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Synthesis of the C18-C27 Fragment of Georatusin

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Dedicated to Professor Dr. Horst Kunz on the occasion of his 80th birthday

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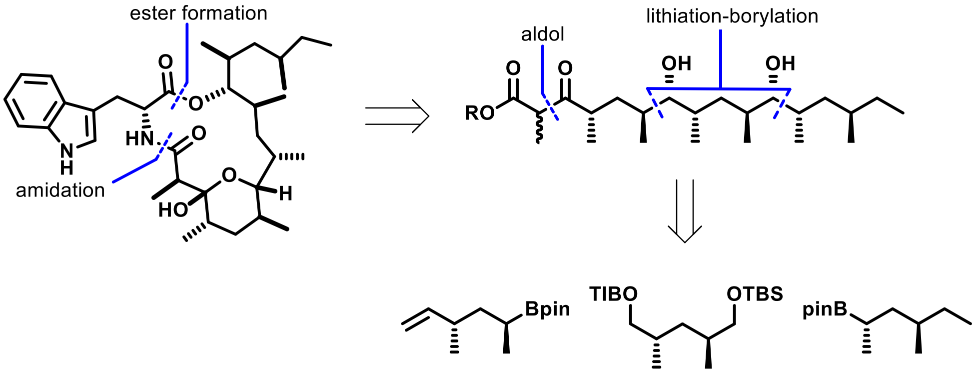
Abstract

Anti-configured 1,3-dimethyl deoxypropionate motifs are important sub-structures in natural products. We describe a bidirectional approach for the rapid construction of highly reduced polyketide fragments for the synthesis of georatusin employing our mono-Zweifel protocol.



Keywords: Georatusin, desymmetrization, C_2-symmetry, mono-Zweifel olefination

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Introduction

In the context of our program to establish synthetic access to various natural products[1-16] we focused on those featuring the 1,3-(poly)deoxypropionate motif. A structurally challenging example is the polyketide-peptide hybrid georatusin (**1**) which was isolated from the soil fungus *Geomyces auratus* in 2018 by Bode and coworkers.[17] Georatusin (**1**) features a highly reduced and methylated polyketide fragment (blue) fused to a D-tryptophan moiety (red) forming a 13-membered ring (Figure 1).[17]

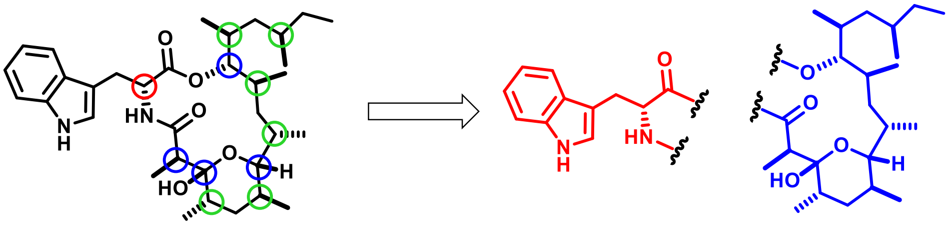

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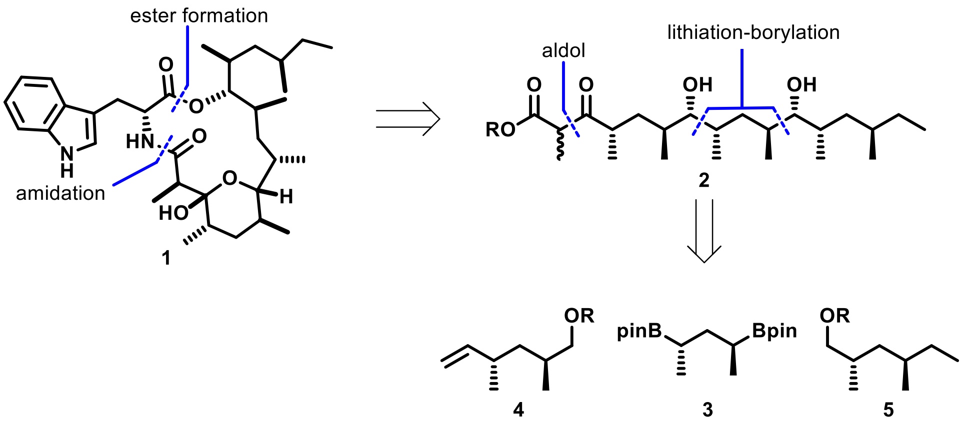
Figure 1. Structure of the highly reduced polyketide-peptide hybrid georatusin (**1**).

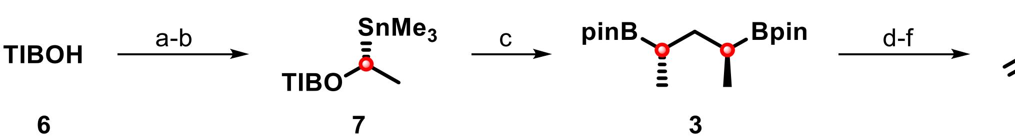
This 13-membered ring contains nine of the overall eleven stereogenic centers. The Bode group was able to determine the absolute configuration of the tryptophan unit via comparison of the ECD spectra of L- and D-tryptophan whereas the other stereogenic centers were determined in a relative fashion using different NMR experiments but could not be set into relation with the D-tryptophan moiety.[17] Due to its highly reduced carbon skeleton georatusin (**1**) is challenging to synthesize without several functional group interconversions using classic aldol chemistry. We planned to synthesize most of the carbon skeleton via lithiation-borylation chemistry using C_2-symmetric 1,3-bis(boronic ester) **3** and its derived fragments **4** and **5** (Scheme 1). The strategic advantage of this strategy is the fact, compound **5** can be directly obtained through hydrogenation from **4** and the C_2-symmetric compound **3** on the other hand allows rapid access to **4**. Due to the C_2-symmetry no side differentiation of **3** is required prior to the Zweifel olefination.



