H), 6.19-6.12 (m, 2H), 6.02 (dd, $J$ = 7.8, 4.4 Hz, 1H), 5.74-5.71 (m, 1H), 5.65 (dd, $J$ = 7.7, 5.6 Hz, 1H), 5.51 (d, $J$ = 18.0 Hz, 1H), 5.08 (d, $J$ = 4.3 Hz, 1H), 4.12-4.11 (m, 1H), 4.07 (d, $J$ = 4.3 Hz, 1H), 3.78-3.77 (m, 1H), 3.41-3.35 (m, 1H), 3.00-2.95 (m, 1H), 2.69 (dd, $J$ = 14.4, 8.3 Hz, 1H), 2.52 (dd, $J$ = 14.4, 5.7 Hz, 1H), 2.38-2.35 (m, 2H), 2.28 (dd, $J$ = 13.8, 6.0 Hz, 1H), 2.22 (dd, $J$ = 13.8, 5.2 Hz, 1H), 2.16-2.05 (m, 2H), 1.78 (s, 3H), 1.37-1.35 (m, 2H), 1.26 (brd, 2OH), 0.89-0.86 (m, 12H), 0.11 (s, 3H), 0.08 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): δ 170.3, 169.7, 168.8, 150.4, 140.5, 137.4, 136.6, 130.7, 129.3, 125.4, 121.3 (deduced from HSQC), 83.3, 77.1, 68.4, 56.4, 54.0, 44.1, 42.3, 40.9, 38.3, 35.7, 33.2, 31.9, 29.42, 29.36, 29.30, 25.9, 24.9, 22.8, 18.1, 14.3, 12.7, -4.6, -4.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{40}$H$_{68}$N$_2$O$_7$BClSiNa) requires 785.4470, found 785.4477.

Yield: 16.3 mg, 37% as a mixture of diastereoisomers (method B). FTIR (CHCl$_3$, cm$^{-1}$): 3302, 2924, 2854, 1714, 1641, 1550, 1458, 1438, 1372, 966. $^1$H NMR (600 MHz, CDCl$_3$): δ 6.54 (dt, $J$ = 18.0, 6.5 Hz, 1H), 6.25 (bs, 3H), 6.10-6.18 (m, 3H), 5.71 (dt, $J$ = 14.2, 6.9 Hz, 1H), 5.61 (dd, $J$ = 8.1, 5.0 Hz, 1H), 5.51 (d, $J$ = 18.0 Hz, 1H), 5.08 (d, $J$ = 4.3 Hz, 1H), 4.06 (d, $J$ = 4.3 Hz, 1H), 3.35 (q, $J$ = 6.6 Hz, 2H), 2.65 (dd, $J$ = 14.6, 8.3 Hz,
$^{1}H$ NMR (600 MHz, CDCl$_3$): $\delta$ 6.89-6.98 (m, 1H), 6.54 (dt, $J = 18.0$, 6.5 Hz, 1H), 6.39 (brd, 1H), 6.22-6.29 (m, 4H), 5.66-5.75 (m, 2H), 5.51 (d, $J = 18.0$ Hz, 1H), 5.10 (d, $J = 4.3$ Hz, 1H), 4.10 (d, $J = 4.3$ Hz, 1H), 3.72-3.82 (m, 2H), 3.42-3.47 (m, 1H), 3.24-3.30 (m, 1H), 2.74-2.80 (m, 1H), 2.64 (dd, $J = 14.6$, 8.0 Hz, 1H), 2.52 (dd, $J = 14.6$, 5.2 Hz, 1H), 2.33-2.43 (m, 3H), 1.88 (s, 3H), 1.25 (s, 12H), 1.13 (d, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.6, 168.6, 168.6, 150.1, 140.6, 136.3, 132.2 (q, $J = 6.8$ Hz), 130.6 (d, $J = 182.7$ Hz), 124.3, 119.6 (q, $J = 28.4$ Hz), 83.2, 75.7, 71.7, 56.2, 53.7, 44.4, 43.0, 40.3, 37.8, 35.7, 25.9, 25.7, 24.8, 24.7, 17.9, 15.4, 13.4, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{35}$H$_{55}$BCl$_3$F$_3$N$_2$O$_7$Si) requires 769.3404, found 769.3401.

Yield: 9.4 mg, 40% as a mixture of diastereoisomers (method B). FTIR (CHCl$_3$, cm$^{-1}$): 3336, 2954, 2858, 1738, 1741, 1645, 1540, 1360, 1315, 1262, 1168, 1143, 1110, 837, 777. $^{1}$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.89-6.98 (m, 1H), 6.54 (dt, $J = 18.0$, 6.5 Hz, 1H), 6.39 (brd, 1H), 6.22-6.29 (m, 4H), 5.66-5.75 (m, 2H), 5.51 (d, $J = 18.0$ Hz, 1H), 5.10 (d, $J = 4.3$ Hz, 1H), 4.10 (d, $J = 4.3$ Hz, 1H), 3.72-3.82 (m, 2H), 3.42-3.47 (m, 1H), 3.24-3.30 (m, 1H), 2.74-2.80 (m, 1H), 2.64 (dd, $J = 14.6$, 8.0 Hz, 1H), 2.52 (dd, $J = 14.6$, 5.2 Hz, 1H), 2.33-2.43 (m, 3H), 1.88 (s, 3H), 1.25 (s, 12H), 1.13 (d, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.6, 168.6, 168.6, 150.1, 140.6, 136.3, 132.2 (q, $J = 6.8$ Hz), 130.6 (d, $J = 182.7$ Hz), 124.3, 119.6 (q, $J = 28.4$ Hz), 83.2, 75.7, 71.7, 56.2, 53.7, 44.4, 43.0, 40.3, 37.8, 35.7, 25.9, 25.7, 24.8, 24.7, 17.9, 15.4, 13.4, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{35}$H$_{55}$BCl$_3$F$_3$N$_2$O$_7$Si) requires 769.3404, found 769.3401.

Yield: 9.5 mg, 40% as a mixture of diastereoisomers (method B). FTIR (CHCl$_3$, cm$^{-1}$): 3304, 2929, 1736, 1644, 1540, 1360, 1325, 1258, 1168, 1143, 1027, 994, 966, 837, 777. $^{1}$H NMR
(600 MHz, CDCl3): δ 7.39 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.93 (dd, J = 15.5, 11.0 Hz, 1H), 6.57 (d, J = 15.5 Hz, 1H), 6.52 (dt, J = 18.0, 6.5 Hz, 1H), 6.35 (d, J = 11.0 Hz, 1H), 6.25-6.29 (m, 3H), 6.14 (m, 1H), 5.71 (t, J = 6.6 Hz, 1H), 5.49 (d, J = 18.0 Hz, 1H), 5.10 (d, J = 4.3 Hz, 1H), 4.10 (d, J = 4.3 Hz, 1H), 3.74-3.84 (m, 2H), 3.33-3.40 (m, 1H), 3.16-3.22 (m, 1H), 2.76-2.81 (m, 1H), 2.71 (dd, J = 14.4, 7.7 Hz, 1H), 2.55 (dd, J = 14.4, 5.8 Hz, 1H), 2.29-2.35 (m, 2H), 2.29 (q, J = 6.6 Hz, 1H), 1.91 (s, 3H), 1.25 (s, 12H), 1.06 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 3H), 0.05 (s, 3H) ppm. \( ^{13} \text{C NMR (151 MHz, CDCl}_{3} \): δ 174.5, 169.0, 168.6, 150.2, 140.5, 137.2, 136.4, 134.1, 133.9, 128.7, 128.6, 127.7, 126.4, 123.9, 83.0, 76.5, 71.8, 56.2, 53.83 44.4, 42.8, 40.7, 37.8, 35.7, 25.8, 24.8, 24.7, 17.9, 15.4, 13.0, -4.5, -5.1 ppm. \( \text{HRMS (ESI) (m/z): calculated for [M+Na]^+ (C}_{40}H_{60}BCIN}_{2}NaO}_{7}Si requires 777.3844, found 777.3873.\)
168.6, 150.2, 140.5, 137.6, 136.4, 134.4, 134.0, 133.4, 129.3, 128.8, 126.3, 123.0, 83.2, 76.6, 71.9, 56.2, 53.9, 44.5, 42.8, 40.7, 37.8, 35.7, 25.9, 24.8, 24.7, 21.2, 17.9, 15.3, 13.1, -4.5, -5.1 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{41}$H$_{62}$BClN$_2$NaO$_7$Si) requires 791.4000, found 791.4007.

**Yield:** 125 mg, 67% as a mixture of diastereoisomers (method B). **FTIR (CHCl$_3$, cm$^{-1}$):** 3320, 2930, 1737, 1646, 1541, 1360, 1324, 1258, 1165, 1143, 1123, 1067, 837, 777.

$^1$H NMR (700 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J = 8.2$ Hz, 2H), 7.47 (d, $J = 8.2$ Hz, 2H), 7.01 (dd, $J = 15.6$, 11.0 Hz, 1H), 6.58 (d, $J = 15.8$ Hz, 1H), 6.53 (dt, $J = 18.0$, 6.5 Hz, 1H), 6.37 (d, $J = 11.0$ Hz, 1H), 6.24-6.35 (m, 3H), 6.19 (t, $J = 5.6$ Hz, 1H), 5.71 (t, $J = 6.6$ Hz, 1H), 5.50 (d, $J = 18.0$ Hz, 1H), 5.10 (d, $J = 4.2$ Hz, 1H), 4.10 (d, $J = 4.2$ Hz, 1H), 3.73-3.83 (m, 2H), 3.37-3.43 (m, 1H), 3.20-3.26 (m, 1H), 2.76-2.82 (m, 1H), 2.69 (dd, $J = 14.5$, 7.9 Hz, 1H), 2.55 (dd, $J = 14.5$, 5.9 Hz, 1H), 2.32-2.41 (m, 3H), 1.92 (s, 3H), 1.25 (s, 3H), 1.07 (d, $J = 7.2$ Hz, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.06 (s, 3H) ppm.

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 174.5, 168.9, 168.6, 150.1, 140.7, 140.5, 136.4, 136.1, 132.1, 129.1 (q, $J = 32.4$ Hz), 128.1, 126.4, 126.3, 125.5 (d, $J = 3.7$ Hz), 117.2, 76.4, 71.7, 56.2, 53.8, 49.7, 44.4, 43.0, 40.6, 37.8, 35.7, 25.8, 25.8, 24.7, 24.7, 17.9, 15.4, 13.2, 8.8, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{41}$H$_{59}$BCIF$_3$N$_2$NaO$_7$Si) requires 845.3717, found 845.3745.

