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# Concise Synthesis of the Macrocyclic Core of Rhizopodin by a Heck Macrocyclization Strategy

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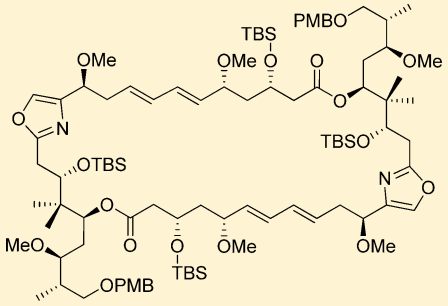
Supporting Information

**ABSTRACT:** A highly convergent synthesis of the central dimeric core of the potent antibiotic macrolide rhizopodin is reported. Notable features of the highly concise route include an effective preparation of the key C8-C22 building block based on an iridium-catalyzed Krische allylation and a chemoselective cross-coupling approach toward the macrocycle involving a highly advantageous Heck reaction for macrocyclization.




## INTRODUCTION

In 1993, the groups of Höfle and Reichenbach reported the isolation and first structural determination of rhizopodin (**1**, Scheme 1) from myxobacteria of *Myxococcus stipitatus*.[1] This macrolide displays impressive biological properties, including antifungal and antiproliferative activities at a low nanomolar concentration, which have been attributed to its ability to specifically bind to globular actin (G-actin) and thus hamper the polymerization to filamentous actin (F-actin).[1b] Its structure was originally proposed to be a 19-membered lactone, which, however, was revised in 2008 to a $C_2$-symmetric dimer during studies aiming at determining its absolute configuration.[2] On the basis of extensive NMR analyses, in combination with derivatization and molecular modeling experiments, a complete stereochemical assignment was made in our group.[3] Independently, the full stereochemistry was assigned by the group of Schubert through an X-ray structure of rabbit-actin bound rhizopodin[4] and further confirmed in the course of an analysis of the biosynthesis of rhizopodin.[5]

The unique structure of rhizopodin comprises 18 stereocenters and consists of a 38-membered macrocyclic core with two side chains terminating in labile *N*-vinyl formamide motifs, which are believed to be critical parts of the pharmacophore. The macrocycle itself embeds two oxazole rings and two diene systems together with an unprecedented stereotetrade between C16 and C21. The combination of its remarkable structure and potent bioactivity together with its low natural abundance makes rhizopodin an attractive target for the synthetic community, and several fragment syntheses have been reported, including a synthesis of the originally assigned monomeric structure.[6−9] So far, only one total synthesis has been accomplished by our group.[10] Along these lines, the only synthesis of a central dimeric core has been developed, which requires, however, a minimum of at least 24 steps.[10] However, to unveil the full biological potential of rhizopodin, a much shorter access to the macrocyclic core was required. Herein, we report a highly concise synthesis of the macrocyclic core **2**, which proceeds in only 17 steps and an overall yield of 11%. As key disconnections, it involves a chemoselective sequential cross-coupling strategy based on a Suzuki and a highly advantageous Heck reaction.

## RESULT AND DISCUSSION

Retrosynthetically, we dissected **2** into building blocks **3** and **4a**/**4b**. In contrast to our previous approach, a Heck coupling of a highly elaborated substrate was envisaged as a key step to close the macrocycle, while connection of the cyclization precursor was planned to arise from a Suzuki coupling and site-selective esterifications (Scheme 1). Importantly, only few examples of Heck reactions in the total synthesis of complex polyketides are known.[11] One of the most elaborate example of a Heck macrocyclization has been reported by our group in the context of the total synthesis of etnangien.[12]

Our efforts to develop a more concise synthesis of the macrocyclic core were first focused on designing a shorter route toward building block **4**. As illustrated in Scheme 2, our initial attempts were based on a Mukaiyama-type aldol coupling of enolate **11** with aldehyde **9**, which would enable a highly convergent access to **4**. Construction of the oxazole core was based on a coupling of acid **5**[13] with L-serin methyl ester using IBC[14] and subsequent cyclodehydration in a two-step protocol using DAST/DBU/$BrCCl_3$.[15] The resulting ester **6** was then reduced to the corresponding aldehyde and treated with

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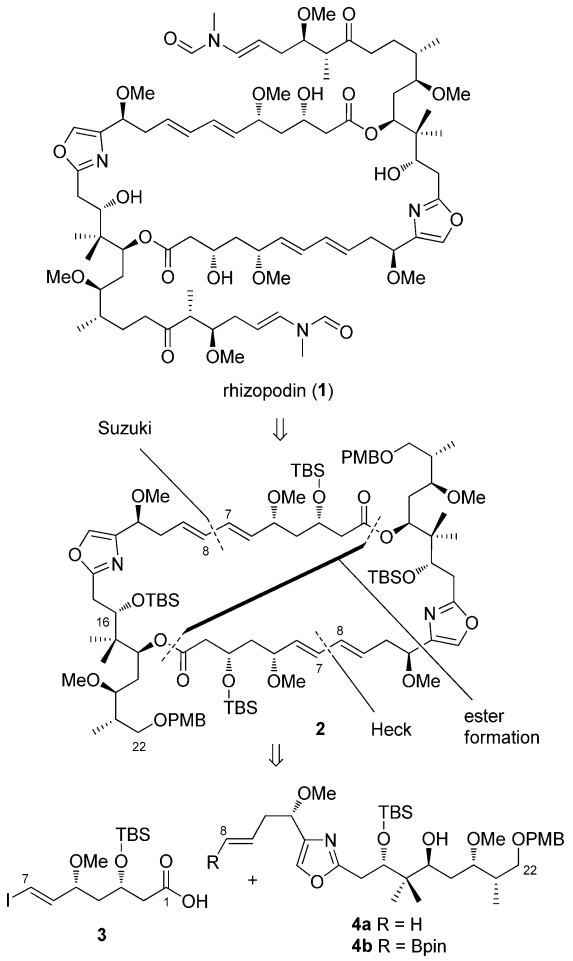
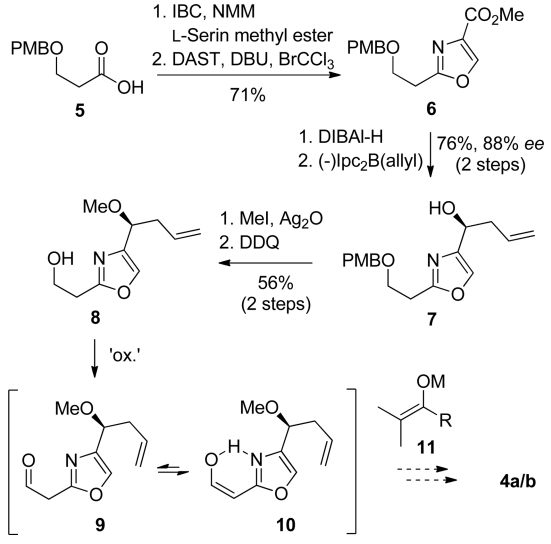
**Scheme 1**