Scheme 1. First generation retrosynthetic analysis of georatusin (**1**).

Results and Discussion

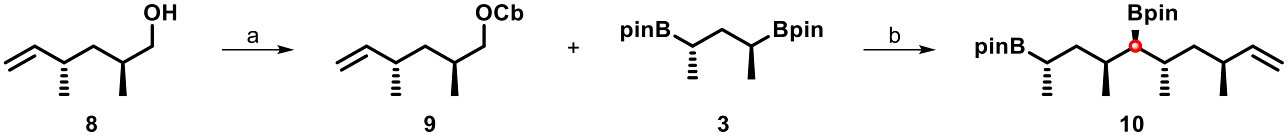
Our synthesis started with the gram-scale preparation of known C_2-symmetric 1,3-bis(boronic ester) **3**[18,19] employing our protocol.[19] Starting from our key building block **3** the precursor of the other two fragments is readily available using a three step sequence consisting of our mono-Zweifel olefination protocol,[19] Matteson-homologation[20] and oxidation (Scheme 2).



a. bromoethane, nBu_4NHSO_4, NaOH, $CHCl_3$, H_2O, rt, o/n, ≥ 95%; b. sBuLi, (+)-sparteine, Et_2O, −78 °C, 5 h, then Me_3SnCl, Et_2O, −78 °C to rt, 1.5 h, 70%, *er* 99:1; c. *n*BuLi, Et_2O, −78 °C, 1.5 h, then $pinBCH_2Bpin$, Et_2O, −78 °C to rt, o/n, 82%, *dr* ≥ 95:5; d. vinylMgBr, THF, 30 min at −78 °C, then 30 min at rt, then I2, MeOH 30 min at −78 °C, then NaOMe, MeOH, 30 min at −78 °C, then rt o/n, 35%, 81% brsm; e. $BrCH_2Cl$, *n*BuLi, Et_2O, −78 °C to rt, o/n; f. H_2O_2, NaOH, THF, 0 °C to rt, 1.5 h, 68% o2s (TIB=2,4,6-triisopropylbenzoyl, pin=pinacolato ; o/n= overnight, o2s= over two steps).

Scheme 2. Synthesis of C_2-symmetric 1,3-bis(boronic ester) **3** and the precursor of the remaining fragments.

Alcohol **8** was then converted into carbamate **9** using established conditions.[21,22] Fragment coupling of the resulting carbamate **9** with C_2-symmetric 1,3-bis(boronic ester) **3** via the lithiation-borylation protocol gave the desired mono-product **10** in 17% yield (Scheme 3).



a. CbCl, Et_3N, $C_2H_4Cl_2$, 70 °C, o/n, 94%; b. sBuLi, (+)-sparteine, Et_2O, −78 °C, 5 h, then 3, $MgBr_2{\cdot}OEt_2$, Et_2O, −78 °C to Δ, o/n, 17%, *dr* ≥ 95:5 (Cb=*N,N*-diisopropylcarbamoyl).

Scheme 3. Synthesis of carbamate **9** and first generation fragment coupling.

Based on deprotonation experiments of carbamate **9** we observed that the H-D exchange was only 35% using the standard lithiation conditions. The best result was obtained with a lithiation time of 16 h and slightly increased equivalents of (+)-sparteine and *s*BuLi (Table 1). The use of different bases did not lead to lithiation or in the case of *i*PrLi only to moderate yields. Therefore, we switched to the corresponding TIB ester **11**[21,22] which could be completely lithiated under the standard conditions.