**Yield:** 57.3 mg, 44%, mixture of diastereoisomers (method A). **FTIR (CHCl$_3$, cm$^{-1}$):** 3337, 2969, 1741, 1637, 1560, 1463, 1362, 1250, 1167, 1143, 836, 776. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.46
(d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.54 (dt, J = 18.0, 6.5 Hz, 1H), 6.29-6.24 (m, 2H), 6.16 (t, J = 7.1 Hz, 1H), 6.14-6.12 (m, 1H), 6.03 (t, J = 5.5 Hz, 1H), 5.51 (d, J = 18.0 Hz, 1H), 5.06 (d, J = 4.2 Hz 1H), 4.08 (d, J = 4.2 Hz, 1H), 3.73-3.69 (m, 1H), 3.66-3.63 (m, 1H), 3.45-3.38 (m, 1H), 3.27-3.22 (m, 1H), 2.91 (dd J = 14.2, 7.5 Hz, 1H), 2.75-2.70 (m, 1H), 2.61 (dd, J = 14.2, 6.8 Hz, 1H), 2.36-2.33 (m, 2H), 1.94-1.90 (m, 1H), 1.25 (s, 12H), 1.14 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.5, 168.7, 168.5, 150.3, 140.7, 138.1, 136.4, 131.7, 129.1, 122.5, 121.4 (deduced from HSQC), 83.4, 73.4, 71.9, 56.4, 53.8, 44.5, 43.5, 42.8, 38.0, 35.8, 26.0, 24.9, 18.1, 15.4, -4.4, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{35}$H$_{53}$N$_2$O$_7$BClBrSiNa) requires 789.2479, found 789.2485.

Yield: 30% as a mixture of diastereoisomers (method B). FTIR (CHCl$_3$, cm$^{-1}$): 3367, 2928, 2856, 1880, 1741, 1644, 1541, 1360, 1325, 1255, 1167, 1143, 837, 777. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.54 (dt, J = 18.0, 6.5 Hz, 1H), 6.45 (s, 1H), 6.24-6.28 (m, 3H), 6.17 (brd, 1H), 5.75 (dd, J = 7.3, 6.3 Hz, 1H), 5.51 (d, J = 18.0 Hz, 1H), 5.09 (d, J = 4.3 Hz, 1H), 4.08 (d, J = 4.3 Hz, 1H), 3.75-3.84 (m, 2H), 3.42-3.49 (m, 1H), 3.22-3.28 (m, 1H), 2.98 (d, J = 14.5 Hz, 1H), 2.74-2.82 (m, 1H), 2.66 (dd, J = 14.5, 7.7 Hz, 1H), 2.50 (dd, J = 14.5, 5.8 Hz, 1H), 2.33-2.37 (m, 3H), 1.83 (s, 3H), 1.25 (s, 12H), 1.13 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.5, 168.5, 168.3, 150.2, 140.6, 137.9, 136.2, 108.8, 83.2, 74.5, 71.8, 56.1, 53.6, 44.5, 42.7, 40.2, 37.8, 35.7, 25.8, 24.8, 24.7, 17.9, 15.3, 15.3, -4.5, -5.1 ppm. HRMS (ESI) (m/z): calculated for [M+H]$^+$ (C$_{32}$H$_{54}$BBrClN$_2$O$_7$Si) requires 731.2660, found 731.2665.
Yield: 55.5 mg, 59% as a mixture of diastereoisomers (method A).

FTIR (CHCl₃, cm⁻¹): 2950, 1737, 1643, 1540, 1359, 1323, 1168, 1143, 837, 777. ¹H NMR (600 MHz, CDCl₃): δ 7.89-7.82 (m, 4H), 7.56-7.55 (m, 1H), 7.50-7.47 (m, 2H), 6.51 (dt, J = 18.0, 6.5 Hz, 1H), 6.38 (t, J = 7.3 Hz, 1H), 6.29-6.27 (m, 1H), 6.24-6.23 (m, 1H), 6.13-6.11 (m, 1H), 5.57 (t, J = 5.6 Hz, 1H), 5.48 (d, J = 18.0 Hz, 1H), 5.08 (d, J = 4.2 Hz, 1H), 4.11 (d, J = 4.2 Hz, 1H), 3.72-3.68 (m, 1H), 3.47-3.45 (m, 1H), 3.30-3.22 (m, 1H), 3.14-3.09 (m, 1H), 3.07 (dd, J = 13.8, 6.8 Hz, 1H), 2.76 (dd, J = 13.8, 7.8 Hz, 1H), 2.65-2.61 (m, 1H), 2.33-2.25 (m, 3H), 1.26 (s, 12H), 0.61 (d, J = 7.1 Hz, 3H), 0.08 (s, 3H), -0.04 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 174.6, 168.8, 168.7, 150.5, 140.6, 136.4, 136.2, 133.2, 133.0, 128.42, 128.41, 127.8, 126.8, 126.6, 126.56,126.52, 124.7, 121.3 (deduced from HSQC), 83.4, 74.3, 71.8, 56.3, 53.9, 44.1, 43.7, 42.4, 37.9, 35.8, 29.8, 25.9, 24.9, 18.0, 15.0, -4.5, -5.0 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₃₉H₅₆N₂O₇BClSiNa) requires 761.3531, found 761.3541.
2.11. Suzuki-Miyaura macrocyclization

Table S5. Optimization of the conditions

| Entry | Conditions | Comments |
|-------|------------|----------|
| 1     | Pd(OAc)$_2$, SPhOS, K$_3$PO$_4$, THF/H$_2$O, 40 °C | Decomposition |
| 2     | Pd(OAc)$_2$, SPhOS, K$_3$PO$_4$, THF/H$_2$O, rt | Not observed |
| 3     | Pd(PPh$_3$)$_4$, TiOEt, THF/H$_2$O, rt | Not observed |
| 4     | Pd(dppf)Cl$_2$, AsPh$_3$, Cs$_2$CO$_3$, DMF/THF/H$_2$O, rt | 67% |
| 5     | Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, THF/H$_2$O, rt | 74% |

Fig. S12. Suzuki-Miyaura/4π-electrocyclic ring opening macrocyclisation
The cis-chloro cyclobutene ester is quite prone to undergo the oxidative addition when treated with a palladium complex. Upon formation of the resulting stereoinvertive η^1-allyl species I, severable possible pathways could lead to the final macrocycle product (Fig. S12).

1. The species I is kinetically unstable and undergoes a 4π-electrocyclic ring opening to give the E,E dienic Pd-complex II. Further transmetalation of complex II leads to a penultimate intermediate IV, which after reductive elimination affords the final macrocycle.

Alternatively, the species I is stable enough under the conditions to allow a transmetalation to form complex III. From complex III, two possible pathways are proposed.

2. Complex III undergoes a 4π-electrocyclic ring opening to intermediate IV, and the final product is released after a reductive elimination.

3. Complex III could be kinetically stable and further subjected to a reductive elimination to form a penultimate intermediate V. Intermediate V readily undergoes a 4π-electrocyclic ring opening under the condition to deliver the final product.

While both pathway 1 and 2 involved the intermediacy of a dienylpalladium complex IV, pathway 3 relied on a vinylcyclobutene moiety V. To shed light on the mechanism of the formation of macrocycle 32a, alkyl boron intermediate 32-2 and pinacol boronic ester 32-3 were prepared through hydroboration of undec-1-ene 32-1 (Fig. S13.). Those boron reagents were then treated with 7 or 7’ under the same Suzuki-Miyaura coupling conditions used for the synthesis of macrocycle 32a. In all the reactions screened, the expected product 32-4 or 32-5 was never observed. Instead, the reduced cyclobutene ester 32-6, probably formed via the hydridopalladium species 32-6’ after a reductive elimination, was isolated in 20% yield (entry 4). These reactions suggest that the dienylpalladium intermediate IV was probably not involved in
the formation of the macrocycle 32a, thus excluding pathway 1 and 2 (Fig. S12). 32a was most likely formed through a Suzuki-Miyaura coupling on the cyclobutene moiety and a sequential spontaneous 4π-electrocyclic ring opening of intermediate V (pathway 3, Fig. S12).

| Entry | Boron reagent | Conditions | Comments       |
|-------|---------------|------------|----------------|
| 1     | 32-3          | Pd(PPh₃)₄, Cs₂CO₃, THF/H₂O, rt | Decomposition  |
| 2     | 32-3          | Pd(dppf)Cl₂, AsPh₃, Cs₂CO₃, DMF/THF/H₂O, rt | Decomposition  |
| 3     | 32-2          | Pd(PPh₃)₄, Cs₂CO₃, THF/H₂O, rt | Decomposition  |
| 4     | 32-2          | Pd(dppf)Cl₂, AsPh₃, Cs₂CO₃, DMF/THF/H₂O, rt | S2-6 (20%)    |

Fig. S13. Mechanistic study of Suzuki-Miyaura/4π-electrocyclic ring opening macrocyclisation
To a stirred solution of alkene 32-1 (41 uL, 0.2 mmol, 2.0 equiv.) in THF (1.0 mL) at 0 °C was added 9-BBN (26 uL, 0.19 mmol, 1.9 equiv.). The mixture was then allowed to warm to room temperature and stirred for 12 h. The boron reagent 32-2 was used without isolation.