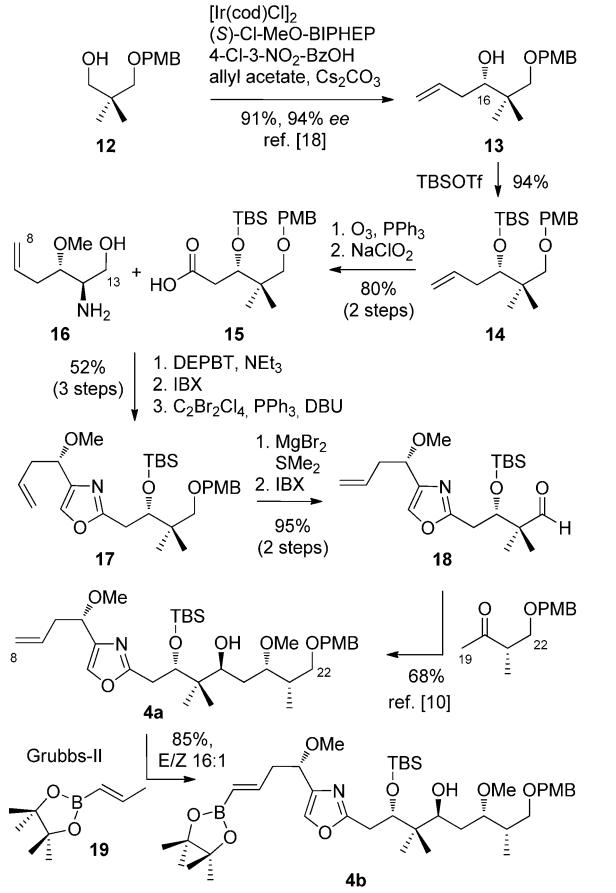

**Scheme 2**




(-)$Ipc_2B$(allyl)[16] to afford **7** in good yield and optical purity. Methylation and PMB-deprotection delivered the primary alcohol **8**. However, oxidation and further derivatization of **8** proved extremely challenging, due to the high tendency of aldehyde **9** to tautomerize to enol **10**,[17] which proved unreactive toward enolates, even toward simple organometalated nucleophiles, such as MeLi and MeMgBr, and decomposed within hours (Scheme 2).

Recognizing that **8** was not a useful building block to synthesize the challenging stereocenters at C16 and C18 adjacent to the neopentylic center, we realized that Krische's allylation strategy would be a valuable alternative to gain an effective access to **13**.[18] As depicted in Scheme 3, iridium-

**Scheme 3**




catalyzed allylation of alcohol **12** gave an easy and scalable entry to homoallylic alcohol **13**, bearing the C16 stereocenter, in excellent yield and optical purity as determined by Mosher-ester analysis.[18] TBS protection of the secondary alcohol, ozonolysis, and subsequent Pinnick oxidation of the terminal double bond furnished acid **15** in good yield. Amide coupling with known amine **16**[9] proceeded best with 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) as coupling reagent,[19] which proved superior to dicyclohexylcarbodiimide (DCC), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), and the corresponding acid chlorides generated by refluxing **15** in oxalyl or thionyl chloride. The respective *β*-hydroxyamide was then oxidized and subsequently transformed into oxazole **17** applying Wipf's conditions[20] in good yield and without further protecting group manipulations.

Orthogonal deprotection of the present PMB-ether and subsequent oxidation of the primary alcohol afforded aldehyde **18** in excellent yield, which could be elaborated to **4a** as described earlier.[10] This sequence delivered building block **4a** in only 13 linear steps and 20% overall yield within a scalable and reproducible route. Notably, this presents the shortest, as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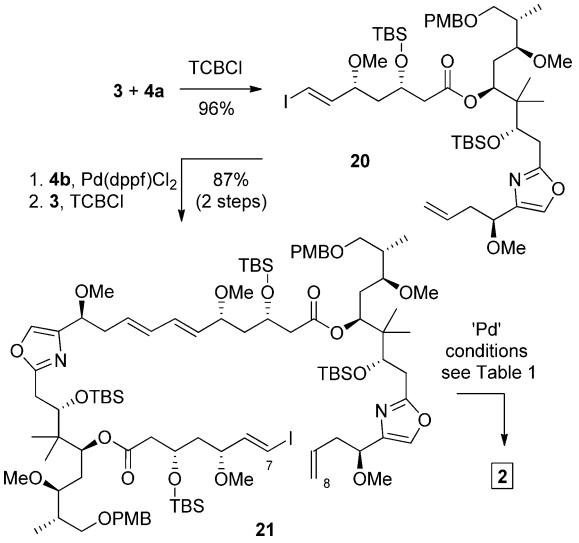
well as most effective, route to this fragment reported so far.[6−10] Subsequent cross-metathesis using the Grubbs-II catalyst in the presence of boronate **19**[21] gave access to vinylboronate **4b** in good yield with an *E*/*Z*-selectivity of 16:1, as judged by $^1$H NMR.

The completion of the synthesis of the macrocyclic core fragment **2** is outlined in Scheme 4. Acid **3**[10] was first esterified

**Scheme 4**




with the sterically hindered secondary alcohol of fragment **4a** in excellent yield by applying Yamaguchi's reagent (2,4,6-trichlorobenzoylchloride, TCBCl).[22] With building block **20** in hand, bearing both a terminal olefin and a vinyl-iodine moiety, the stage was set for a chemoselective cross-coupling strategy. First, an intermolecular Suzuki coupling[23] with boronate **4b** (Scheme 3) proceeded smoothly at the vinyl-iodine terminus and afforded only the *E*-isomer, as judged from $^1$H NMR. Second, another Yamaguchi esterification with acid **3** gave rise to the macrocyclization precursor **21**, again in very good yield.

While these transformations required essentially no optimization, the key Heck coupling of our strategy proved more challenging (see Table 1). While more conventional conditions resulted in extensive decomposition of the starting material (entries 1 and 2),[24,25] traces of the desired macrocycle **2** could initially only be detected when a protocol described by Fu[26] was used (entry 3). Gratifyingly, we finally found that careful optimization of the conditions described by Jeffery[27] in terms of temperature and reaction time[28] allowed the formation

**Table 1. Optimization of the Heck Macrocyclization Conditions of 21 to Macrocyclic Core 2 of Rhizopodin**

| entry | "PdL$_n$" | additives | conditions | yield [%] |
|---|---|---|---|---|
| 1 | $PdCl_2(CH_3CN)_2$ | $NEt_3$, $HCO_2H$ | $CH_3CN$, rt, 2 h | decomp. |
| 2 | $Pd(PPh_3)_2Cl_2$ | $K_2CO_3$, $NBu_4Cl$ | DMF, 70 °C, 1 h | decomp. |
| 3 | $Pd_2(dba)_3{\cdot}CHCl_3$/$^t$Bu$_3$P | $c$Hex$_2$NMe | dioxane, rt, 24 h | traces |
| 4 | $Pd(OAc)_2$ | $K_2CO_3$, $NBu_4Cl$ | DMF, 60 °C, 50 min | 77%[a] |

[a] *E*/*Z* = 5:1 mixture; 65% pure *E*-isomer was obtained after separation.

of **2** in 77% yield and an *E*/*Z* selectivity of 5:1 in favor of the desired product **2** (entry 4, 65% isolated *E*-isomer).[29] The undesired *Z*-isomer could be removed by careful column chromatography, which adds to the efficiency of the process.

Importantly, this represents one of the most complex examples for the successful implementation of an intramolecular Heck macrocyclization in natural product synthesis. Applying carefully optimized reaction conditions to an advanced precursor allowed the construction of a highly functionalized polyketide macrocycle in a straightforward manner.

## CONCLUSION

In summary, we have developed a highly concise synthesis of the macrocyclic core of rhizopodin (**1**). The expedient route proceeds in only 17 linear steps and an overall yield of 11%. Notable features of the convergent route involve a Krische allylation of an alcohol starting material to construct the stereogenic center at C16, a convergent construction of the oxazole core by a cyclodehydration strategy, thus allowing rapid access to building block **4a**/**4b**, followed by a highly chemoselective cross-coupling strategy. Exploiting the orthogonal reactivity of a dual functionalized precursor, sequential application of a Suzuki coupling and a Heck macrocyclization enabled the formation of the macrocyclic core of rhizopodin. These results demonstrate the power of intramolecular Heck reactions in complex natural product synthesis. Present efforts in designing simplified rhizopodin analogues will be reported in due course.