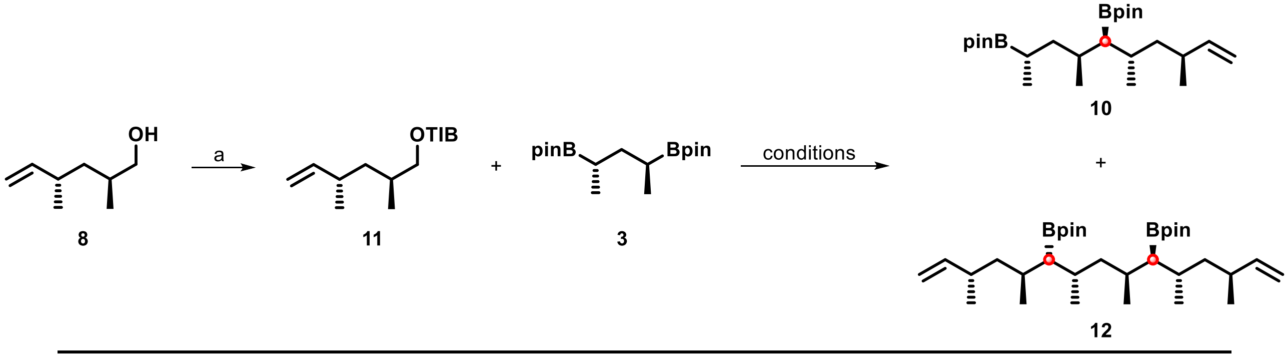
Table 1. Lithiation experiments

entry	substrate	base	lithiation time [h]	H-D-exchange [%][d]
1[a]	carbamate **9**	*s*BuLi	5	35
2[a]	carbamate **9**	*s*BuLi	13	35
3[b]	carbamate **9**	*s*BuLi	5	19
4[c]	carbamate **9**	*s*BuLi	16	56
5[a]	carbamate **9**	*t*BuLi	5	0
6[c]	carbamate **9**	*n*BuLi	22	0
7[c]	carbamate **9**	MeLi	8	0
8[c]	carbamate **9**	*i*PrLi	17	42
9[c]	TIB ester **11**	*s*BuLi	5	100

[a] Lithiation conditions: substrate (1.0 equiv.), (+)-sparteine (1.3 equiv.), base (1.3 equiv.), Et_2O, −78 °C, lithiation time, then D_2O (excess), −78 °C to rt, 0.5 h. [b] Base (1.8 equiv.). [c] (+)-Sparteine (1.6 equiv.), base (1.5 equiv.). [d] Determined by ^{1}H-NMR.

With an effective lithiation strategy in hands, we again performed the fragment coupling and obtained the desired 1,4-bis(boronic ester) **10** in 41% yield. Since the desired product was hard to separate from the double homologation product, we started to optimize the borylation step (Table 2). The addition of additives like Et_3N and PPh_3 which should form an ate-complex with one of the boronic esters did not improve the yield. Short time for ate-complex formation (1 h) increases the mono:di ratio in a significant way but an even shorter ate-complex formation (< 1 h) resulted in a remarkable drop of the yield.

Table 2. Optimization of first generation fragment coupling

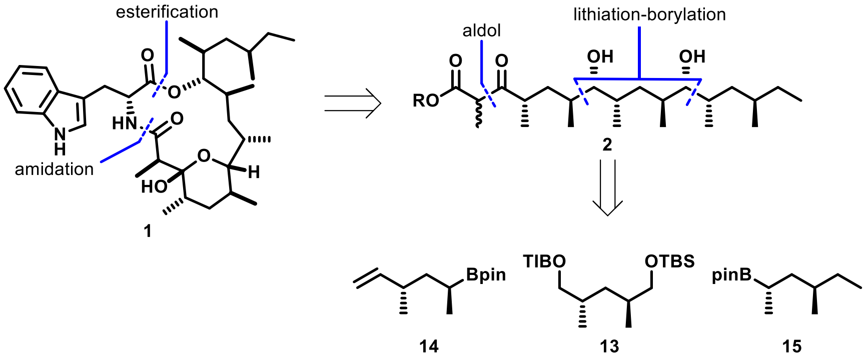


entry	additive	time ate-complex [h]	yield [%][b]	mono : di ratio[c]
1[a]	-	2.5	22	1.5:1
2[a]	Et_3N	1.5	20	1.7:1
3[a]	PPh_3	1.5	19	1.6:1
4[a]	-	1	41	4.1:1
5[a]	-	0.5	20	2.5:1

Table 2. Continued

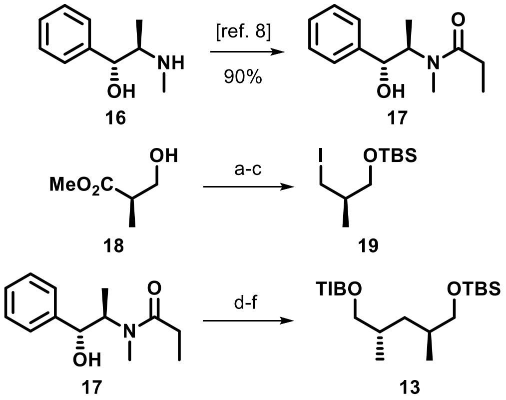
a DIAD, TIBOH, PPh_3, THF, 0 °C to rt, o/n, 94%. [a] reaction conditions: **11** (1.0 equiv.), (+)-sparteine (1.6 equiv.), *s*BuLi (1.5 equiv.), additive (1.5 equiv.), Et_2O, −78 °C, 5 h, then **3**, Et_2O, −78 °C to rt, o/n. [b] Isolated yield after flash column chromatography. [c] Based on the isolated yield (DIAD=Di*iso*propyl azodicarboxylate).

Due to the low yields and the impractical separation of the desired product **10** from the double homologation product, we reconsidered our retrosynthetic approach. In our second generation retrosynthesis we shifted the bonds formed via lithiation-borylation chemistry by one carbon atom each, making middle fragment **13** and mono-Zweifel product **14** the new target molecules (Scheme 4).



Scheme 4. Second generation retrosynthetic analysis of georatusin (**1**).