In a separated flask charged with 7’ (22.3 mg, 0.10 mmol, 1.0 equiv.), Cs₂CO₃ (163 mg, 0.50 mmol, 5.0 equiv.), Pd(dppf)Cl₂ (7.3 mg, 0.01 mmol, 10 mmol%) and AsPh₃ (10.1 mg, 0.033 mmol, 33 mmol%) was added DMF (1.5 mL) and H₂O (0.5 mL). The mixture was stirred vigorously at room temperature, then the above boron reagent 32-2 was added to the reaction mixture. After 18 h at room temperature, the reaction was quenched by sat. NH₄Cl (aq.) and extracted with CH₂Cl₂ (5 x 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 10:1) afforded 3.8 mg (20%) of product 32-6. FTIR (CHCl₃, cm⁻¹): 3026, 3035, 2931, 1732, 1377, 1155, 1084, 1026, 697. ¹H NMR (400 MHz, CDCl₃): 7.39-7.31 (m, 5H), 6.23-6.22 (m, 1H), 6.06 (dd, J = 2.7, 0.9 Hz, 1H), 5.14 (s, 2H), 3.74-3.72 (m, 1H), 2.83 (ddd, J = 13.6, 4.4, 0.8 Hz, 1H), 2.76 (ddd, J = 13.6, 1.9, 0.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): 173.2, 139.4, 136.2, 135.0, 128.7, 128.3, 128.2, 66.4, 46.1, 34.7. HRMS (ESI) (m/z): calculated for [M+Na⁺]⁺ (C₁₂H₁₂O₂Na) requires 211.0730, found 211.0727.
General procedure for the macrocyclization

Fig. S14. Suzuki-Miyaura/4π-electrocyclic ring opening

The substrate (1.0 equiv.) was dissolved in a mixture THF/H₂O (3/1) (0.002 M, degassed by bubbling with argon for 10 min), and then Cs₂CO₃ (5 equiv.) was added. The mixture was stirred at rt for 5-10 min, then Pd(PPh₃)₄ (10 mol%) was added. The reaction was then covered by aluminum foil and stirred at room temperature for 18 h-24 h. The reaction was quenched by sat. NH₄Cl (aq.), extracted with CH₂Cl₂ (5 times). The resulting organic layers were combined, washed by brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 2:1 to 1:1) afforded the desired product.

Yield: 20.6 mg, 74%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3336, 2926, 2854, 1702, 1617, 1534, 1253, 1229, 1102, 1012, 835, 775.

¹H NMR (600 MHz, CDCl₃): ∆ 7.26 (dd, J = 15.3, 11.3 Hz, 1H), 6.46 (dd, J = 14.8, 10.9 Hz, 1H), 6.23-6.14 (m, 2H), 6.12-6.08 (m, 2H), 6.05 (brd, 1H), 5.98 (brd, 1H), 5.93-5.88 (m, 1H), 5.76-5.70 (m, 2H), 5.63 (dd, J = 11.1, 3.1 Hz, 1H), 4.11-4.05 (m, 1H), 4.01 (brd, 1H), 3.49-3.44 (m, 1H), 2.96 (d, J = 13.9, 1H), 2.55-2.39 (m, 5H), 2.22-2.16 (m, 1H), 2.11-2.08 (m, 2H), 1.78 (s, 3H), 1.39-1.36 (m, 2H), 1.30-1.25 (m, 8H), 1.13 (d, J = 7.3 Hz, 3H), 0.89-0.84 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): ∆ 174.1, 169.9, 166.3, 146.7, 143.2, 138.8, 136.7, 132.1, 131.5, 127.6, 126.5, 125.6, 119.5, 77.2, 72.3, 45.3, 43.0, 42.2, 37.4, 34.4, 33.2, 32.0, 29.8, 29.5, 29.3, 25.8, 22.8, 18.0, 14.3, 13.3, 12.4, -
4.5, -4.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]+ (C35H58N2O5SiNa) requires 637.4007, found 637.4008. \([\alpha]_D^{20} = -78.7\) (c = 0.85, CHCl3).

Yield: 8.2 mg, 82%, colorless powder. FTIR (CHCl3, cm\(^{-1}\)): 3354, 2926, 2854, 1703, 1616, 1532, 1463, 1255, 1103, 1012, 836, 779. \(^1\)H NMR (600 MHz, CDCl3): \(\delta\) 7.23 (dd, \(J = 15.5, 11.2\) Hz, 1H), 6.44 (dd, \(J = 14.9, 10.8\) Hz, 1H), 6.22 (dd, \(J = 14.8, 10.9\) Hz, 1H), 6.16 (dd, \(J = 14.9, 11.3\) Hz, 1H), 6.12-6.08 (m, 2H), 5.99 (brd, 1H), 5.93-5.88 (m, 1H), 5.81 (brd, 1H), 5.76-5.70 (m, 3H), 5.63 (dd, \(J = 11.2, 3.0\) Hz, 1H), 5.40-4.03 (m, 1H), 5.00 (brd, 1H), 3.49-3.44 (m, 1H), 2.96 (d, \(J = 13.9\) Hz, 1H), 2.54-2.39 (m, 5H), 2.22-2.16 (m, 1H), 2.12-2.08 (m, 2H), 1.79 (s, 3H), 1.38-1.36 (m, 2H), 1.30-1.25 (m, 1H), 1.13 (d, \(J = 7.3\) Hz, 3H), 0.89-0.85 (m, 3H), 0.10 (s, 3H) ppm. \(^1\)C NMR (151 MHz, CDCl3): \(\delta\) 174.1, 169.8, 166.4, 146.6, 143.2, 138.8, 136.7, 132.0, 131.5, 127.6, 126.5, 125.6, 119.5, 77.2, 72.3, 45.3, 43.0, 42.3, 37.5, 34.5, 33.2, 32.0, 29.71, 29.66, 29.51, 29.48, 29.38, 25.8, 22.8, 18.0, 14.3, 13.4, 12.4, -4.5, -4.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]+ (C37H62N2O5SiNa) requires 665.4320, found 665.4319. \([\alpha]_D^{20} = -71.9\) (c = 0.16, CHCl3).

Yield: 8.0 mg, 71%, colorless powder. FTIR (CHCl3, cm\(^{-1}\)): 3327, 2926, 2855, 1709, 1617, 1533, 1252, 1229, 1100, 1011, 987, 835. \(^1\)H NMR (700 MHz, CDCl3): \(\delta\) 7.25 (dd, \(J = 15.6, 11.2\) Hz, 1H), 6.46 (dd, \(J = 14.8, 10.7\) Hz, 1H), 6.29 (dd, \(J = 14.8, 10.9\) Hz, 1H), 6.22 (dd, \(J = 14.8, 10.3\) Hz, 1H), 6.18-6.14 (m, 2H), 6.12-6.08 (m, 2H), 5.98 (brd, 1H), 5.93-5.89 (m, 1H), 5.81 (brd, 1H), 5.74-5.70 (m, 2H), 5.65 (dd, \(J = 11.0, 3.0\) Hz, 1H), 4.11-4.04
(m, 1H), 4.01 (brd, 1H), 3.50-3.45 (m, 1H), 2.97 (d, J = 13.8, 1H), 2.54-2.52 (m, 2H), 2.49-2.46 (m, 1H), 2.44-2.39 (m, 2H), 2.22-2.16 (m, 1H), 2.11-2.08 (m, 2H), 1.81 (s, 3H), 1.39-1.37 (m, 2H), 1.28-1.25 (m, 8H), 1.13 (d, J = 7.3 Hz, 3H), 0.89-0.85 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H) ppm. $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 174.0, 169.8, 166.3, 146.7, 143.2, 138.9, 136.1, 134.5, 133.9, 131.5, 130.6, 127.6, 126.5, 125.8, 119.5, 77.1, 72.3, 45.3, 43.0, 42.3, 37.5, 34.5, 33.0, 32.0, 29.8, 29.4, 29.3, 25.8, 22.8, 18.0, 14.3, 13.6, 12.3, -4.5, -4.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{37}$H$_{60}$N$_2$O$_5$SiNa) requires 663.4164, found 663.4147. [$a$]$_{D}^{20} = -96.9$ (c = 1.09, CHCl$_3$).

1H NMR (600 MHz, CDCl$_3$): $\delta$ 7.21 (dd, J = 15.3, 11.2 Hz, 1H), 6.45 (dd, J = 14.9, 10.9 Hz, 1H), 6.15 (dd, J = 14.8, 11.2 Hz, 1H), 6.08 (dd, J = 14.9, 10.9 Hz, 1H), 6.00 (brd, 1H), 5.92-5.87 (m, 1H), 5.84 (brd, 1H), 5.71 (d, J = 15.4 Hz, 1H), 5.28-5.24 (m, 1H), 4.07-4.00 (m, 1H), 3.94 (brd, 1H), 3.39-3.34 (m, 1H), 2.99-2.96 (m, 1H), 2.53-2.50 (m, 2H), 2.48-2.45 (m, 2H), 2.25 (dd, J = 13.8, 10.3 Hz, 1H), 2.22-2.15 (m, 1H), 1.73-1.67 (m, 1H), 1.62-1.57 (m, 1H), 1.38-1.37 (m, 2H), 1.25 (m, 16H), 1.12 (d, J = 7.3 Hz, 3H), 0.89-0.86 (m, 12H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.2, 170.1, 167.0, 146.6, 143.1, 138.7, 131.6, 127.6, 119.7, 73.7, 72.3, 45.3, 43.4, 43.0, 37.5, 35.0, 34.5, 32.1, 29.80, 29.77, 29.73, 29.66, 29.59, 29.50, 25.8, 25.6, 25.0, 22.8, 18.0, 14.3, 12.9, -4.4, -4.8 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{34}$H$_{60}$N$_2$O$_5$SiNa) requires 627.4164, found 627.4157. [$a$]$_{D}^{20} = -5.8$ (c = 0.76, CHCl$_3$).
Yield: 10.3 mg, 84%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3348, 2951, 2855, 1700, 1652, 1616, 1532, 1463, 1384, 1255, 1037, 1011, 834; ¹H NMR (600 MHz, CDCl₃): δ 7.22 (dd, J = 15.4, 11.2 Hz, 1H), 6.45 (dd, J = 14.9, 10.8 Hz, 1H), 6.15 (dd, J = 14.9, 11.2 Hz, 1H), 6.09 (dd, J = 14.4, 11.4 Hz, 1H), 5.90-5.82 (m, 2H), 5.71 (m, 1H), 5.69 (d, J = 15.5 Hz, 1H), 5.30-5.39 (m, 1H), 3.98-4.06 (m, 2H), 3.37 (dd, J = 13.8, 7.9 Hz, 1H), 2.96-3.02 (m, 1H), 2.45-2.58 (m, 5H), 2.26 (dd, J = 13.8, 10.2 Hz, 1H), 2.18 (m, 1H), 1.39 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 173.8, 169.7, 166.6, 146.7, 143.2, 138.8, 131.3, 127.3, 119.3, 72.1, 70.0, 45.3, 44.8, 42.8, 37.3, 34.3, 25.7, 20.6, 17.9, -4.6, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₄H₄₀N₂NaO₅Si) requires 487.2599, found 487.2598. [α]D²⁰ = +5.90 (c = 0.60, CHCl₃).