## EXPERIMENTAL SECTION

**(*S*)-Methyl 2-(2-(4-Methoxybenzyloxy)ethyl)oxazole-4-carboxylate (6).** A solution of 3-(4-methoxybenzyloxy)propanoic acid (**5**) (1.00 g, 4.76 mmol, 1.0 equiv) in THF (25.0 mL) under an argon atmosphere was cooled to −30 °C and treated with NMM (1.1 mL, 9.99 mol, 2.1 equiv) and IBC (0.68 mL, 5.23 mmol, 1.1 equiv). The resulting mixture was stirred at this temperature for 30 min, before L-serin methylester hydrochloride (0.81 g, 5.23 mmol, 1.1 equiv) was added as a solid. The reaction mixture was slowly warmed to rt and stirred overnight. The solvent was removed *in vacuo*, the residue was suspended in EtOAc (50 mL), filtered, and washed with EtOAc (5 × 50 mL), before the solution was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The obtained crude product was purified by column chromatography on silica gel (EtOAc) to give the desired amide as a colorless oil (1.46 g, 4.69 mmol, 99%). $R_f$ = 0.38 (EtOAc). $[\alpha]_D^{20}$ = +21.7 ($c$ = 1.00, $CHCl_3$).$^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 2.25 (br. s, 1H), 2.54 (t, $J$ = 5.8 Hz, 2H), 3.72 (dt, $J$ = 8.5, 3.1 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.91 (d, $J$ = 3.8 Hz, 2H), 4.49 (dd, $J$ = 18.0, 11.3 Hz, 2H), 4.65 (dt, $J$ = 7.4, 3.7 Hz, 1H), 6.87 (d, $J$ = 8.7 Hz, 2H), 7.12 (d, $J$ = 6.4 Hz, 1H), 7.27 (d, $J$ = 9.6 Hz, 2H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 37.0, 52.7, 54.9, 55.3, 63.5, 65.9, 73.2, 113.9, 129.6, 159.5, 170.9, 172.0. HRMS (ESI+) calculated for $C_{15}H_{21}NO_6Na^+$ $[M + Na]^+$: 334.1267. Found: 334.1266.

The amide (106 mg, 340 μmol, 1.0 equiv) obtained from above was dissolved in $CH_2Cl_2$ (5.0 mL) under argon. The resulting solution was cooled to −78 °C, and DAST (68 μL, 510 μmol, 1.5 equiv) was added slowly over 15 min. This mixture was stirred at −78 °C for 1.5 h, before it was very slowly poured into a saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). After drying over $MgSO_4$ and filtering, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 1:2) to give the oxazoline (81.0 mg, 276 μmol, 81%) as a colorless oil. $R_f$ = 0.33 (petrol ether/ethyl acetate = 1:2). $[\alpha]_D^{20}$ = +64.9 ($c$ = 1.00, $CHCl_3$). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 2.60 (ddd, $J$ = 14.9, 7.5, 6.9 Hz, 2H), 3.69 (t, $J$ = 6.9 Hz, 2H), 3.74 (s,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3H), 3.75 (s, 3H), 4.34 (dd, $J$ = 10.7, 8.7 Hz, 1H), 4.42 (s, 2H), 4.44 (dd, $J$ = 8.1, 8.0 Hz, 1H), 4.69 (dd, $J$ = 10.4, 7.9 Hz, 1H), 6.83 (d, $J$ = 8.7 Hz, 2H), 7.20 (d, $J$ = 8.1 Hz, 2H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 28.8, 52.5, 55.2, 65.7, 68.0, 69.1, 72.5, 113.7, 129.2, 130.1, 159.1, 168.2, 171.5. The oxazoline (70.0 mg, 239 $\mu$mol, 1.0 equiv) obtained from above was dissolved in $CH_2Cl_2$ (2.0 mL) under argon. This solution was cooled to 0 °C. DBU (71.3 $\mu$L, 477 $\mu$mol, 2.0 equiv) and $BrCCl_3$ (25.9 $\mu$L, 263 $\mu$mol, 1.1 equiv) were then added successively. The resulting mixture was stirred without further cooling for 20 h. The resulting dark brown solution was quenched with saturated aqueous $NH_4Cl$ solution (5 mL). The organic layer was separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The obtained crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 1:2) to give the desired oxazole **6** as white crystals (61.4 mg, 211 $\mu$mol, 88%). $R_f$ = 0.60 (petrol ether/ethyl acetate = 1:2). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 3.07 (t, $J$ = 6.7 Hz, 2H), 3.76 (s, 3H), 3.82 (t, $J$ = 6.7 Hz, 2H), 3.87 (s, 3H), 4.43 (s, 2H), 6.83 (d, $J$ = 8.7 Hz, 2H), 7.18 (d, $J$ = 8.7 Hz, 2H), 8.13 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 29.0, 52.0, 55.2, 66.2, 72.6, 113.8, 129.2, 129.9, 133.2, 143.8, 159.3, 161.6, 163.4. HRMS (ESI+) calculated for $C_{15}H_{17}NO_5Na^+$ $[M + Na]^+$: 314.1004. Found: 314.0985.

**(*S*)-1-(2-(2-(4-Methoxybenzyloxy)ethyl)oxazol-4-yl)but-3-en-1-ol (7).** The methyl ester **6** (15.5 mg, 53.2 $\mu$mol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (1.0 mL) under an argon atmosphere. The solution was cooled to −78 °C, followed by the slow addition of DIBAL-H (1.0 M in hexane, 85 $\mu$L, 85.0 $\mu$mol, 1.6 equiv). The resulting mixture was stirred for 2 h at this temperature. The reaction was then quenched by successive addition of MeOH (0.5 mL), EtOAc (5 mL), and saturated, aqueous $NH_4Cl$ solution (5 mL). This biphasic mixture was warmed to rt. An aqueous solution of tartaric acid was added (1 M, 10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated *in vacuo*. The crude product was filtered over Celite and washed with EtOAc to give the desired aldehyde (13.0 mg, 49.8 $\mu$mol, 94%) as a colorless oil. $R_f$ = 0.60 (petrol ether/ethyl acetate = 1:2). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 3.11 (t, $J$ = 6.6 Hz, 2H), 3.79 (s, 3H), 3.85 (t, $J$ = 6.6 Hz, 2H), 6.85 (d, $J$ = 8.9 Hz, 2H), 7.21 (d, $J$ = 8.7 Hz, 2H), 8.17 (s, 1H), 9.91 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 29.1, 55.3, 66.1, 72.8, 113.9, 129.4, 129.5, 141.0, 144.4, 159.4, 184.0.

A solution of (-)-$(Ipc)_2$BOMe (216 mg, 0.68 mmol, 2.2 equiv) in $Et_2O$ (2 mL) under argon was cooled to −78 °C and treated slowly with allylmagnesiumbromide (0.59 mL of a 1 M solution in $Et_2O$, 0.59 mmol, 1.9 equiv). After stirring for 15 min at this temperature, the solution was warmed to room temperature and stirred for 1 h. The precipitate was forced to settle down by centrifugation. The supernatant solution was decanted into another flask under argon, and the residue was washed with pentane (2 × 5 mL). The combined solution was then concentrated, and the residue was dissolved in $Et_2O$ (2.0 mL), before the resulting solution was cooled to −78 °C. A solution of aldehyde (81.0 mg, 0.31 mmol, 1.0 equiv) obtained from above in $Et_2O$ (1.0 mL) was then added, and the reaction mixture was stirred at −78 °C for 2 h. Afterward, the reaction was warmed to room temperature and treated with a 3 M aqueous NaOH solution (1 mL) and $H_2O_2$ (0.5 mL of an 30% aqueous solution). The biphasic mixture was stirred for 1 h at room temperature. The organic layer was separated, the aqueous phase was extracted with $Et_2O$ (3 × 5 mL), and the combined organic layer was washed with $H_2O$ (1 × 15 mL) and brine (1 × 15 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 1:1) to give the title compound **7** as a light yellow oil (75.8 mg, 0.25 mmol, 81%). $R_f$ = 0.34 (petrol ether/ethyl acetate = 1:1). $[\alpha]_D^{20}$ = −7.7 ($c$ = 0.98, $CHCl_3$). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 2.58 (m, 2H), 3.03 (t, $J$ = 6.4 Hz, 2H), 3.79 (s, 3H), 3.81 (t, $J$ = 6.6 Hz, 2H), 4.46 (s, 2H), 4.70 (m, 1H), 5.14 (d, $J$ = 5.6 Hz, 1H), 5.19 (d, $J$ = 11.1 Hz, 1H), 5.82 (ddt, $J$ = 17.1, 10.2, 7.1 Hz, 1H), 6.85 (d, $J$ = 8.7 Hz, 2H), 7.21 (d, $J$ = 8.7 Hz, 2H), 7.46 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 29.3, 29.7, 40.9, 55.3, 66.6, 72.7, 113.9, 118.7, 129.3, 130.1, 133.9, 134.1, 159.3. HRMS (ESI+) calculated for $C_{17}H_{21}NO_4Na^+$ $[M + Na]^+$: 326.1368. Found: 326.1376.