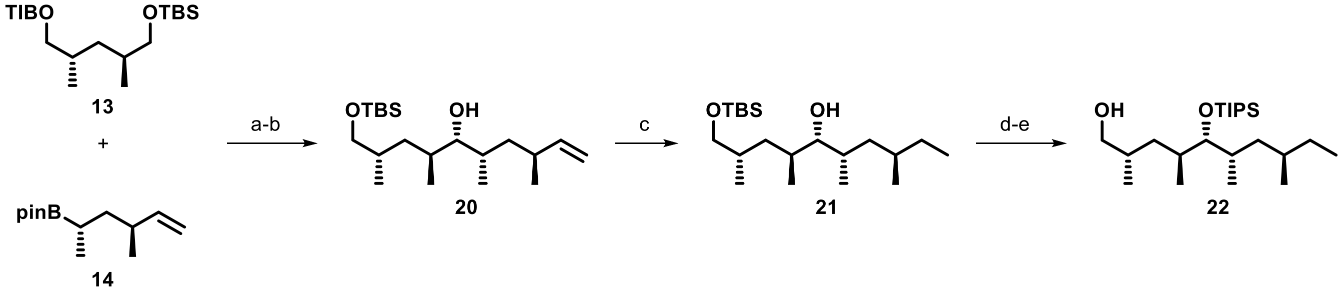
For the synthesis of the new middle fragment **13**, (−)-pseudoephedrine (**16**) was propionated.[23,24] Then, the (*R*)-Roche ester (**18**) was transformed into iodide **19** in a known three step sequence.[25] A literature known sequence consisting of Myers alkylation and reductive removal of the auxiliary gave us the corresponding alcohol[26] which was then converted into middle fragment **13** using a Mitsunobu reaction[22] (Scheme 5).



a. TBSCl, imid., CH_2Cl_2, 0 °C to rt, 2.5 h, 95%; b. D*i*BAl-H, CH_2Cl_2, −78 °C to −40 °C, 3.5 h, 92%; c. I_2, PPh_3, imid., CH_2Cl_2, 0 °C to rt, 2.5 h, 82%; d. LDA, LiCl, 19, THF, −78 °C to rt, o/n, *dr* ≥ 95:5; e. LDA, $BH_3{\cdot}NH_3$, THF, 0 °C to rt, 4.5 h, 81% o2s; f. DIAD, TIBOH, PPh_3, THF, 0 °C to rt, o/n, 87% (TBS=*tert*-Butyldimethylsilyl, imid=imidazole, LDA=lithium di*iso*propylamide).

Scheme 5. Synthesis of middle fragment **13**.

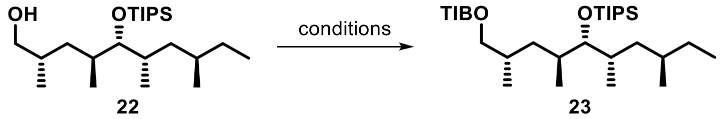
With middle fragment **13** and our mono-Zweifel product **14**[19] in hands, we investigated the new fragment coupling using lithiation-borylation chemistry. Secondary alcohol **20** was isolated in a good yield of 64% over two steps. The following hydrogenation with Wilkinson's catalyst proceeds smoothly to give us **21**. Our first intention was a PMB protection of secondary alcohol **21** that could not be performed employing different conditions. So, a two-step sequence of TIPS-protection and selective TBS-deprotection led to primary alcohol **22** (Scheme 6). With alcohol **22** in hands, next in line was another TIB-esterification[22] but unfortunately the best result we could achieve was a yield of 31% (Table 3). Higher temperatures for the Mitsunobu reaction as well as usage of TIB chloride led to decomposition.



a. *s*BuLi, (+)-sparteine, Et_2O, −78 °C, 5 h, then **14**, THF, −78 °C to Δ, o/n; b. H_2O_2, NaOH, THF, −20 °C to rt, 3 h, 64% o2s, *dr* ≥ 95:5; c. H_2, $[Ph_3P]_3RhCl$, PhH, rt, o/n, 95%, d. TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt, o/n, ≥ 95%; e. PPTS, $MeOH/CH_2Cl_2$, 45 °C, 1.5 h, 88% (PhH=benzene, TIPSOTf=triisopropylsilyl trifluoromethanesulfonate, PPTS=pyridinium *p*-toluenesulfonate).

Scheme 6. Second generation fragment coupling.

Table 3. Conditions for the second TIB-esterification



entry	conditions	Reagent	result
1	**22** (1.0 equiv.), PPh_3 (1.0 equiv.), DIAD (1.1 equiv.), THF, 0 °C to rt, 3 d	TIBOH (1.0 equiv.)	31%
2	**22** (1.0 equiv.), PPh_3 (1.0 equiv.), DIAD (1.1 equiv.), THF, 0 °C to 50 °C, o/n	TIBOH (1.0 equiv.)	10%
3	**22** (1.0 equiv.), NaH (1.5 equiv.), THF, 0 °C to 90 °C, o/n	TIBCl (1.5 equiv.)	decomp.
4	**22** (1.0 equiv.), NaH (1.5 equiv.), THF, 0 °C to 50 °C, o/n	TIBCl (1.5 equiv.)	decomp.

Conclusions

In conclusion, we have developed a rapid access to complex, highly reduced polyketide fragments using lithiation-borylation chemistry and our developed mono-Zweifel protocol.[19] With our strategy we were able to synthesize the C18-C27 fragment of the polyketide-peptide hybrid georatusin (**1**) in 8% over twelve steps in the longest linear sequence. Completion of the synthesis will be reported in due course.