In order to remove traces of Ph₃PO, the product was purified a second time using the previously described conditions. In the course of the purification, the product isomerized to give a mixture of 3:2 of (E, E, E) and (E, E, Z)

¹H NMR (600 MHz, CDCl₃): δ Minor isomer (E, E, Z) 7.29 (dd, J = 15.4, 10.9 Hz, 1H), 7.08 (dd, J = 14.1, 11.8 Hz, 1H), 6.31 (dd, J = 14.1, 11.8 Hz, 1H), 6.28 (t, J = 10.8 Hz, 1H), 5.86 (d, J = 15.4 Hz, 1H), 5.79 (q, J = 9.2 Hz, 1H), 5.12-5.18 (m, 1H), 3.83-3.88 (m, 1H), 3.76-3.82 (m, 1H), 3.04-3.11 (m, 1H), 2.82-2.88 (m, 1H), 1.42 (d, J = 6.2 Hz, 3H), 1.14 (masked, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H) ppm

Yield: 17.3 mg, 73%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3315, 2925, 2855, 1709, 1640, 1548, 1254, 1230, 1087, 1006, 975, 836, 777. ¹H NMR (600 MHz, CDCl₃): δ 7.26 (dd, J =
15.3, 11.3 Hz, 1H), 6.48 (dd, J = 14.8, 10.9 Hz, 1H), 6.21 (dd, J = 14.9, 10.8 Hz, 1H), 6.14 (dd, J = 14.8, 11.3 Hz, 1H), 6.12 (d, J = 10.8 Hz, 1H), 6.08 (brd, 1H), 6.06 (dd, J = 14.8, 11.4 Hz, 1H), 5.92-5.88 (m, 1H), 5.79 (brd, 1H), 5.76-5.72 (m, 1H), 5.70 (d, J = 15.3 Hz, 1H), 5.62 (dd, J = 11.0, 2.9 Hz, 1H), 4.19-4.15 (m, 1H), 4.06-4.00 (m, 1H), 3.36-3.32 (m, 1H), 2.96 (d, J = 13.9, 1H), 2.70 (dt, J = 13.5, 3.8 Hz, 1H), 2.53 (dd, J = 13.9, 3.3 Hz, 1H), 2.52-2.49 (m, 1H), 2.45 (dd, J = 13.6, 11.3 Hz, 1H), 2.35 (dd, J = 15.6, 4.3 Hz, 1H), 2.28-2.24 (m, 1H), 2.17 (dd, J = 15.6, 7.8 Hz, 1H), 2.11-2.08 (m, 2H), 1.79 (s, 3H), 1.39-1.37 (m, 2H), 1.30-1.25 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 170.9, 169.5, 166.3, 146.2, 142.8, 138.8, 136.8, 132.0, 131.9, 127.5, 126.7, 125.6, 119.7, 76.6, 69.4, 45.8, 42.9, 42.3, 37.5, 34.6, 33.2, 32.0, 29.8, 29.5, 29.3, 29.32, 25.9, 25.0, 22.8, 18.1, 14.2, 13.3, -4.49, -4.53 ppm. HRMS (ESI) (m/z): calculated for [M+Na]+ (C₃₄H₅₆N₂O₅SiNa) requires 623.3851, found 623.3851. \[\alpha\]D²⁰ = -107 (c = 0.64, CHCl₃).

Yield: 7.0 mg, 55%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3302, 2924, 2854, 1714, 1641, 1550, 1458, 1438, 1372, 1267.

¹H NMR (600 MHz, CDCl₃): δ 7.21 (dd, J = 15.4, 7.8 Hz, 1H), 6.14-6.24 (m, 2H), 6.03-6.12 (m, 2H), 5.91 (t, J = 6.0 Hz, 1H), 5.75 (d, J = 15.5 Hz, 1H), 5.68-5.75 (m, 3H), 5.58 (dd, J = 9.5, 4.1 Hz, 1H), 5.43 (t, J = 6.0 Hz, 1H), 3.40-3.51 (m, 2H), 3.06-3.14 (m, 1H), 2.90-2.97 (m, 1H) 2.49-2.55 (m, 2H), 2.08-2.22 (m, 4H), 1.76 (s, 3H), 1.51-1.65 (m, 3H), 1.33-1.44 (m, 2H), 1.25-1.31 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 172.2, 169.6, 165.25, 144.5, 144.2, 136.7, 131.6, 129.8, 127.0, 125.3, 119.8, 75.4, 41.6, 39.2, 38.7, 34.3, 33.0, 31.8, 31.6, 29.3, 29.2, 29.2, 27.2,
26.5, 25.2, 22.7, 14.1, 13.0 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]+ (C28H42N2NaO4) requires 493.3037, found 493.3039. \([a]_D^{20} = +12.3 \ (c = 0.61, \text{CHCl}_3)\).

**Yield:** 5.8 mg, 73%, colorless powder. **FTIR (CHCl3, cm\textsuperscript{-1}):** 3331, 2929, 1702, 1633, 1533, 1450, 1299, 1252, 1229, 1106, 1011. **\(1^H\)-NMR (600 MHz, CDCl3):** \(\delta\) 7.27 (masked, 1H), 6.96-7.02 (m, 1H), 6.47 (dd, \(J = 14.8, 10.9\) Hz, 1H), 6.08-6.19 (m, 2H), 5.98 (brd, 1H), 5.92 (m,1H), 5.70-5.75 (m, 2H), 5.65 (d, \(J = 8.6\) Hz, 1H), 5.31-5.37 (m, 2H), 4.02-4.10 (m, 2H), 3.45-3.52 (m, 1H), 2.97 (dm, \(J = 13.6\) Hz, 1H), 2.60 (dd, \(J = 13.6, 3.4\) Hz, 1H), 2.55 (dm, \(J = 13.9\) Hz, 1H), 2.47 (m, 1H), 2.40 (dt, \(J = 13.7, 4.7\) Hz, 1H), 2.35 (dd, \(J = 13.5, 11.5\) Hz, 1H), 2.19-2.25 (m, 1H), 1.97-2.04 (m, 1H), 1.89 (s, 3H), 1.13 (d, \(J = 7.2\) Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. **\(13C\) NMR (151 MHz; CDCl3):** \(\delta\) 174.0, 169.1, 166.0, 147.1, 143.6, 139.2, 132.4 (d, \(J = 6.6\) Hz), 131.7, 127.3, 121.8, 118.7, 76.1, 72.0, 45.1, 42.8, 41.9, 37.3, 34.4, 29.7, 25.6, 22.7, 17.8, 13.9, 1.0, -4.7, -5.0 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]+ (C29H43F3N2NaO5Si) requires 607.2786, found 607.2786. \([a]_D^{20} = -25.9 \ (c = 0.58, \text{CHCl}_3)\).

**Yield:** 10.9 mg, 80%, colorless powder. **FTIR (CHCl3, cm\textsuperscript{-1}):** 2973, 2872, 1706, 1650, 1616, 1533, 1463, 1254, 1100, 832. **\(1^H\) NMR (600 MHz, CDCl3):** \(\delta\) 7.41 (d, \(J = 7.6\) Hz, 2H), 7.32 (t, \(J = 7.2\) Hz, 2H), 7.28 (masked, 1H), 7.22 (t, \(J = 7.2\) Hz, 1H), 6.98 (dd, \(J = 15.3, 11.1\) Hz, 1H), 6.59 (d, \(J = 15.4\) Hz, 1H), 6.47 (dd, \(J = 14.1, 11.3\) Hz, 1H), 6.32 (d, \(J = 10.9\) Hz, 1H), 6.18 (dd, \(J = 14.4, 12.3\) Hz, 1H), 6.10 (dd, \(J = 15.3, 12.3\) Hz, 1H), 5.99 (brd, 1H), 5.87-5.94 (m,2H), 5.69-5.75 (m, 2H), 4.01-4.13 (m, 2H), 3.46-3.53 (m, 1H), 3.46-3.53 (m, 1H), 3.46-3.53 (m, 1H), 3.46-3.53 (m, 1H), 3.46-3.53 (m, 1H).
2.98 (d, J = 13.7 Hz, 1H), 2.39-2.60 (m, 5H), 2.16-2.24 (m, 1H), 1.92 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 173.9, 169.5, 166.2, 146.6, 143.2, 138.8, 137.5, 135.4, 133.4, 131.4, 128.6, 127.5, 127.4, 126.4, 126.1, 124.2, 119.2, 72.1, 45.1, 42.8, 42.1, 37.3, 34.4, 25.7, 17.8, 13.7, -4.6, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{34}$H$_{48}$N$_2$NaO$_5$Si) requires 615.3225, found 615.3231. $[^a]D_{20}^0 = -74.7$ (c = 1.09, CHCl$_3$).