**(*S*)-2-(4-(1-Methoxybut-3-enyl)oxazol-2-yl)ethanol (8).** To a solution of the homoallylic secondary alcohol **7** (52.0 mg, 0.17 mmol, 1.0 equiv) in MeI (1.5 mL, 24 mmol, 141 equiv) were added molecular sieves (3 Å) and $Ag_2O$ (199 mg, 0.85 mmol, 5.0 equiv). The resulting mixture was stirred for 18 h at room temperature, before it was filtered through a pad of cotton/silica gel and washed with $Et_2O$ (3 × 5 mL). The solvent was removed *in vacuo*, and the crude product was further purified by column chromatography on silica gel (petrol ether/ethyl acetate = 2:1) to give the corresponding methyl ether (54.0 mg, 0.17 mmol, 99%) as a colorless oil. $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 2.50 (t, $J$ = 6.6 Hz, 2H), 3.04 (t, $J$ = 6.9 Hz, 2H), 3.32 (s, 3H), 3.79 (s, 3H), 3.82 (t, $J$ = 6.9 Hz, 2H), 4.20 (t, $J$ = 6.4 Hz, 1H), 4.46 (s, 2H), 5.03 (dd, $J$ = 9.5, 1.4 Hz, 1 H), 5.08 (dd, $J$ = 17.0, 1.8 Hz, 1H), 5.77 (m, 1H), 6.85 (d, $J$ = 8.7 Hz, 2H), 7.21 (d, $J$ = 8.7 Hz, 2H), 7.46 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 29.3, 38.9, 55.3, 56.9, 66.7, 72.7, 76.1, 113.8, 117.3, 129.3, 130.1, 134.2, 135.4, 140.6, 159.3, 162.7. HRMS (ESI+) calculated for $C_{18}H_{23}NO_4Na^+$ $[M + Na]^+$: 340.1519. Found: 340.1526.

The PMB-protected alcohol (54.0 mg, 0.17 mmol, 1.0 equiv) obtained from above was dissolved in $CH_2Cl_2$/pH 7 buffer (10:1, 5.0 mL) under an argon atmosphere. DDQ (77.3 mg, 0.34 mmol, 2.0 equiv) was then added as a solid, and the resulting mixture was stirred for 1 h at room temperature. A saturated aqueous $NaHCO_3$ solution (4 mL) was added, the organic layer was separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over $MgSO_4$, and filtered, and the solvent was removed *in vacuo*. The obtained crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 1:1); the desired primary alcohol **8** (19.0 mg, 96.0 $\mu$mol, 56%) was obtained as a colorless oil. $[\alpha]_D^{20}$ = −41.7 ($c$ = 0.75, $CHCl_3$). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 2.57 (t, $J$ = 6.4 Hz, 2H), 2.97 (t, $J$ = 5.6 Hz, 2H), 3.32 (s, 3H), 4.00 (t, $J$ = 5.9 Hz, 2H), 4.20 (t, $J$ = 6.6 Hz, 1H), 5.04 (m, 1H), 5.07 (dd, $J$ = 18.8, 1.5 Hz, 1H), 5.76 (m, 1H), 7.47 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = 31.8, 38.8, 56.9, 59.3, 75.9, 117.4, 134.1, 135.5, 140.4, 163.4. HRMS (ESI+) calculated for $C_{10}H_{15}NO_3Na^+$ $[M + Na]^+$: 220.0950. Found: 220.0943.

**(*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-4,4-dimethylpentanoic acid (15).** Terminal olefin **14** (221 mg, 581 $\mu$mol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (4.0 mL), a few drops of a solution of Sudan III in dichloromethane were added, and the slightly red mixture was cooled to −78 °C. A steam of ozone was bubbled through this solution, until it became colorless. Oxygen was then bubbled through the solution for a few minutes before $PPh_3$ (280 mg, 1.06 mmol, 1.8 equiv) was added. The resulting mixture was stirred for 2 h at room temperature, before the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 19:1) to give the desired aldehyde as a yellowish oil (177 mg, 465 $\mu$mol, 80%). $R_f$ = 0.33 (petrol ether/ethyl acetate = 19:1). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 0.01 (s, 3H), 0.06 (s, 3H), 0.84 (s, 3H), 0.86 (s, 9H), 0.90 (s, 3H), 2.45 (ddd, $J$ = 16.7, 5.2, 2.8 Hz, 1H), 2.66 (ddd, $J$ = 16.7, 5.5, 1.9 Hz, 1H), 3.11 (d, $J$ = 8.9 Hz, 1H), 3.20 (d, $J$ = 8.9 Hz, 1H), 3.82 (s, 3H), 4.20 (t, $J$ = 5.3 Hz, 1H), 4.30 (d, $J$ = 11.7 Hz, 1H), 4.38 (d, $J$ = 11.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.22 (d, $J$ = 8.7 Hz, 2H), 9.76 (t, $J$ = 1.9 Hz, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = −4.7, −3.9, 18.2, 21.1, 21.6, 26.0, 39.9, 48.2, 55.3, 71.5, 72.7, 76.3, 113.7, 129.1, 130.7, 159.1, 202.3.

The aldehyde (620 mg, 1.63 mmol, 1.0 equiv) obtained from above was dissolved in *tert*-butanol (120 mL) and $H_2O$ (30 mL). 2-Methyl-2-butene (13.0 mL, 130 mmol, 80 equiv), sodium dihydrogen phosphate (586 mg, 9.77 mmol, 6.0 equiv), and sodium chlorite (884 mg, 4.89 mmol, 3.0 equiv) were added, and the mixture was stirred for 1.5 h at room temperature under an argon atmosphere. The solvent was removed *in vacuo*, and the residue was dissolved in EtOAc (200 mL) and washed with brine. The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic phases were washed again


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with brine (1 × 200 mL), dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 4:1) to give the desired acid **15** as a colorless oil (635 mg, 1.63 mmol, 99%). $R_f$ = 0.30 (petrol ether/ethyl acetate = 4:1). $[\alpha]_D^{20}$ = −8.1 (*c* = 1.11, $CHCl_3$). IR (film): 2955, 2929, 2855, 1708, 1513, 1463, 1302, 1246, 1084, 1037, 945, 830, 774, 678. $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = 0.06 (m, 6H), 0.87 (m, 9H), 0.9 (s, 6H), 2.41 (m, 1H), 2.67 (dd, *J* = 16.4, 4.7 Hz, 1H), 3.17 (m, 2H), 3.79 (s, 3H), 4.11 (m, 1H), 4.38 (m, 2H), 6.59 (d, *J* = 8.7, 2H), 7.23 (m, 2H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = −4.2, −4.9, 18.2, 21.1, 21.4, 26.0, 38.3, 40.0, 55.3, 72.8, 73.6, 76.3, 113.7, 128.6, 129.1, 130.7, 159.1, 176.0. HRMS (ESI-) calculated for $C_{21}H_{35}O_5Si^-$ $[M - H]^-$: 395.2254. Found: 395.2245.