Experimental Section

General methods. Unless otherwise noted all reactions were carried out under an argon atmosphere using a Drierite^{TM} gas-drying unit. The used glassware was flame dried under high vacuum. Air- and moisture-sensitive liquids and solutions were transferred via syringe flushed with argon prior to use. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Stated temperatures, except room temperature, refer to bath temperatures.

Dry solvents: Dichloromethane and all amine bases were distilled under an inert atmosphere over calcium hydride. Tetrahydrofuran, diethyl ether, methanol and 1,2-dichloroethane were purchased from Acros Organics over molecular sieves and under inert atmosphere. Benzene was bought from Sigma Aldrich.

(+)-Sparteine was purchased from Chem-Impex and was distilled under high vacuum and stored under argon at −25 °C.

Thin layer chromatography : All reactions were stirred magnetically and monitored using pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV$_{254}$ (0.2 mm, silica gel, F$_{254}$, aluminum-backed, MACHEREY-NAGEL) with detection by UV light (λ = 254 nm) and/or by staining with either basic potassium permanganate, acidic ceric ammonium molybdate or acidic vanillin stain.

Flash column chromatography was performed using silica gel (0.04-0.063 mm, 240-400 mesh) obtained from MACHEREY-NAGEL. The applied petroleum ether fraction had a bp of 40-60 °C. The eluent is given in volume ratios (v/v).

^{1}H-NMR experiments were recorded in $CDCl_3$ using either a DPX 400 (Bruker), an AMX 400 (Bruker), an Ascend 400 Avance III HD (Bruker) or an Ascend 600 MHz (Bruker). The spectra were calibrated using the residual solvent peak: $\delta(CDCl_3) = 7.26$ ppm. Chemical shift δ is given in parts per million (ppm), coupling constant J in hertz (Hz) and multiplicity as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; p, pentett; sex, sextet; sep, septet; m, multiplet; m$_c$, centered multiplet; bs, broad signal or combination of these acronyms. NMR spectra were processed using TopSpin (Bruker).

^{13}C-NMR experiments were recorded in $CDCl_3$ using either a DPX 400 (Bruker), an AMX 400 (Bruker), an Ascend 400 Avance III HD (Bruker) or an Ascend 600 MHz (Bruker). The spectra were calibrated using the residual solvent peak: $\delta(CDCl_3) = 77.16$ ppm. Chemical shift δ is given in parts per million (ppm). NMR spectra were processed using TopSpin (Bruker).

High Resolution Mass Spectra (HRMS) were obtained either using a Q-Tof Premier (Waters), a LCT Premier (Waters) or a GC-system Agilent 6890 coupled with an Agilent 5973. Both the masses found and the masses calculated are given.

Melting points were determined in °C using an OptiMelt MPA 100 (Stanford Research System).

Optical rotation [α_D^{20}] were measured either on a P3000 polarimeter (A. Krüss Optronic, λ = 589 nm) or a Perkin-Elmer 341 (λ = 589 nm). The sample concentration (in g/100 mL) is given with every single experiment.

Chiral HPLC was performed on a Merck/Hitachi L-7150 system with a Merck/Hitachi L-7400 UV-detector using a Daicel Chiralcel® OD-H column (4.6 x 250 mm, 5 µm). Further information can be found in the individual procedure.

The names of the compounds not shown were created using ChemDraw 19.1.

Ethyl 2,4,6-triisopropylbenzoate (24). Following Beak's procedure[27], a solution of TIBOH (**6**, 10.0 g, 40.3 mmol, 1.0 equiv.) in $CHCl_3$ (200 mL) was treated with a solution of NaOH (4.99 g, 125 mmol, 3.1 equiv.) and *n*Bu_4NHSO_4 (1.09 g, 3.22 mmol, 8 mol%) in H_2O (160 mL). After addition of ethyl bromide (15.0 mL, 21.9 g, 201 mmol, 5.0 equiv.) the biphasic reaction mixture was stirred overnight at rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was filtered through a short plug of silica using petroleum ether (PE):EtOAc (9:1) as eluent. The solvent was removed under reduced pressure to afford ethyl 2,4,6-tri*iso*propylbenzoate (**24**, 10.8 g, 38.9 mmol, ≥ 95%) as a yellow oil.

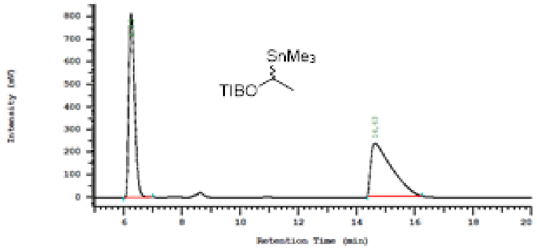
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.87 (m_c, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 7.0 Hz) and 1.24 (d, *J* = 7.0 Hz, 18H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.0, 150.2, 144.9, 130.8, 121.0, 60.9, 34.6, 31.6, 24.3, 24.1, 14.4 ppm; HRMS (ESI): $C_{18}H_{28}O_2Na$ $[M+Na]^+$ calculated: 299.1987, found: 299.1986; R_f = 0.6 (PE:EtOAc 10:1, UV, $KMnO_4$).