Yield: 6.1 mg, 20%, colorless powder. FTIR (CHCl$_3$, cm$^{-1}$): 2924, 2812, 1710, 1660, 1641, 1615, 1566, 1460, 1373, 1252, 1229, 1039, 834. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.31 (d, J = 8.0 Hz, 2H), 7.28 (masked, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.93 (dd, J = 15.5, 11.0 Hz, 1H), 6.56 (d, J = 15.5 Hz, 1H), 6.48 (dd, J = 14.8, 10.8 Hz, 1H), 6.31 (d, J = 10.9 Hz, 1H), 6.17 (dd, J = 14.8, 11.3 Hz, 1H), 6.10 (dd, J = 14.8, 11.0 Hz, 1H), 6.05 (brd, 2H), 5.88-5.95 (m, 1H), 5.73 (d, J = 15.4 Hz, 1H), 5.69 (dd, J = 11.1, 2.9 Hz, 1H), 4.04-4.14 (m, 1H), 4.00 (brd, 1H), 3.45-3.53 (m, 1H), 2.97 (d, J = 14.0 Hz, 1H), 2.40-2.58 (m, 5H), 2.34 (s, 3H), 2.14-2.24 (m, 1H), 1.91 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.1, 169.6, 166.2, 146.6, 143.2, 138.7, 137.4, 134.7, 134.7, 133.3, 131.4, 129.3, 127.4, 126.3, 126.3, 123.3, 119.2, 76.9, 72.2, 45.1, 42.9, 42.1, 37.3, 34.3, 29.7, 25.7, 21.2, 17.8, 13.6, -4.6, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]$^+$ (C$_{35}$H$_{50}$N$_2$NaO$_5$Si) requires 629.3381, found 629.3381. $[^a]D_{20}^0 = -222.2$ (c = 0.60, CHCl$_3$).
Yield: 3.3 mg, 47%, colorless powder. FTIR (CHCl₃, cm⁻¹): 2953, 2856, 1707, 1641, 1324, 1253, 1164, 1123, 1067, 1014. ¹H NMR (600 MHz, CDCl₃): δ 7.56 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 15.5, 11.4 Hz, 1H), 7.06 (dd, J = 15.5, 11.1 Hz, 1H), 6.60 (d, J = 15.5 Hz, 1H), 6.48 (dd, J = 14.8, 11.3 Hz, 1H), 6.34 (d, J = 11.0 Hz, 1H), 6.18 (dd, J = 14.8, 11.3 Hz, 1H), 6.10 (dd, J = 14.8, 11.0 Hz, 1H), 5.99 (brd, 1H), 5.86-5.96 (m, 2H), 5.73 (d, J = 15.4 Hz, 1H), 5.70 (dd, J = 11.3, 2.8 Hz, 1H), 4.00-4.11 (m, 2H), 3.47-3.53 (m, 1H), 2.97 (d, J = 13.7 Hz, 1H), 2.40-2.61 (m, 5H), 2.18-2.27 (m, 1H), 1.94 (s, 3H), 1.13 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 173.9, 169.4, 166.1, 146.8, 143.3, 140.9, 139.0, 137.4, 131.7, 131.3, 129.1 (q, J = 32.4 Hz), 127.3, 126.5, 126.4, 125.6, 125.6 (q, J = 3.8 Hz), 119.1, 76.7, 72.1, 45.1, 42.8, 42.1, 37.3, 34.4, 31.0, 29.7, 25.7, 17.8, 13.8, -4.6, -4.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₃₅H₄₇F₃N₂NaO₅Si) requires 683.3099, found 683.3106. [α]D²⁰ = -164.0 (c = 0.68, CHCl₃).

Yield: 44.6 mg, 58%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3354, 2926, 2857, 1707, 1614, 1533, 1253, 1229, 1102, 1009, 835, 775. ¹H NMR (600 MHz, CDCl₃): δ 7.50 (d, J = 8.5 Hz, 2H), 7.31 (dd, J = 15.4, 11.2 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 6.47 (dd, J = 14.9, 10.8 Hz, 1H), 6.22 (dd, J = 11.4, 3.3 Hz, 1H), 6.19 (dd, J = 14.8, 11.2 Hz, 1H), 6.11 (dd, J = 14.8, 11.9 Hz, 1H), 5.96-5.91 (m, 2H), 5.74 (d, J = 15.3 Hz, 1H), 5.74 (brd, 1H), 4.08-4.04 (m, 2H), 3.56-3.51 (m, 1H), 2.98 (d, J = 13.9, 1H), 2.72 (dd, J = 13.9, 3.4 Hz, 1H), 2.56 (dd, J = 13.9, 11.6 Hz, 1H), 2.56-2.53 (m, 1H), 2.49-2.46 (m, 2H), 2.23-2.17 (m, 1H), 1.13 (d, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 173.7, 169.1, 166.2, 147.2, 143.6, 139.3, 138.8,
131.9, 131.4, 127.9, 127.4, 122.2, 119.0, 73.8, 72.1, 45.3, 45.1, 42.8, 37.4, 34.6, 25.8, 18.0, 11.6, -4.5, -4.8 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{29}$H$_{41}$N$_2$O$_5$SiBrNa) requires 627.1860, found 627.1862. $[\alpha]_D^{20} = -104$ (c = 0.23, CHCl$_3$).

**Yield:** 10.0 mg, 54%, colorless powder. **FTIR (CHCl$_3$, cm$^{-1}$):** 3348, 2929, 2855, 1708, 1633, 1615, 1533, 1465, 1382, 1252, 1228, 1101, 1011, 836. **$^1$H NMR (600 MHz, CDCl$_3$):** $\delta$ 7.23 (dd, $J$ = 15.5, 11.4 Hz, 1H), 6.46 (dd, $J$ = 14.9, 10.8 Hz, 1H), 6.38 (s, 1H), 6.16 (dd, $J$ = 14.8, 11.3 Hz, 1H), 6.09 (dd, $J$ = 15.0, 10.6 Hz, 1H), 5.87-6.01 (m, 2H), 5.70 (d, $J$ = 15.2 Hz, 1H), 5.67 (masked, 1H), 4.02-4.10 (m, 2H), 3.44-3.52 (m, 1H), 2.97 (dm, $J$ = 13.8 Hz, 1H), 2.53-2.57 (m, 2H), 2.44-2.49 (m, 1H), 2.36-2.42 (m, 2H), 2.15-2.22 (m, 1H), 1.86 (s, 3H), 1.12 (d, $J$ = 7.2 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. **$^{13}$C NMR (151 MHz, CDCl$_3$):** $\delta$ 173.9, 168.9, 165.9, 147.0, 143.5, 139.1, 139.1, 131.3, 127.3, 118.7, 106.2, 75.4, 72.0, 45.1, 42.7, 41.9, 37.3, 34.5, 31.0, 25.6, 17.8, 16.2, -4.7, -4.9 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{26}$H$_{41}$Br$_3$NaO$_5$Si) requires 591.1860, found 591.1854. $[\alpha]_D^{20} = -85.6$ (c = 0.20, CHCl$_3$).

**Yield:** 22.1 mg, 51%, colorless powder. **FTIR (CHCl$_3$, cm$^{-1}$):** 3320, 2927, 2855, 1705, 1615, 1532, 1253, 1229, 1102, 1016, 836, 776. **$^1$H NMR (600 MHz, CDCl$_3$):** $\delta$ 7.86-7.82 (m, 4H), 7.52-7.41 (m, 4H), 6.55-6.51 (m, 1H), 6.44 (dd, $J$ = 11.4, 2.8 Hz, 1H), 6.21 (dd, $J$ = 14.5, 11.5 Hz, 1H), 6.13 (dd, $J$ = 14.7, 10.8 Hz, 1H), 6.21-6.13 (brd, 1H), 6.06 (brd, 1H), 5.96-5.92 (m, 1H), 5.78 (d, $J$ = 15.3 Hz, 1H), 4.11-4.07 (m, 2H), 3.59-3.54 (m, 1H), 2.97 (d, $J$ = 13.8, 1H), 2.82 (d, $J$ = 13.3 Hz, 1H), 2.75-2.71 (m, 1H), 2.57-2.46 (m, 3H), 2.25-2.18 (m, 1H), 1.15 (d, $J$ = 7.3 Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H) ppm. **$^{13}$C NMR (151 MHz, CDCl$_3$):** $\delta$ 174.1, 169.6, 166.4,
147.2, 143.6, 139.1, 137.2, 133.3, 133.2, 131.5, 128.6, 128.2, 127.8, 127.6, 126.5, 126.3, 125.0, 124.1, 119.2, 74.6, 72.3, 45.3, 45.2, 43.0, 37.4, 34.5, 25.8, 18.0, -4.5, -4.8 ppm. **HRMS (ESI)** (m/z): calculated for [M+Na]$^+$ (C$_{33}$H$_{44}$N$_2$O$_5$SiNa) requires 599.2912, found 599.2914. \( \beta_d = -135 \) (c = 0.67, CHCl$_3$).
2.12. General procedure for TBS deprotection

\[
\text{Protected alcohol (1.0 equiv.) was dissolved in THF (1 mL) and cooled down to 0 °C. TBAF (1 M in THF, 1.2 equiv.) was then charged and the reaction was monitored by TLC (Heptane/EtOAc = 3:7). Generally, within 5 min the reaction is finished. The reaction was then quenched with a drop of saturated NH}_4\text{Cl, concentrated in vacuo and directly purified by chromatography (silica gel, CHCl}_3/\text{MeOH = 20:1).}
\]

**Fig. S15. OTBS deprotection mediated by TBAF**

Yield: 8.8 mg, 90%, colorless powder.

\[R_f = 0.46 \ (\text{CHCl}_3/\text{MeOH} = 10:1).\]

**FTIR (CHCl\textsubscript{3}, cm\textsuperscript{-1}):** 3316, 2923, 1704, 1536, 1254, 1063, 1006, 965.

**HRMS (ESI) (m/z):** calculated for [M+Na]	extsuperscript{+} (C\textsubscript{29}H\textsubscript{44}N\textsubscript{2}O\textsubscript{5}Na) requires 523.3142, found 523.3140.

Lit.\textsuperscript{19} [\alpha]_D\textsuperscript{20} = -220 (c = 0.2, DMSO), found [\alpha]_D\textsuperscript{20} = -178 (c = 0.21, DMSO).
Characterization and comparison of FR252921.