**Oxazole 17.** Carboxylic acid **15** (20 mg, 50.4 μmol, 1.0 equiv) and amine **16** (8.1 mg, 55.5 μmol, 1.1 equiv) were dissolved in dry THF (1.5 mL). At room temperature, dry triethylamine (35 μL, 252 μmol, 5.0 equiv) was added, followed by 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) (25.6 mg, 85.7 μmol, 1.7 equiv). The yellow solution was stirred at room temperature overnight (20 h). Saturated aqueous $NH_4Cl$ solution (5 mL) was added, the mixture was extracted with ethyl acetate (5 × 7 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. After purification by column chromatography ($SiO_2$, petroleum ether/ethyl acetate, 2:1 + 1% (v/v) $NEt_3$), the corresponding amide was obtained as a colorless oil (24.5 mg, 46.8 μmol, 93%). $R_f$ = 0.21 (petrol ether/ethyl acetate = 2:1 + 1% (v/v) $NEt_3$). $[\alpha]_D^{20}$ = −11.3 (*c* = 0.9, $CHCl_3$). IR (film): 3322, 2927, 2930, 2855, 1624, 1569, 1537, 1243, 1086, 835, 775, 641. $^1$H NMR (600.24 MHz, $CDCl_3$): $\delta$ = 0.05 (s, 3H), 0.09 (s, 3H), 0.89 (s, 3H), 0.90 (s, 9H), 0.92 (s, 3H), 2.23 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.24−2.27 (m, 1H), 2.49 (ddd, *J* = 14.4, 6.4, 5.9 Hz, 1H), 2.62 (dd, *J* = 15.4, 4.3 Hz, 1H), 3.21 (s, 2H), 3.38 (s, 3H), 3.50 (dt, *J* = 6.8, 3.3 Hz, 1H), 3.58 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.81 (s, 3H), 3.92 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.99 (ddd, *J* = 7.6, 7.2, 3.5 Hz, 1H), 4.15 (t, *J* = 5.0 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 5.11−5.17 (m, 2H), 5.77−5.84 (m, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H). $^{13}$C NMR (150.93 MHz, $CDCl_3$): $\delta$ = −5.1, 4.0, 18.2, 21.1, 21.8, 26.1, 35.0, 40.1, 41.0, 52.0, 55.2, 58.1, 61.9, 72.8, 73.6, 76.4, 83.1, 113.6, 118.1, 129.0, 130.8, 133.5, 158.9, 172.1. HRMS (ESI+) calculated for $C_{26}H_{45}NNaO_5Si^+$ $[M + Na]^+$: 526.2959. Found: 526.2954.

The amide (20.0 mg, 38.2 μmol, 1.0 equiv) obtained from above was dissolved in DMSO (1.0 mL) before 2-iodoxy-benzoic acid (IBX) (32.0 mg, 115 μmol, 3.0 equiv) was added, and the solution was stirred for 4 h at room temperature. Dichloromethane (15 mL) was added, and the solution was stirred for another 30 min. The formed white precipitate was removed by filtration, and the clear organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 15 mL). The aqueous layers were extracted with dichloromethane (3 × 15 mL); the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The remaining DMSO was removed by purification over a short silica gel column chromatography. The unstable aldehyde was obtained as a colorless oil and was directly used in the next step.

The aldehyde obtained from above (16.0 mg, 30.6 μmol, 1.0 equiv) was dissolved in dry dichloromethane (1.0 mL) under argon. Triphenylphosphine (20.2 mg, 76.6 μmol, 2.5 equiv) and 2,6-di-*tert*-butyl-4-methyl-pyridine (31.4 mg, 153 μmol, 5.0 equiv) were added subsequently at room temperature and stirred for 20 min. The mixture was cooled to 0 °C, 1,2-dibrom-tetrachlor-ethane (25.0 mg, 76.6 μmol, 2.5 equiv) was added, and the mixture was stirred overnight (15 h) at 0 °C. A solution of DBU (22 μL, 153 μmol, 5.0 equiv) in dry acetonitrile (0.5 mL) was added, and the mixture was stirred for 5 h at 0 °C. An aqueous saturated solution of $NH_4Cl$ (2 mL) and dichloromethane (5 mL) was added. After washing, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 4 mL). The organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography (3 g of $SiO_2$, petrol ether/ethyl acetate 10:1 to 4:1) gave the title compound **17** as a yellowish oil (8.6 mg, 17.1 μmol, 56% over 2 steps). $R_f$ = 0.72 (petrol ether/ethyl acetate = 2:1). $[\alpha]_D^{20}$ = −31.7 (*c* = 0.90, $CHCl_3$). IR (film): 2956, 2927, 2857, 1728, 1462, 1271, 1120, 1073, 836, 775, 741. $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = −0.32 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 0.86 (s, 3H), 0.90 (s, 3H), 2.56 (virt. t, *J* = 6.4 Hz, 2H), 2.82 (dd, *J* = 15.3, 7.6 Hz, 1H), 3.03 (dd, *J* = 15.5, 3.8 Hz, 1H), 3.15 (d, *J* = 8.7 Hz, 1H), 3.24 (d, *J* = 8.7 Hz, 1H), 3.31 (s, 3 H), 3.79 (s, 3 H), 4.19 (m, 1 H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 5.04 (m, 1H), 5.09 (m, 1H), 5.80 (ddd, *J* = 17.2 Hz, *J* = 10.2 Hz, *J* = 7.0 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.44 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = −4.8, 18.2, 20.8, 21.4, 26.0, 32.9, 39.1, 40.1, 55.3, 57.0, 72.8, 74.7, 76.0, 76.4, 113.7, 117.4, 129.0, 130.9, 134.1, 135.1, 140.3, 159.0, 164.2. HRMS (ESI+) calculated for $C_{28}H_{45}NO_5SiNa^+$ $[M + Na]^+$: 526.2965. Found: 526.2977.

**Aldehyde 18.** To a stirred solution of the PMB-ether **17** (106 mg, 211 μmol, 1.0 equiv) in dry dichloromethane (10.0 mL) at room temperature was added $MgBr_2 \cdot OEt_2$ (1.30 g, 5.06 mmol, 24.0 equiv) and dimethylsulfide (0.74 mL, 10.1 mmol, 48.0 equiv). The mixture was stirred at room temperature for 18 h in a sealed tube. Water (15 mL), an aqueous saturated solution of NaCl (10 mL), and dichloromethane (10 mL) were added. After washing, the aqueous phase was separated and extracted with dichloromethane (5 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica column chromatography (10 g of $SiO_2$, petrol ether/ethyl acetate = 4:1 to 1:1) gave the corresponding primary alcohol (75.6 mg, 197 μmol, 98%) as a colorless oil. $R_f$ = 0.19 (petrol ether/ethyl acetate = 4:1). $[\alpha]_D^{20}$ = −53.1 (*c* = 1.8 in $CHCl_3$). IR (film): 2955, 2928, 2854, 1682, 1512, 1082, 1035, 832, 777. $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = −0.17 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.89 (s, 3H), 0.96 (s, 3H), 1.86 (br s, 1H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.90 (dd, *J* = 16.1, 5.7 Hz, 1H), 3.15 (dd, *J* = 16.1, 5.7 Hz, 1H), 3.33 (d, *J* = 11.3 Hz, 1H), 3.33 (s, 3H), 3.54 (d, *J* = 11.3 Hz, 1H), 4.13−4.25 (m, 2H), 5.02−5.15 (m, 2H), 5.71−5.87 (m, 1H), 7.48 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = −4.9, −5.8, 18.0, 21.5, 21.6, 25.9, 32.9, 38.9, 40.1, 56.9, 69.4, 76.0, 77.2, 117.4, 134.0, 135.2, 140.6, 163.6. HR-MS (ESI+) calculated for $C_{20}H_{37}NO_4SiNa^+$ $[M + Na]^+$: 406.2384. Found: 406.2381.