Analytical data are in accordance with the literature.[28]

Stannane 7. Ethyl 2,4,6-tri*iso*propylbenzoate (**24**, 5.00 g, 18.1 mmol, 1.0 equiv.) and (+)-sparteine (5.4 mL, 5.51 g, 23.5 mmol, 1.3 equiv.) were dissolved in Et_2O (90 mL). The solution was cooled to −78 °C, *s*BuLi (1.3 M in hexanes, 18.0 mL, 23.5 mmol, 1.3 equiv., 0.5 mL/min , color change: colorless → brown/purple) was added and the reaction mixture stirred for 5 h at this temperature. Then a freshly prepared solution of Me_3SnCl (1.0 M in Et_2O, 23.5 mL, 23.5 mmol, 1.3 equiv.) was added dropwise (color change: brown/purple → yellow/colorless) and the reaction mixture was stirred for 1 h at −78 °C before being warmed to rt. After 30 min at rt 5% aq. H_3PO_4 was added and the biphasic mixture was stirred for further 20 min. The organic layer was separated and washed with 5% aq. H_3PO_4 (3x). The combined aqueous layers were extracted with Et_2O (3x). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to afford a slightly yellow solid, which was then recrystallized from MeOH (3 mL/g) to give stannane **7** (5.55 g, 12.7 mmol, 70%, *er* 99:1) as colorless needles. The racemic sample was prepared by the use of tetramethylethylenediamine (TMEDA) instead of (+)-sparteine.

Sparteine-recovery: After adjusting the pH of the combined aqueous phases to 11 by using aq. 2.0 M NaOH, they were extracted with Et_2O (3x). The organic layers were combined, dried over K_2CO_3 and concentrated *in vacuo*. The residue was then distilled under high vacuum over calcium hydride (100 mg/g) at 150 °C to afford the respective enantiomer of sparteine (70-80%) as a colorless oil, which solidified in the freezer.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 2H), 5.08-5.00 (m, 1H), 2.92-2.80 (m, 3H), 1.68-1.51 (m, 3H), 1.24 (d, *J* = 6.9 Hz, 18H), 0.18 (s, d, *J* = 54.2 Hz and *J* = 51.6 Hz, 9H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.4, 150.1, 145.0, 130.9, 120.9, 67.2, 34.5, 31.5, 24.5, 24.2, 24.1, 19.4, −9.8 ppm; HRMS (ESI):$C_{21}H_{36}O_2SnNa$ $[M+Na]^+$ calculated: 463.1635, found: 463.1634; R_f = 0.9 (PE:EtOAc 95:5); $[\alpha_D{}^{20}]$ = –42.0 (*c* 1.0, $CHCl_3$); m.p. = 65 °C Chiral HPLC: (Daicel Chiracel® OD-H column (25 cm), hexanes, 0.7 mL/min, rt, 210 nm): t_R = 6.4 min (*S*), 14.6 min (*R*), *er* 1:99.



Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Conc 1	BC
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2	14,63	11584068	50,822	BB
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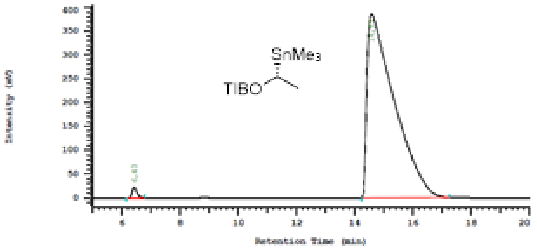

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Conc 1	BC
1	6,43	251399	0,994	BB
2	14,57	25035472	99,006	BB
		25286871	100,000	

Analytical data are in accordance with the literature.[18,28]

1,3-Bis(boronic ester) 3. Following Aggarwal's procedure[18], a stirred solution of stannane **7** (5.00 g, 11.4 mmol, 2.05 equiv.) in Et_2O (57 mL) at −78 °C was treated with *n*BuLi (1.6 M in hexanes, 7.0 mL, 11.1 mmol, 2.0 equiv., 0.5 mL/min). The reaction mixture was stirred for 1.5 h at this temperature. Then a solution of $pinBCH_2Bpin$[29] (1.49 g, 5.56 mmol, 1.0 equiv., 0.5 mL/min) in Et_2O (11.0 mL) was added. After 2.5 h at this temperature, the reaction mixture was warmed to rt and stirred overnight. H_2O and Et_2O were added and the organic layer was separated. The aqueous phase was extracted with Et_2O (3x), the organic layers were combined and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material purified by flash column chromatography (PE:EtOAc 98:2) to afford C_2-symmetric 1,3-bis(boronic ester) **3** (1.47 g, 4.54 mmol, 82%, *dr* ≥ 95:5). as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.8 Hz, 2H), 1.23 (s, 24H), 1.12-1.03 (m, 2H), 0.93 (d, *J* = 7.4 Hz, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 82.9, 36.1, 24.90, 24.89, 15.5 ppm (carbon attached to boron not observed); HRMS (ESI): $C_{17}H_{34}B_2O_4Na$ $[M+Na]^+$ calculated: 347.2541, found: 347.2542; R_f = 0.3 (PE:EtOAc 9:1, CAN); $[\alpha_D^{20}]$ = +10.5 (*c* 1.0, $CHCl_3$);