|   |   |   |   |   |   |
|---|---|---|---|---|---|
|   |   | \(^1\)H NMR [(CD3)\textsubscript{2}SO, (ppm)] (synthetic) | \(^1\)H NMR [(CD3)\textsubscript{2}SO, (ppm)] (literature)\(^9, 20\) | \(^13\)C NMR [(CD3)\textsubscript{2}SO, (ppm)] (synthetic) | \(^13\)C NMR [(CD3)\textsubscript{2}SO, (ppm)] (literature)\(^9, 20\) |
| 1 | C | - | - | 165.40 | 165.4 |
| 2 | CH | 5.65 (d, J = 15.3 Hz) | 5.65 (d, J = 16 Hz) | 118.23 | 118.2 |
| 3 | CH | 7.36 (dd, J = 15.3, 11.4, 0.7 Hz) | 7.35 (dd, J = 16, 12 Hz) | 147.37 | 147.4 |
| 4 | CH | 6.26 (dd, J = 14.8, 11.4 Hz) | 6.26 (dd, J = 15, 11 Hz) | 126.46 | 126.5 |
| 5 | CH | 6.56 (dd, J = 14.8, 10.8 Hz) | 6.56 (dd, J = 15, 11 Hz) | 143.82 | 143.8 |
| 6 | CH | 6.15 (dd, J = 15.1, 10.9 Hz) | 6.15 (dd, J = 15, 11 Hz) | 131.43 | 131.4 |
| 7 | CH | 5.85 (ddd, J = 15.1, 10.5, 4.8 Hz) | 5.85 (ddd, J = 15, 11, 5 Hz) | 139.09 | 139.1 |
| 8 | CH\textsubscript{2} | 2.33 (m, 1H) | 2.36-2.17 (4H, m) | 32.09 | 32.1 |
| 9 | CH\textsubscript{2} | 3.43 (m, 1H) | 3.45-3.42 (m) | 37.12 | 37.1 |
| 10 | NH | 7.61 (dd, J = 6.2, 6.2 Hz) | 7.63 (t, J = 6 Hz) | - | - |
| 11 | C | - | - | 173.75 | 173.7 |
| 12 | CH | 2.27 (m, 1H) | 2.36-2.17 (4H, m) | 44.44 | 44.4 |
| 13 | CH | 3.58 (ddd, J = 10.6, 6.4, 4.0, 2.3 Hz) | 3.61-3.56 (m) | 70.69 | 70.7 |
| 14 | CH\textsubscript{2} | 2.98 (ddd, J = 13.3, 5.3, 2.2 Hz) | 2.98-2.94 (m) | 42.42 | 42.4 |
| 15 | NH | 7.87 (dd, J = 5.3, 4.9 Hz) | 7.90 (t, J = 5 Hz) | - | - |
| 16 | C | - | - | 169.41 | 169.4 |
| 17 | CH\textsubscript{2} | 2.71 (dd, J = 13.9, 11.6 Hz) | 2.70 (dd, J = 14, 12 Hz) | 40.60 | 40.7 |
| 18 | CH | 5.29 (dd, J = 11.6, 2.7 Hz) | 5.29 (d, J = 10 Hz) | 76.21 | 76.2 |
| 19 | C | - | - | 133.02 | 133.0 |
| 20 | CH\textsubscript{3} | 1.72 (d, J = 1.4 Hz) | 1.72 (s) | 12.96 | 12.9 |
| 21 | CH | 6.01 (dq, J = 11.0, 1.4 Hz) | 6.01 (d, J = 11 Hz) | 125.42 | 125.4 |
| 22 | CH | 6.24 (dd, J = 15.0, 11.0, 1.4 Hz) | 6.24 (dd, J = 15, 11 Hz) | 125.77 | 125.8 |
| 23 | CH\textsubscript{2} | 2.08 (td, J = 7.1, 7.2 Hz) | 2.10-2.05 (m) | 32.35 | 32.3 |
| 24 | CH\textsubscript{2} | 1.35 (m) | 1.36-1.18 (10H, m) | 28.86 | 28.9 |
| 25 | CH\textsubscript{2} | 1.25 (m) | 1.36-1.18 (10H, m) | 28.61 | 28.59 |
| 26 | CH\textsubscript{2} | 1.25 (m) | 1.36-1.18 (10H, m) | 29.56 | 28.55 |
| 27 | CH\textsubscript{2} | 1.24 (m) | 1.36-1.18 (10H, m) | 31.25 | 31.3 |
| 28 | CH\textsubscript{2} | 1.26 (m) | 1.36-1.18 (10H, m) | 22.10 | 22.1 |
| 29 | CH\textsubscript{3} | 0.85 (t, J = 7.1 Hz) | 0.85 (t, J = 8 Hz) | 13.97 | 14.0 |

S70
Yield: 6.5 mg, 95%, colorless powder.

Rf = 0.39 (CHCl₃/MeOH = 10:1).

FTIR (CHCl₃, cm⁻¹): 3320, 2924, 2854, 1706, 1641, 1542, 1458, 1265, 1008, 967.

¹H NMR (600 MHz, CDCl₃): δ 7.27 (dd, J = 15.2, 11.4 Hz, 1H, H₃), 6.50 (dd, J = 14.9, 10.9 Hz, 1H, H₅), 6.27-6.12 (m, 4H, H₄, H₂₀, H₂₁, NH), 6.07 (dd, J = 14.9, 11.8 Hz, 1H, H₆), 6.00 (s, 1H, OH), 5.80-5.69 (m, 4H, H₂, H₂₂, NH, H₇), 5.67 (dd, J = 11.4, 3.2 Hz, 1H, H₁₈), 4.17-4.10 (m, 1H, H₂₃), 3.82-3.78 (m, 1H, H₁₄), 3.32 (td, J = 10.4, 2.5 Hz, 1H, H₁₃), 3.01 (d, J = 14.0, 1H, H₉), 2.65-2.48 (m, 2H, H₈, H₁₄), 2.56 (dd, J = 13.9, 3.1 Hz, 1H, H₁₇), 2.50 (dd, J = 13.8, 11.4 Hz, 1H, H₁₇), 2.24-2.20 (m, 1H, H₁₂), 1.79 (s, 3H, 19-Me), 1.37-1.36 (m, 2H, H₂₄), 1.25 (brd, 12H, H₂₅-H₃₀), 0.98 (d, J = 7.1 Hz, 3H, 12-Me), 0.87 (t, J = 7.1 Hz, 3H, H₃₁) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 176.0 (C₁₁), 169.4 (C₁₆), 165.4 (C₁), 144.6 (C₃), 140.8 (C₅), 136.7 (C₇), 136.0 (C₂₂), 133.0 (C₆), 131.9 (C₁₉), 128.7 (C₄), 126.7 (C₂₀), 125.6 (C₂₁), 121.3 (C₂), 76.1 (C₁₈), 71.6 (C₁₃), 44.0 (C₁₄), 43.0 (C₁₂), 41.9 (C₁₇), 36.9 (C₉), 34.6 (C₈), 33.2 (C₂₃), 32.0, 29.71, 29.66, 29.5, 29.4, 22.8, 14.3 (C₃₁), 13.3 (C₁₉-Me), 11.0 (C₁₂-Me) ppm.

HRMS (ESI) (m/z): calculated for [M+Na]+ (C₃₁H₄₈N₂O₅Na) requires 551.3455, found 551.3460.

Lit.¹⁹ [α]D²⁰ = -235 (C = 0.2, DMSO), found [α]D²⁰ = -201 (C = 0.08, DMSO).
Yield: 4.7 mg, 90%, colorless powder.

Rf = 0.40 (CHCl$_3$/MeOH = 10:1).

**FTIR (CHCl$_3$, cm$^{-1}$):** 3310, 2924, 1704, 1642, 1538, 1256, 1008, 987.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.27 (dd, $J = 15.5$, 11.2 Hz, 1H, H3), 6.51 (dd, $J = 14.8$, 10.9 Hz, 1H, H5), 6.31-6.16 (m, 5H, including H4, H21, H20), 6.12-6.05 (m, 2H, including H6), 6.00 (s, 1H), 5.81-5.68 (m 5H, including H2, H7, NH$_{10}$, H18), 4.17-4.10 (m, 1H, H9), 3.82-3.78 (m, 1H, H14), 3.32 (td, $J = 10.3$, 2.6 Hz, 1H, H13), 3.02-3.00 (m, 1H, H9), 2.65-2.48 (m, 4H, H13, H17, H8), 2.29-2.16 (m, 2H, H12, H8), 2.10-2.07 (m, 2H, H25), 1.81 (s, 3H, H19-Me), 1.40-1.36 (m, 2H, H26), 1.28-1.25 (m, 8H, H27-H30), 0.98 (d, $J = 7.1$ Hz, 3H, H12-Me), 0.87 (t, $J = 6.9$ Hz, 3H, H31) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 176.0 (C11), 169.4 (C16), 165.4 (C1), 144.8 (C3), 140.9 (C5), 136.2, 136.1, 134.4, 133.8 (C19), 133.0 (C6), 130.6, 128.7 (C4), 126.7 (C20), 125.8 (C21), 121.2 (C2), 76.1 (C18), 71.6 (C13), 44.1 (C14), 43.0 (C12), 42.0 (C17), 36.9 (C9), 34.6 (C8), 33.0 (C25), 32.0, 29.4, 29.31, 29.30, 22.8, 14.3 (C31), 13.5 (C19-Me), 11.0 (C12-Me) ppm.

**HRMS (ESI) (m/z):** calculated for [M+Na]$^+$ (C$_{31}$H$_{46}$N$_2$O$_5$Na) requires 549.3299, found 549.3300.

Lit.$^{19}$ [a]$_{D}^{20}$ = -72 (C = 0.2, DMSO), found [a]$_{D}^{20}$ = -106 (c = 0.19, DMSO).
Yield: 2.9 mg, 90%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3317, 2922, 1703, 1642, 1536, 1242, 1221, 1008, 775. ¹H NMR (600 MHz, CDCl₃): δ 7.22 (dd, J = 15.3, 11.3 Hz, 1H), 6.48 (dd, J = 14.9, 10.8 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 6.18 (dd, J = 14.8, 11.3 Hz, 1H), 6.06 (dd, J = 15.0, 10.9 Hz, 1H), 5.90 (brd, 1H), 5.79-5.76 (m, 1H), 5.76 (d, J = 15.4 Hz, 1H), 5.68 (d, J = 7.6 Hz, 1H), 5.39-5.34 (m, 1H), 4.11-4.04 (m, 1H), 3.78-3.74 (m, 1H), 3.34-3.30 (m, 1H), 3.04 (d, J = 13.7 Hz, 1H), 2.63-2.53 (m, 3H), 2.35 (dd, J = 13.9, 11.1 Hz, 1H), 2.27-2.20 (m, 2H), 1.72-1.68 (m, 1H), 1.62-1.58 (m, 1H), 1.37-1.32 (m, 2H), 0.97 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 176.0, 169.8, 166.1, 144.4, 140.6, 135.8, 133.0, 128.8, 121.4, 72.5, 71.6, 43.9, 43.0, 42.8, 36.9, 34.9, 34.6, 32.0, 29.80, 29.77, 29.71, 29.65, 29.50, 25.4, 22.8, 14.3, 11.2 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₈H₄₆N₂O₅Na) requires 513.3299, found 513.3297. [α]D²⁰ = -49 (c = 0.11, CHCl₃).