A solution of alcohol (75.6 mg, 197 μmol, 1.0 equiv) obtained from above in wet DMSO (2.5 mL) was treated with 2-iodoxy-benzoic acid (IBX) (138 mg, 493 μmol, 2.5 equiv) at room temperature and stirred for 2 h. The reaction was quenched by the addition of dichloromethane (25 mL) and stirred for a further 30 min. The formed white precipitate was removed by filtration, and the clear organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered over a short plug of silica gel to afford aldehyde **18** as a colorless oil (72.9 mg, 191 μmol, 97%). $R_f$ = 0.34 (petrol ether/ethyl acetate = 4:1). $[\alpha]_D^{20}$ = −49.1 (*c* = 1.2 in $CHCl_3$). $^1$H NMR (300.51 MHz, $CDCl_3$): $\delta$ = −0.22 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.02 (s, 3H), 1.11 (s, 3H), 2.50−2.66 (m, 2H), 2.88 (dd, *J* = 15.5, 7.2 Hz, 1H), 2.97 (dd, *J* = 15.5, 4.8 Hz, 1H), 3.32 (s, 3H), 4.20 (t, *J* = 6.1 Hz, 1H), 4.46 (dd, *J* = 7.0, 5.0 Hz, 1H), 5.02−5.15 (m, 2H), 5.72−5.88 (m, 1H), 7.48 (s, 1H), 9.51 (s, 1H). $^{13}$C NMR (75.56 MHz, $CDCl_3$): $\delta$ = −4.9, −4.8, 17.3, 18.0, 18.5, 25.8, 32.9, 39.1, 40.8, 56.8, 74.1, 76.0, 117.3, 134.1, 135.3, 140.9, 162.2, 204.9. HR-MS (ESI+) calculated for $C_{20}H_{35}NO_4SiNa^+$ $[M + Na]^+$: 404.2228. Found: 404.2226.

For the preparation of **4a** from aldehyde **18**, see ref 10.

**Vinyl-boronate (4b).** To a stirred solution of terminal alkene **4a** (6.7 mg, 10.8 μmol, 1.0 equiv) under argon in dichloromethane (0.6 mL) was added 1-propenyl-pinacol-boronate **19**[21] (3.6 mg, 21.6 μmol, 2.0 equiv) and Grubbs-II catalyst (0.5 mg, 0.54 μmol, 0.05 equiv). The mixture was refluxed for 18 h and cooled to room temperature. Purification by silica column chromatography (3 g of $SiO_2$, pentane/ethyl acetate = 3:1) afforded vinyl-boronate **4b** (6.8 mg, 9.20 μmol, 85%, 95% brsm, *E*/*Z* = 16/1) besides recovered starting material **4a** (0.7 mg, 1.20 μmol) as a slightly brown oil. $R_f$ = 0.16 (pentane/ethyl acetate = 3:1). $[\alpha]_D^{20}$ = −32.8 (*c* = 0.6 in $CHCl_3$). IR (film): 3500, 2960, 2930, 2898, 2856, 1638, 1513, 1464, 1361, 1321, 1247, 1144, 1080, 1005, 970, 835, 775. $^1$H NMR (600.13 MHz, $CDCl_3$): $\delta$ = −0.32 (s, 3H), 0.05 (s, 3H), 0.75 (s, 3H), 0.82 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 3H), 1.23 (br. s., 12H), 1.36−1.42 (m, 2H), 1.95−2.02

(m, 1H), 2.60−2.71 (m, 2H), 2.97 (dd, $J$ = 15.7, 7.8 Hz, 1H), 3.12 (dd, $J$ = 15.6, 3.2 Hz, 1H), 3.25−3.29 (m, 1H), 3.28 (s, 3H), 3.41 (s, 3H), 3.47 (dd, $J$ = 9.0, 5.7 Hz, 1H), 3.54 (ddd, $J$ = 7.8, 4.3 Hz, 1H), 3.78 (s, 3H), 3.92 (dd, $J$ = 6.3, 5.8 Hz, 1H), 4.18 (dd, $J$ = 7.7, 3.3 Hz, 1H), 4.22 (dd, $J$ = 6.6, 6.3 Hz, 1H), 4.39 (d, $J$ = 11.5 Hz, 2H), 4.43 (d, $J$ = 11.5 Hz, 2H), 5.50 (d, $J$ = 18.0 Hz, 1H), 6.56 (ddd, $J$ = 18.0, 6.6, 6.5 Hz, 1H), 6.85 (d, $J$ = 8.6 Hz, 2H), 7.24 (d, $J$ = 8.6 Hz, 2H), 7.45 (s, 1H). $^{13}$C NMR (150.90 MHz, $CDCl_3$): $\delta$ = −5.2, −4.7, 12.7, 18.0, 19.8, 22.5, 24.8, 26.0, 32.7, 34.1, 37.4, 40.9, 41.0, 43.9, 55.3, 56.8, 59.2, 71.4, 72.4, 72.6, 75.4 (2C), 79.1, 83.1, 113.7, 121.5, 129.2, 130.8, 135.3, 140.7, 149.3, 159.0, 163.3. HRMS (ESI+) calculated for $C_{40}H_{68}BNO_9SiNa^+$ [M + Na]$^+$: 768.4654. Found: 768.4653.

**Ester 20.** To a stirred solution of alcohol **4a** (9.0 mg, 14.5 μmol, 1.0 equiv) and acid **3** (18.0 mg, 43.6 μmol, 3.0 equiv) in dry toluene (400 μL) at 0 °C were added dry $NEt_3$ (30.0 μL, 218 μmol, 15 equiv) and 2,4,6-trichlorobenzoylchloride (23.0 μL, 145 μmol, 10 equiv) successively. The mixture was allowed to warm to room temperature and was stirred for 3 h before the addition of *N*,*N*-dimethylaminopyridine (26.6 mg, 218 μmol, 15.0 equiv). The opaque yellow mixture was stirred for 1.5 h. Dichloromethane (2.0 mL) and phosphate buffer solution (1.5 mL, pH = 7.0) were added. The aqueous phase was separated and extracted with dichloromethane (5 × 2 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (1 × 7.0 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by silica column chromatography (3 g of $SiO_2$, pentane/ethyl acetate = 9:1 to 3:1) gave the ester **20** (14.1 mg, 13.9 μmol, 96%) as a yellowish oil. $R_f$ = 0.62 (pentane/ethyl acetate = 3:1). $[\alpha]_D^{20}$ = −17.8 ($c$ = 0.62 in $CHCl_3$). IR (film): 2952, 2927, 2893, 2855, 1733, 1513, 1463, 1364, 1248, 1172, 1086, 834, 810, 775. $^1$H NMR (600.13 MHz, $CDCl_3$): $\delta$ = −0.38 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 0.85 (s, 3H), 0.88 (s, 9H), 0.90 (s, 3H), 0.91 (s, 3H), 0.93 (d, $J$ = 6.9 Hz, 3H), 1.61 (dd, $J$ = 14.3, 9.8 Hz, 1H), 1.68 (d, $J$ = 14.3 Hz, 1H), 1.72 (ddd, $J$ = 14.3, 5.3, 5.3 Hz, 1H), 1.84 (ddd, $J$ = 14.1, 7.4, 5.9 Hz, 1H), 1.95−2.08 (m, 1H), 2.48−2.62 (m, 4H), 2.89 (dd, $J$ = 15.7, 8.4 Hz, 1H), 3.05−3.17 (m, 2H), 3.23 (s, 3H), 3.25−3.32 (m, 1H), 3.31 (s, 3H), 3.34 (s, 3H), 3.49 (dd, $J$ = 9.0, 5.4 Hz, 1H), 3.75 (ddd, $J$ = 7.4, 7.4, 5.8 Hz, 1H), 3.81 (s, 3H), 4.10 (dd, $J$ = 8.4, 2.2 Hz, 1H), 4.20 (dd, $J$ = 6.5, 6.2 Hz, 1H), 4.23 (dddd, $J$ = 6.2, 6.2, 5.3, 5.3 Hz, 1H), 4.42 (d, $J$ = 11.6 Hz, 1H), 4.45 (d, $J$ = 11.6 Hz, 1H), 5.06 (d, $J$ = 9.5 Hz, 1H), 5.11 (d, $J$ = 17.3 Hz, 1H), 5.19 (d, $J$ = 9.8 Hz, 1H), 5.82 (dddd, $J$ = 17.1, 10.0, 6.9, 6.9 Hz, 1H), 6.30 (d, $J$ = 14.6 Hz, 1H), 6.39 (dd, $J$ = 14.5, 7.8 Hz, 1H), 6.88 (d, $J$ = 8.5 Hz, 2H), 7.27 (d, $J$ = 8.5 Hz, 2H), 7.45 (s, 1H). $^{13}$C NMR (150.90 MHz, $CDCl_3$): $\delta$ = −4.9, −4.6, −4.6, −4.4, 12.9, 17.9, 18.2, 20.6, 21.1, 25.8, 26.0, 32.5, 32.8, 36.7, 39.1, 41.8, 42.2, 42.7, 55.2, 56.3, 56.9, 58.5, 66.0, 72.0, 72.7, 75.7, 75.8, 76.3, 78.3, 79.2, 80.5, 113.7, 117.2, 129.1, 130.8, 134.3, 134.9, 140.9, 146.3, 159.0, 163.4, 170.9. HRMS (ESI+) calculated for $C_{48}H_{82}INO_{10}Si_2Na^+$ [M + Na]$^+$: 1038.4409. Found: 1038.4408.