Analytical data are in accordance with the literature.[18]

Mono-Zweifel product 14. To a stirred solution of 1,3-bis(boronic ester) **3** (100 mg, 0.31 mmol, 1.0 equiv.) in THF (1.5 mL) at −78 °C, was added vinylMgBr (1.0 M in THF, 0.52 mL, 0.52 mmol, 1.7 equiv., 0.5 mL/min) and stirring was continued for 30 min at this temperature. Then the solution was warmed to rt and stirred for further 30 min. After cooling to −78 °C, iodine (313 mg, 1.23 mmol, 4.0 equiv.) was added in two portions over a period of 5 min. MeOH (2.5 mL, 0.15 mL/min) was added to the dark solution and the reaction mixture was stirred for 30 min. Then, a suspension of NaOMe (1.0 M in MeOH, 2.5 mL, 2.50 mmol, 8.0 equiv., 0.5 mL/min) was added and the red reaction mixture was stirred for further 30 min at −78 °C. After warming to rt, the black reaction mixture was stirred overnight. Methyl *tert*-butyl ether (MTBE) and sat. aq. $Na_2S_2O_3$ were added until the dark color disappeared. The phases were separated and the aqueous phase was extracted with MTBE (3x). The combined organic phases were washed with sat. aq. NaCl and dried over Na_2SO_4, concentrated *in vacuo* and the crude residue was purified by flash column chromatography (PE:MTBE 98:2 → 9:1) to afford mono-Zweifel product **14** (33 mg, 0.15 mmol, 48%, 94% brsm[a,b]) as a yellow oil and reisolated 1,3-bis(boronic ester) **3** (48 mg, 0.15 mmol) as a slightly yellow oil.

[a] At a 5.99 mmol scale (1.94 g) of 1,3-bis(boronic ester) **3** mono-Zweifel product **14** was obtained in 35% (470 mg, 2.10 mmol, 81% brsm).

[b] After three cycles mono-Zweifel product **14** was obtained in 62% (831 mg, 3.71 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.68 (m_c, 1H), 4.98-4.87 (m, 2H), 2.23-2.12 (m, 1H), 1.49-1.41 (m, 1H), 1.30-1.25 (m, 1H), 1.24 (s, 12H), 1.12-1.03 (m, 1H), 0.98-0.92 (m, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.2, 112.6, 82.9, 40.4, 37.2, 24.90, 24.85, 20.3, 15.8 ppm (carbon attached to boron not observed); HRMS (EI): $C_{13}H_{25}BO_2$ $[M]^{\bullet+}$ calculated: 224.1948, found: 224.1947; R_f = 0.4 (PE:MTBE 97:3, $KMnO_4$); $[\alpha_D^{20}]$ = +14.5 (*c* 1.2, $CHCl_3$). Analytical data are in accordance with the literature.[4]

Alcohol 8. Mono-Zweifel product **14** (90.0 mg, 0.40 mmol, 1.0 equiv.) and bromochloromethane (0.08 mL, 156 mg, 1.20 mmol, 3.0 equiv.) were dissolved in Et_2O (2.0 mL) and cooled to −78 °C. Then, *n*BuLi (1.6 M in hexanes, 0.63 mL, 1.00 mmol, 2.5 equiv., 20 µL/min) was added and the reaction mixture was stirred for 20 min at that temperature. After warming to rt, the cloudy reaction mixture was stirred overnight. The reaction mixture was then filtered through a short plug of silica using Et_2O as eluent. The solvent was removed *in vacuo*, the residue was dissolved in THF (3.0 mL) and cooled to 0 °C. A premixed solution of NaOH (3.0 M)/H_2O_2 (35%, 2/1 v/v, 4.5 mL) was added dropwise. The reaction mixture was stirred for 1.5 h at rt before being quenched by addition of sat. aq. $Na_2S_2O_3$ at 0 °C. The solution was diluted with MTBE, the phases were separated and the aqueous phase was extracted with MTBE (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane:Et_2O 5:1) to afford alcohol **8** (35 mg, 0.27 mmol, 68% o2s) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.77-5.66 (m, 1H), 5.01-4.88 (m, 2H), 3.57-3.39 (m, 2H), 2.29-2.20 (m, 1H), 1.75-1.66 (m, 1H), 1.36-1.29 (m, 1H), 1.25 (bs, 1H), 1.19-1.11 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.2, 112.5, 68.3, 40.3, 35.3, 33.4, 20.2, 17.1 ppm; HRMS (EI): C_7H_{13} $[M-CH_3O]^+$ calculated: 97.1017, found: 97.1017; R_f = 0.3 (pentane:Et_2O 5:1, $KMnO_4$); $[\alpha_D^{20}]$ = +3.9 (*c* 0.7, $CHCl_3$).