Yield: 1.5 mg, 95%, mixture E:Z = 1.2:1 colorless powder. ¹H NMR (700 MHz, CDCl₃): Major isomer (E, E, E): δ 7.22 (dd, J = 15.4, 11.8 Hz, 1H), 6.48 (dd, J = 14.8, 10.6 Hz, 1H), 6.03-6.36 (m, 3H), 5.75 (d, J = 15.4 Hz, 1H), 5.63-5.84 (m, 2H), 5.40-5.36 (m, 1H), 4.10-4.05 (m, 1H), 3.82-3.76 (m, 1H), 3.45-3.50 (m, 1H), 3.30-3.36 (m, 1H), 2.82-2.90 (m, 1H), 2.46-2.62 (m, 2H), 2.32-2.41 (m, 1H), 2.17-2.24 (m, 1H), 1.38 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H) ppm. Minor isomer (E, E, Z): δ 7.20 (dd, J = 15.4, 11.8 Hz, 1H), 6.69 (dd, J = 14.8, 11.7 Hz, 1H), 5.82 (d, J = 15.4 Hz, 1H), 5.31-5.24 (m, 1H), 3.04-3.07 (m, 1H), 1.41 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H) ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₁₈H₂₆N₂NaO₅) requires 373.1734, found 373.1728.
Yield: 3.7 mg, 90%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3290, 2924, 1705, 1638, 1436, 1230, 1020, 1005, 963, 775. ¹H NMR (600 MHz, CDCl₃): δ 7.29 (dd, J = 15.2, 11.4 Hz, 1H), 6.59 (d, J = 9.4 Hz, 1H), 6.56 (dd, J = 14.8, 10.9 Hz, 1H), 6.24-6.19 (m, 2H), 6.14-6.07 (m, 3H), 5.89-5.84 (m, 1H), 5.78-5.72 (m, 2H), 5.70-5.66 (m, 2H), 4.13-4.06 (m, 1H), 3.66-3.62 (m, 1H), 3.36-3.32 (m, 1H), 2.98 (dd, J = 12.2, 4.2 Hz, 1H), 2.66 (t, J = 11.8 Hz, 1H), 2.58-2.50 (m, 3H), 2.38-2.31 (m, 1H), 2.20-2.16 (m, 1H), 2.12-2.08 (m, 3H), 1.80 (s, 3H), 1.39-1.36 (m, 2H), 1.30-1.25 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 173.9, 169.3, 166.2, 145.2, 141.9, 137.5, 137.0, 133.2, 131.5, 128.0, 126.9, 125.5, 120.5, 76.2, 68.1, 45.3, 41.6, 38.7, 36.9, 34.5, 33.2, 32.0, 29.5, 29.3, 22.8, 14.3, 13.3 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₈H₄₂N₂O₅Na) requires 509.2986, found 509.2985. [α]D²⁰ = -195 (c = 0.13, CHCl₃).

Yield: 1.9 mg, 88% colorless powder. FTIR (CHCl₃, cm⁻¹): 3314, 2926, 1704, 1641, 1545, 1300, 12352, 1229, 1116, 1102, 1068, 1007. ¹H NMR (700 MHz, CDCl₃): δ 7.30 (dd, J = 15.3, 11.2 Hz, 1H), 6.96-7.02 (m, 1H), 6.53 (dd, J = 14.9, 10.8 Hz, 1H), 6.29 (d, J = 8.8 Hz, 1H), 6.18-6.22 (m, 2H), 6.08 (dd, J = 15.0, 11.0 Hz, 1H), 5.99 (s, 1H), 5.80 (ddd, J = 15.5, 11.6, 3.8 Hz, 1H), 5.77 (d, J = 15.4 Hz, 1H), 5.67-5.70 (m, 3H), 4.10-4.20 (m, 1H), 3.83 (t, J = 10.9 Hz, 1H), 3.32 (td, J = 10.4, 2.7 Hz, 1H), 3.02 (dm, J = 14.3 Hz, 1H), 2.59-2.65 (m, 3H), 2.45 (dd, J = 13.8, 11.7 Hz, 1H), 2.20-2.28 (m, 2H), 1.91 (s, 3H), 0.99 (d, J = 7.2 Hz, 3H) ppm. ¹³C NMR (176 MHz, CDCl₃): δ 175.8, 168.6, 165.1, 145.0, 141.2, 136.3, 132.7, 128.3, 122.1, 120.5, 75.1,
71.5, 44.0, 42.9, 41.6, 36.8, 34.5, 13.9, 10.9 ppm. **HRMS (ESI) (m/z):** calculated for [M+Na]$^+$

$(C_{23}H_{29}F_3N_2NaO_5)$ requires 493.1921, found 493.1910. $\left[a\right]_{D}^{20} = -119$ (c = 0.05, CHCl$_3$).
Yield: 3.1 mg, 95%, colorless powder. FTIR (CHCl₃, cm⁻¹):
2970, 1704, 1639, 1544, 1379, 1234, 1067, 1006, 913. ¹H NMR (700 MHz, CDCl₃): δ 7.41 (d, J = 7.5 Hz, 2H), 7.28-7.32 (m, 3H), 7.22 (t, J = 7.3 Hz, 1H), 6.97 (dd, J = 15.5, 11.0 Hz, 1H), 6.58 (d, J = 15.5 Hz, 1H), 6.53 (dd, J = 14.9, 10.8 Hz, 1H), 6.34 (d, J = 10.8 Hz, 1H), 6.29 (d, J = 8.6 Hz, 1H), 6.20 (dd, J = 14.9, 11.3 Hz, 1H), 6.08 (dd, J = 14.8, 11.2 Hz, 1H), 5.97 (s, 1H), 5.80 (masked, 1H), 5.78 (d, J = 15.4 Hz, 1H), 5.74 (dd, J = 11.5, 2.7 Hz, 1H), 5.70 (d, J = 8.0 Hz, 1H), 4.12-4.18 (m, 1H), 3.83 (t, J = 10.0 Hz, 1H), 3.34 (td, J = 10.5, 2.7 Hz, 1H), 3.02 (dm, J = 13.7 Hz, 1H), 2.58-2.66 (m, 3H), 2.53 (dd, J = 13.8, 11.6 Hz, 1H), 2.20-2.28 (m, 2H), 1.92 (s, 3H), 0.99 (d, J = 7.2 Hz, 3H) ppm. ¹³C NMR (176 MHz, CDCl₃): δ 175.8, 169.1, 165.2, 144.6, 140.8, 137.5, 136.0, 135.3, 133.4, 132.8, 128.6, 128.5, 127.5, 126.4, 126.4, 124.2, 121.0, 75.9, 71.5, 44.0, 42.9, 41.8, 36.8, 34.5, 13.6, 10.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₈H₃₄N₂NaO₅) requires 501.2360, found 501.2353. [α]D²₀ = -289 (c = 0.08, CHCl₃).

Yield: 4.8 mg, 90%, colorless powder. FTIR (CHCl₃, cm⁻¹):
2926, 1703, 1641, 1615, 1542, 1234, 1006, 913. ¹H NMR (700 MHz, CDCl₃): δ 7.28-7.32 (m, 3H), 7.22 (d, J = 7.9 Hz, 2H), 6.92 (dd, J = 15.5, 11.0 Hz, 1H), 6.55 (d, J = 15.8 Hz, 1H), 6.52 (dd, J = 14.8, 10.6 Hz, 1H), 6.33 (d, J = 11.0 Hz, 1H), 6.28 (d, J = 8.7 Hz, 1H), 6.20 (dd, J = 14.9, 11.3 Hz, 1H), 6.08 (dd, J = 14.8, 11.2 Hz, 1H), 5.97 (s, 1H), 5.80 (masked, 1H), 5.78 (d, J = 15.4 Hz, 1H), 5.73 (dd, J = 11.4, 2.5 Hz, 1H), 5.69 (d, J = 8.1 Hz, 1H), 4.12-4.18 (m, 1H), 3.82 (t, J = 10.2 Hz, 1H), 3.34 (td, J = 10.4, 2.5 Hz, 1H), 3.02 (dm, J = 13.5 Hz, 1H), 2.58-2.66 (m, 3H), 2.53 (dd, J = 13.7, 11.7 Hz, 1H), 2.33 (s, 3H), 2.19-2.28 (m, 2H), 1.91 (s, 3H), 0.98 (d, J = 7.2 Hz, 3H) ppm.
\(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \(\delta\) 175.8, 169.2, 165.2, 144.5, 140.7, 135.9, 134.7, 134.6, 133.4, 132.8, 129.3, 128.5, 126.6, 126.3, 123.3, 121.0, 75.9, 71.5, 43.9, 42.9, 41.8, 36.8, 34.5, 21.2, 13.6, 10.9 ppm. \(\text{HRMS (ESI) (m/z):}\) calculated for [M+Na]\(^+\) \((C_{29}H_{36}N_2NaO_5)\) requires 515.2516, found 515.2513. \([\alpha]_{D}^{20}= -201\) (c = 0.08, CHCl\(_3\)).

Yield: 3.5 mg, 90%, colorless powder. \(\text{FTIR (CHCl}_3, \text{cm}^{-1})\): 1706, 1643, 1543, 1327, 1234, 1069, 1006, 913. \(^1\)H NMR (700 MHz, CDCl\(_3\)): \(\delta\) 7.55 (d, \(J\) = 8.2 Hz, 2H), 7.31 (dd, \(J\) = 15.2, 11.3 Hz, 1H), 7.05 (dd, \(J\) = 15.5, 11.0 Hz, 1H), 6.59 (d, \(J\) = 15.4 Hz, 1H), 6.53 (dd, \(J\) = 14.9, 10.9Hz, 1H), 6.35 (d, \(J\) = 11.4 Hz, 1H), 6.30 (d, \(J\) = 8.5 Hz, 1H), 6.21 (dd, \(J\) = 14.9, 11.2 Hz, 1H), 6.08 (dd, \(J\) = 14.7, 11.2 Hz, 1H), 5.99 (s, 1H), 5.80 (masked, 1H), 5.78 (d, \(J\) = 15.4 Hz, 1H), 5.73 (dd, \(J\) = 11.6, 2.6 Hz, 1H), 5.69 (d, \(J\) = 7.8 Hz, 1H), 4.11-4.19 (m, 1H), 3.84 (t, \(J\) = 10.1 Hz, 1H), 3.34 (td, \(J\) = 10.4, 2.7 Hz, 1H), 3.02 (dm, \(J\) = 14.2 Hz, 1H), 2.57-2.66 (m, 3H), 2.52 (dd, \(J\) = 13.8, 11.6 Hz, 1H), 2.12-2.28 (m, 2H), 1.94 (s, 3H), 0.99 (d, \(J\) = 7.2 Hz, 3H) ppm. \(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \(\delta\) 136.1, 132.8, 131.7, 126.6, 126.4, 126.4, 125.6, 44.0, 41.8, 36.7, 34.5, 13.7, 10.9 ppm. \(\text{HRMS (ESI) (m/z):}\) calculated for [M+Na]\(^+\) \((C_{29}H_{33}BrN_2NaO_5)\) requires 569.2234, found 569.2225. \([\alpha]_{D}^{20}= -192\) (c = 0.03, CHCl\(_3\)).