**Bisester 21.** To a stirred solution of vinyl-iodine **20** (9.0 mg, 8.86 μmol, 1.0 equiv) and vinyl-boronate **4b** (6.6 mg, 8.86 μmol, 1.0 equiv) in DMF (300 μL) were added Pd(dppf)$Cl_2$ (1.9 mg, 2.66 μmol, 0.3 equiv) and $Ba(OH)_2{\cdot}8H_2O$ (8.4 mg, 26.6 μmol, 3.0 equiv). The mixture was stirred under argon at room temperature for 75 min. Phosphate buffer solution (1.5 mL, pH = 7.0) was added, and the aqueous phase was separated and extracted with dichloromethane (5 × 2 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (1 × 10.0 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by silica column chromatography (3 g of $SiO_2$, pentane/ethyl acetate = 3:1) gave the corresponding diene (12.1 mg, 8.02 μmol, 91%) as a yellowish oil. $R_f$ = 0.13 (pentane/ethyl acetate = 3:1). $[\alpha]_D^{20}$ = −25.2 ($c$ = 0.70 in $CHCl_3$). IR (film): 2950, 2926, 2854, 2362, 2335, 1734, 1514, 1463, 1376, 1249, 1173, 1088, 836, 809, 776. $^1$H NMR (600.13 MHz, $CDCl_3$): $\delta$ = −0.03 (s, 3H), 0.03 (s, 6H), 0.06 (s, 3H), 0.75 (s, 3H), 0.80 (s, 9H), 0.82 (s, 3H), 0.83 (s, 9H), 0.85 (s, 9H), 0.86 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.90 (d, $J$ = 7.0 Hz, 3H), 0.94 (d, $J$ = 7.0 Hz, 3H), 0.95 (s, 3H), 1.39 (dd, $J$ = 6.4, 5.9 Hz, 2H), 1.60−1.70 (m, 3H), 1.82 (ddd, $J$ = 14.0, 7.0, 5.8 Hz, 1H), 1.95−2.02 (m, 2H), 2.51−2.60 (m, 6H), 2.86 (dd, $J$ = 15.7, 8.4 Hz, 1H), 2.98 (dd, $J$ = 15.6, 7.9 Hz, 1H), 3.02−3.15 (m, 3H), 3.17 (s, 1H), 3.23−3.29 (m, 2H), 3.27 (s, 2H), 3.29 (s, 2H), 3.31 (s, 2H), 3.41 (s, 2H), 3.46 (dd, $J$ = 9.0, 5.4 Hz, 2H), 3.54 (ddd, $J$ = 7.3, 4.5, 4.5 Hz, 1H), 3.71 (ddd, $J$ = 7.8, 5.9 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.93 (dd, $J$ = 6.1 Hz, 6.1 Hz, 1H), 4.06 (dd, $J$ = 8.2, 2.3 Hz, 1H), 4.12−4.23 (m, 4H), 4.37−4.45 (m, 4H), 5.03 (d, $J$ = 9.6 Hz, 1H), 5.08 (d, $J$ = 17.2 Hz, 1H), 5.15 (d, $J$ = 9.8 Hz, 1H), 5.36 (dd, $J$ = 14.4, 8.1 Hz, 1H), 5.65 (ddd, $J$ = 14.4, 7.0, 7.0 Hz, 1H), 5.79 (dddd, $J$ = 17.1, 10.0, 6.9 Hz, 1H), 6.07 (dd, $J$ = 16.3, 9.9 Hz, 1H), 6.09 (dd, $J$ = 16.6, 10.5 Hz, 1H), 6.85 (d, $J$ = 8.2 Hz, 4H), 7.24 (d, $J$ = 8.2 Hz, 4H), 7.42 (s, 1H), 7.44 (s, 1H). $^{13}$C NMR (150.90 MHz, $CDCl_3$): $\delta$ = −5.2, −4.9, −4.7, −4.6, −4.6, −4.4, 12.7, 13.0, 14.1, 18.0, 18.0, 18.2, 19.8, 21.2, 22.3, 25.9, 25.9, 26.0, 32.3, 32.7, 32.8, 34.1, 36.6, 37.4, 38.0, 39.1, 41.0, 42.3, 42.7, 55.2, 55.3, 55.9, 56.9, 56.9, 58.5, 59.2, 66.2, 71.4, 72.0, 72.4, 72.7, 72.7, 75.6, 75.9, 76.2, 76.3, 78.7, 79.1, 79.3, 113.7, 113.7, 117.2, 129.1, 129.2, 130.1, 130.8, 130.8, 131.9, 131.9, 132.7, 134.4, 134.9, 135.1, 140.9, 140.9, 159.0, 163.3, 163.4, 171.1. HRMS (ESI+) calculated for $C_{82}H_{138}N_2O_{17}Si_3Na^+$ [M + Na]$^+$: 1529.9196. Found: 1529.9196.