Yield: 14.6 mg, 95%, colorless powder. Insoluble in most of solvents, such as CHCl\(_3\), DMF, MeOH, H\(_2\)O, DMSO, THF. \(\text{HRMS (ESI) (m/z):}\) calculated for [M+Na]\(^+\) \((C_{23}H_{27}BrN_2NaO_5)\) requires 513.0996, found 513.0990.
Yield: 5.9 mg, 95%, colorless powder. FTIR (CHCl₃, cm⁻¹): 3304, 2925, 1698, 1641, 1538, 1234, 1063, 1004. ¹H NMR (700 MHz, CDCl₃): δ 7.26 (masked, 1H), 6.51 (dd, J = 14.9, 10.8 Hz, 1H), 6.40 (s, 1H), 6.28 (d, J = 8.8 Hz, 1H), 6.19 (dd, J = 14.9, 11.3 Hz, 1H), 6.09 (dd, J = 14.8, 11.1 Hz, 1H), 5.99 (s, 1H), 5.80 (ddd, J = 15.1, 11.1, 3.7 Hz, 1H), 5.75 (d, J = 15.3 Hz, 1H), 5.73 (masked, 1H), 5.68 (d, J = 8.3 Hz, 1H), 4.12-4.18 (m, 1H), 3.82 (t, J = 10.2 Hz, 1H), 3.31 (td, J = 10.2, 2.7 Hz, 1H), 3.01 (dm, J = 14.2 Hz, 1H), 2.53-2.63 (m, 3H), 2.51 (dd, J = 13.9, 11.5 Hz, 1H), 2.20-2.27 (m, 2H), 1.86 (s, 3H), 0.98 (d, J = 7.2 Hz, 3H) ppm. ¹³C NMR (176 MHz, CDCl₃): δ 175.8, 168.4, 165.0, 144.9, 141.1, 139.0, 136.3, 132.8, 128.4, 120.5, 106.5, 74.3, 71.4, 43.9, 42.8, 41.5, 36.7, 34.5, 16.0, 10.9 ppm. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₀H₂₇BrN₂NaO₅) requires 477.0996, found 477.0989. [α]D²⁰ = -108 (c = 0.04, CHCl₃).

Yield: 8.2 mg, 90%, colorless powder. Insoluble in most of solvents, such as CHCl₃, DMF, MeOH, H₂O, DMSO, THF. HRMS (ESI) (m/z): calculated for [M+Na]⁺ (C₂₇H₃₀N₂NaO₅) requires 485.2047, found 485.2045.
3. Computational studies

3.1. Results and discussions

It is possible to infer from the studies of Falk et al.9 and Cossy et al.21 that indulging in the synthesis of complex natural products such as the FR will result problematic. These two aforementioned groups attempt to deliver the final product by the mean of the Shiina marolactonization, which invokes the use of activated carboxylic acids and rely on the presence of Michael competitive nucleophiles. Taking into account the nature of the FR natural product and the presence of the conjugated triene it is possible to think that the nucleophile would engage it in a Michael–retro–Michael reaction, eventually delivering products with scrambled double bonds. Falk et al. and Cossy et al. observe, indeed, as major side product the isomer with (ZEE) double bond geometry.

We have undertaken computational studies, demonstrating that the (EEZ) isomer of FR252921 is considerably more stable than the natural (EEE) isomer presumably as a result of two intramolecular hydrogen bonding interactions involving the N–15 CONH moiety and the C–11 CO FR252921 thus appears to be a kinetic product compared to its (EEZ)-isomer, meaning that the stereoselective construction of the (EEE)-triene embedded in this compound stands as a considerable challenge.

The methodology we exploited in attempting the synthesis of the FR derivatives allow us to get rid of the aforementioned flaws and gives us a route to exclusively access the desired isomer.
Fig. S16. Relative energies and computed structures of the FR252921 isomers.

Besides, going from the most to the least stable, the macrocycle changes in a way that it starts resembling a circular ribbon being a funnel in the case of EEZ to be almost flat for ZEE. Both strain, dipole moment and solvent can therefore influence the relative stability.

Fig. S17. Structure flattening from EEZ isomer to ZEE.
3.2. Computational details

The conformational space of all flexible molecules has been initially explored using OPLS_2005 force field and the systematic search routine implemented in MACROMODEL 11.5. The structures found at force field level have then been re-optimized at the B3LYP-D3/6-31G(d,p) level of theory. The nature of all stationary points was verified through computation of the vibrational frequencies. Thermochemical corrections to 298.15 K have been calculated from unscaled vibrational frequencies obtained at the same level. The thermochemical corrections have been combined with single point energies calculated at the MP2(FC)/def2-TZVP level of theory to yield Gibbs free energies \( G_{298} \) at 298.15 K. The density-based solvation model SMD (THF) was applied to consider solvent effects. Calculations have been performed with the Gaussian09 program package and with the Gaussian16 program package using Gaussian09 restraints.

\( FR-252921 \ EEZ \)

\[ \text{\ldots} \]

\[ \text{\ldots} \]
4. NMR spectra
$\text{C}_8\text{H}_{15}$

$\text{6}$

$^1\text{H NMR (500 MHz, CDCl}_3)$

$\text{CHCl}_3$

$^13\text{C NMR (128 MHz, CDCl}_3)$

$\text{CHCl}_3$
$^{1}H$ NMR (500 MHz, CDCl$_3$)

$^{13}C$ NMR (126 MHz, CDCl$_3$)
$^1H$ NMR (600 MHz, CDCl$_3$)

$^{13}C$ NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^1$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{1}H$ NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
\[ ^1H\text{NMR} (600 \text{ MHz, } \text{CDCl}_3) \]

\[ ^{13}\text{C}\text{NMR} (151 \text{ MHz, } \text{CDCl}_3) \]
**1H NMR (600 MHz, CDCl₃)**

**13C NMR (151 MHz, CDCl₃)**
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
\[ ^1\text{H NMR (600 MHz, CDCl}_3 \]\]

\[ ^13\text{C NMR (151 MHz, CDCl}_3 \]\]
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

$^{13}$C NMR (151 MHz, CDCl$_3$)

CHCl$_3$
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1H$ NMR (600 MHz, CDCl$_3$)

$^{13}C$ NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
cis-31c

$^1$H NMR (600 MHz, CDCl$_3$)

$^13$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CDCl$_3$)

CHCl$_3$

$^{13}$C NMR (176 MHz, CDCl$_3$)

CHCl$_3$
cis-31n

^1H NMR (600 MHz, CDCl₃)

CHCl₃

^13C NMR (151 MHz, CDCl₃)

CHCl₃
$^1$H NMR (600 MHz, CDCl₃)

$^{13}$C NMR (151 MHz, CDCl₃)
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{1}$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CDCl$_3$)

$^{13}$C NMR (176 MHz, CDCl$_3$)
**1H NMR (600 MHz, CDCl$_3$)**

**13C NMR (151 MHz, CDCl$_3$)**

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Traces of PhPO

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S145
$^1$H NMR (600 M Hz, CDCl$_3$) after 1$^{st}$ purification

5:1 - mixture of $E,E,E;E,E,Z$

$^1$H NMR (600 M Hz, CDCl$_3$) after 2$^{nd}$ purification

1.3:1 - mixture of $E,E,E;E,E,Z$

32e
$^1$H NMR (600 MHz, CDCl$_3$)

$^1$C NMR (151 MHz, CDCl$_3$)
$^{1}H$ NMR (600 M Hz, CDCl$_3$)

$^{13}$C NMR (151 M Hz, CDCl$_3$)
CHCl₃ ¹H NMR (600 MHz, CDCl₃)

CHCl₃ ¹³C NMR (151 MHz, CDCl₃)
$\text{CHCl}_3$

$^1\text{H NMR} (600 \text{ M Hz, CDCl}_3$)

$13\text{C NMR} (151 \text{ M Hz, CDCl}_3$)
32-6

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CD$_3$S(O)CD$_3$)

$^{13}$C NMR (176 MHz, CD$_3$S(O)CD$_3$)
CHCl₃  

$^1$H NMR (600 MHz, CDCl₃)

$^{13}$C NMR (151 MHz, CDCl₃)

S160
1H NMR (700 MHz, CDCl₃)

1,2:1 mixture of E/Z FR2

CHCl₃
**S162**

**1H NMR (600 MHz, CDCl₃)**

**13C NMR (151 MHz, CDCl₃)**
$^1$H NMR (700 M Hz, CDCl$_3$)

$^{13}$C NMR (176 M Hz, CDCl$_3$)

S165
$^1$H NMR (700 M Hz, CDCl$_3$)

$^{13}$C NMR (176 M Hz, CDCl$_3$)
5. Biological study - Methods

5.1. Cell Culture

EL4 cells (ATCC® TIB-39™) were cultured in Dulbecco's Modified Eagle Medium (DMEM, Thermo Fischer Scientific, D5030-10L) supplemented with 10% heat inactivated fetal bovine serum (FBS, Thermo Fisher Scientific, 10500).

5.2. Cell Viability Assay

Compounds from 16 mM stocks in DMSO were dispensed with a Labcyte Echo 550 to 96 well plates (Corning, CLS3904-100EA). For each compound multiple volumes were plated, resulting in six final assay concentrations ranging from 20 µM to 6.4 nM in 5-fold dilutions. Volumes of the solvent DMSO in each well were adjusted to 0.25 µL. Eight wells per plate were filled with DMSO only as negative controls. 2000 EL4 cells in 100 µL medium were seeded per well. After 72 hours incubation, cell viability was measured using the CellTiter-Glo Luminescent Cell Viability Assay (Promega, G7572). After equilibration of the plates and the reagent to room temperature, the CellTiter-Glo reagent was added to the wells using a Multidrop™ Combi Reagent Dispenser (Thermo Fisher Scientific) and cells lysed by shaking. The luminescence signal was read after 20 min incubation at room temperature using an EnVision™ Multilabel Plate Reader (PerkinElmer). Signals were normalized to negative control wells on each plate. Dose-response curves and IC50 values were calculated with Graph Pad PRISM 7.
Fig. S18. Curve dose response on T-lymphocyte cell line EL4 proliferation.
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