To a stirred solution of the diene (6.7 mg, 4.44 μmol, 1.0 equiv) prepared from above and acid **3** (4.4 mg, 10.6 μmol, 2.4 equiv) in dry toluene (200 μL) at 0 °C was added subsequently dry $NEt_3$ (9.0 μL, 61.5 μmol, 15.0 equiv) and 2,4,6-trichlorobenzoylchloride (7.0 μL, 41.0 μmol, 10.0 equiv) successively. The mixture was allowed to warm to room temperature and was stirred for 3 h before the addition of *N*,*N*-dimethylaminopyridine (7.5 mg, 61.5 μmol, 15.0 equiv). The opaque yellow mixture was stirred for 1.5 h. Dichloromethane (2.0 mL) and phosphate buffer solution (1.5 mL, pH = 7.0) were added. The aqueous phase was separated and extracted with dichloromethane (5 × 2 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (1 × 10.0 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by silica column chromatography (3 g of $SiO_2$, pentane/ethyl acetate = 9:1 to 3:1) gave bis-ester **21** (8.0 mg, 4.24 μmol, 95%) as a yellowish oil. $R_f$ = 0.38 (pentane/ethyl acetate = 3:1). $[\alpha]_D^{20}$ = −11.9 ($c$ = 0.94 in $CHCl_3$). IR (film): 2950, 2928, 2898, 2855, 2361, 2327, 1733, 1513, 1463, 1362, 1248, 1172, 1085, 834, 810, 775, 667. $^1$H NMR (600.13 MHz, $CDCl_3$): $\delta$ = −0.41 (s, 3H), −0.39 (s, 3H), 0.01 (s, 6H), 0.06 (s, 6H), 0.07 (s, 6H), 0.83 (s, 18H), 0.84 (s, 3H), 0.85 (s, 3H), 0.88 (s, 18H), 0.91 (d, $J$ = 6.9 Hz, 3H), 0.89 (s, 3H), 0.91 (s, 3H), 0.93 (d, $J$ = 6.9 Hz, 3H), 1.55−1.76 (m, 4H), 1.79−1.90 (m, 2H), 1.97−2.08 (m, 2H), 2.48−2.64 (m, 8H), 2.84−2.96 (m, 2H), 3.03−3.15 (m, 4H), 3.20 (s, 3H), 3.20−3.31 (m, 2H), 3.23 (s, 3H), 3.30 (s, 3H), 3.33 (s, 3H), 3.34 (s, 3H), 3.49 (ddd, $J$ = 8.7, 5.6, 4.7 Hz, 2H), 3.71−3.77 (m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.09 (d, $J$ = 8.3 Hz, 2H), 4.15−4.26 (m, 4H), 4.41 (d, $J$ = 11.3 Hz, 2H), 4.45 (d, $J$ = 11.3 Hz, 2H), 5.06 (d, $J$ = 10.3 Hz, 1H), 5.11 (d, $J$ = 17.2 Hz, 1H), 5.16−5.23 (m, 2H), 5.39 (dd, $J$ = 14.2, 8.0 Hz, 1H), 5.70 (ddd, $J$ = 14.4, 7.0, 7.0 Hz, 1H), 5.82 (dddd, $J$ = 17.0, 10.0, 6.9, 6.9 Hz, 1H), 6.05−6.18 (m, 2H), 6.30 (d, $J$ = 14.5 Hz, 1H), 6.39 (dd, $J$ = 14.5, 7.7 Hz, 1H), 6.88 (d, $J$ = 7.4 Hz, 4H), 7.26 (d, $J$ = 7.3 Hz, 4H), 7.45 (s, 2H). $^{13}$C NMR (150.90 MHz, $CDCl_3$): $\delta$ = −4.9, −4.9, −4.6, −4.6, −4.6, −4.4, −4.4, 12.8, 13.0, 17.9, 18.0, 18.2, 18.2, 20.6, 21.2, 25.8, 25.9, 26.0, 26.1, 26.1, 32.4, 32.6, 32.8, 36.6, 36.8, 38.1, 39.1, 41.8, 42.2, 42.3, 42.7, 55.2, 55.2, 55.9, 56.3, 56.9, 57.0, 58.5, 58.6, 66.0, 66.2, 72.0, 72.0, 72.7, 72.7, 75.6, 75.7, 75.9, 76.3, 76.4, 78.3, 78.7, 79.2, 79.3, 80.5, 113.7, 117.2, 129.1, 129.1, 130.3, 130.7, 130.8, 131.8, 131.9, 134.4, 134.9, 140.9, 146.3, 159.0, 159.0, 163.4, 163.5, 170.9, 171.1. HRMS (ESI+) calculated for $C_{96}H_{163}IN_2O_{20}Si_4K^+$ [M + K]$^+$: 1941.9558. Found: 1941.9552.

**Macrocycle 2.** Compound **21** (5.6 mg, 2.94 μmol, 1.0 equiv) was dissolved in DMF (600 μL, degassed with three pump−freeze−thaw cycles). Pd$(OAc)_2$ (0.7 mg, 2.94 μmol, 1.0 equiv), dry $K_2CO_3$ (4.1 mg, 29.4 μmol, 10.0 equiv), and $Bu_4NCl$ (2.5 mg, 8.82 μmol, 3.0 equiv) were added, and the mixture was once again degassed (1 × pump−freeze−thaw). The solution was stirred under argon and heated to 60 °C for 50 min in a sealed tube. After cooling to room temperature, diethyl ether (5 mL) was added, and the solution was washed with water (4 × 5 mL) to remove DMF. The combined aqueous phases were extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica column chromatography (3 g of $SiO_2$, pentane/ethyl acetate = 4:1 to 3:1) gave macrocyclic core **2** (3.4 mg, 1.89 μmol, 65%) as a


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colorless oil, besides its corresponding *Z*-isomer (0.6 mg, 0.36 μmol, 12%). $R_f$ = 0.49 (pentane/ethyl acetate = 3:1). $[\alpha]_D^{20}$ = −7.1 (*c* = 0.56 in $CHCl_3$). IR (film): 2925, 2854, 2360, 2325, 1733, 1514, 1464, 1250, 1088, 1038, 835, 808, 776. $^1$H NMR (500.13 MHz, $CDCl_3$): δ = −0.33 (s, 6H), 0.01 (s, 6H), 0.06 (s, 6H), 0.84 (s, 18H), 0.87 (s, 18H), 0.87 (s, 6H), 0.90 (s, 6H), 0.93 (d, *J* = 6.9 Hz, 6H), 1.61−1.70 (m, 4H), 1.71−1.76 (m, 2H), 1.84−1.88 (m, 2H), 2.00−2.05 (m, 2H), 2.56 (d, *J* = 6.0 Hz, 4H), 2.61−2.63 (m, 4H), 2.92 (dd, *J* = 15.6, 8.2 Hz, 2H), 3.04−3.08 (m, 2H), 3.16 (dd, *J* = 15.6, 3.8 Hz, 2H), 3.19 (s, 6H), 3.25−3.27 (m, 2H), 3.30 (s, 6H), 3.32 (s, 6H), 3.49 (dd, *J* = 14.3, 5.5 Hz, 2H), 3.68−3.72 (m, 2H), 3.80 (s, 6H), 4.07 (dd, *J* = 8.2, 3.3 Hz, 2H), 4.16−4.18 (m, 2H), 4.17−4.20 (m, 2H), 4.40−4.46 (m, 4H), 5.18 (d, *J* = 9.6 Hz, 2H), 5.37 (dd, *J* = 14.6, 8.0 Hz, 2H), 5.67 (ddd, *J* = 16.0, 7.5, 6.5 Hz, 2H), 6.07 (dd, *J* = 14.2, 10.3 Hz, 2H), 6.11 (dd, *J* = 14.8, 10.3 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 4H), 7.26 (d, *J* = 8.8 Hz, 4H), 7.43 (s, 2H). $^{13}$C NMR (125.76 MHz, $CDCl_3$): δ = −4.9, −4.6, −4.5, −4.3, 13.0, 18.0, 18.2, 21.3, 21.7, 25.9, 26.1, 32.9, 33.2, 36.7, 37.7, 42.5, 42.7, 43.2, 55.3, 55.9, 56.8, 58.5, 66.4, 72.0, 72.7, 75.9, 76.2, 79.1, 79.4, 113.8, 130.0, 130.8, 131.8, 131.9, 133.1, 135.1, 140.1, 159.1, 163.5, 170.8. HRMS (ESI+) calculated for $C_{96}H_{162}N_2O_{20}Si_4Na^+$ $[M + Na]^+$: 1799.0729. Found: 1799.0724.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

General experimental procedures and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(28) Longer reaction time or higher temperature led to decomposition of the material.

(29) As previously reported,[10] the PMB group may be conveniently removed at an earlier stage of the synthesis, while efforts to effectuate an oxidative PMB deprotection at this stage are thwarted by concomitant cleavage of the OMe-ether and subsequent oxidation. A Heck coupling with an analogous substrate with terminal TBS groups may be carried out in an analogous manner. These results are in agreement with DFT calculations on the electronic nature of **2**. According to these calculations, the highest occupied orbitals are located at the conjugated system in the macrocycle (HOMO1) and at the aromatic ring of the PMB group (HOMO2). They show very similar energy values, which may explain the almost identical reactivity for both functionalities. For details on the calculations, see the Supporting Information.