Carbamate 9. A solution of alcohol **8** (200 mg, 1.56 mmol, 1.0 equiv.) in 1,2-dichloroethane (5.2 mL) was treated with Et_3N (0.32 mL, 2.34 mmol, 1.5 equiv.) and CbCl (383 mg, 2.34 mmol, 1.5 equiv.). The reaction mixture was stirred overnight at 70 °C. H_2O and CH_2Cl_2 were added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane:Et_2O 95:5) to give carbamate **9** (372 mg, 1.46 mmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.75-5.65 (m, 1H), 5.01-4.89 (m, 2H), 4.19-3.65 (m, 4H), 2.30-2.19 (m, 1H), 1.93-1.81 (m, 1H), 1.39-1.32 (m, 1H), 1.25-1.16 (m, 13H), 0.98-0.94 (m, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 156.2, 145.0, 112.7, 69.6, 45.6 (bs), 40.7, 35.3, 30.7, 21.0 (bs), 20.3, 17.9 ppm; HRMS (ESI): $C_{15}H_{29}NO_2Na$ $[M+Na]^+$ calculated: 278.2096, found: 278.2095; R_f = 0.3 (pentane:Et_2O 95:5, $KMnO_4$); $[\alpha_D^{20}]$ = +6.3 (*c* 1.0, $CHCl_3$).

TIB ester 11. Alcohol **8** (300 mg, 2.34 mmol, 1.0 equiv.) was dissolved in anhydrous THF (7.8 mL) and PPh_3 (614 mg, 2.34 mmol, 1.0 equiv.) and TIBOH (**6**, 639 mg, 2.57 mmol, 1.1 equiv.) were added successively. After cooling to 0 °C, DIAD (0.51 mL, 2.57 mmol, 1.1 equiv., 0.12 mL/min) was added, the reaction mixture was slowly warmed to rt and stirred overnight at that temperature. Et_2O and sat. aq. $NaHCO_3$ were added and the phases separated. The aqueous phase was extracted with Et_2O (3x), the organic layers combined and dried over Na_2SO_4. The solvent was removed *in vacuo* to leave a crude oil, which was then triturated with PE. The white suspension was filtered through a short plug of silica using PE:EtOAc (9:1) as eluent. The solvent was removed under reduced pressure and the residue was further purified by flash column chromatography (PE:EtOAc 98:2) to afford TIB ester **11** (792 mg, 2.21 mmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 2H), 5.68 (m_c, 1H), 4.95 (m_c, 2H), 4.16 (m_c, 2H), 2.93-2.81 (m, 3H), 2.26 (m_c, 1H), 1.95 (m_c, 1H), 1.43-1.36 (m, 1H), 1.27-1.17 (m, 19H), 0.98 (d, *J* = 5.2 Hz, 3H), 0.97 (d, *J* = 5.1 Hz, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.4, 150.1, 144.9, 144.7, 130.9, 121.0, 112.9, 69.8, 40.3, 35.4, 34.6, 31.7, 30.3, 24.3, 24.1, 20.3, 17.6 ppm; HRMS (ESI): $C_{24}H_{38}O_2Na$ $[M+Na]^+$ calculated: 381.2770, found: 381.2771; R_f = 0.3 (PE:EtOAc 98:2, UV, $KMnO_4$); $[\alpha_D^{20}]$ = −8.0 (*c* 0.5, $CHCl_3$).

1,4-bis(boronic ester) 10. To a stirred solution of TIB ester **11** (78 mg, 0.22 mmol, 1.0 equiv.) and (+)-sparteine (0.08 mL, 0.35 mmol, 1.6 equiv.) in Et_2O (1.1 mL) at −78 °C was added *s*BuLi (1.3 M in hexanes, 0.25 mL, 0.32 mmol, 1.5 equiv., 0.5 mL/min). The brown reaction mixture was stirred for 5 h at that temperature before a solution of 1,3-bis(boronic ester) **3** (105 mg, 0.32 mmol, 1.5 equiv.) in Et_2O (0.43 mL, 0.5 mL/min) was added. After stirring for further 1 h at −78 °C, the yellow reaction mixture was warmed to rt and stirred overnight. The reaction mixture was cooled to rt and HCl (2.0 M) was added and the biphasic mixture was stirred for 10 min. The phases were separated, the organic layer was washed with HCl (2.0 M, 3x) and the combined aqueous phases were extracted with Et_2O (3x). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → PE:EtOAc 200:1 → 100:1 → 98:2 → 95:5) to afford 1,4-bis(boronic ester) **10** (37 mg, 0.09 mmol, 41%, *dr* ≥ 95:5) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82-5.72 (m, 1H), 4.98-4.82 (m, 2H), 2.26-2.16 (m, 1H), 1.84-1.72 (m, 2H), 1.31-1.27 (m, 2H), 1.26-1.20 (m, 24H), 1.19-1.08 (m, 4H), 0.97-0.90 (m, 6H), 0.88-0.83 (m, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 146.3, 111.2, 82.8, 82.8, 43.9, 40.7, 35.2, 30.2, 29.4, 25.4, 25.1, 24.9, 24.9, 18.9, 18.6, 17.6, 15.7 ppm (carbon attached to boron not observed); HRMS (ESI): $C_{25}H_{48}B_2O_4Na$ $[M+Na]^+$ calculated: 457.3636, found: 457.3636; R_f = 0.5 (PE:EtOAc 95:5, vanillin); $[\alpha_D^{20}]$ = −6.1 (*c* 0.2, $CHCl_3$).

Methyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (25). (*R*)-Roche ester (**18**, 4.0 mL, 36.3 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (360 mL) and the resulting solution was cooled to 0 °C. Imidazole (3.70 g, 54.4 mmol, 1.5 equiv.) and TBSCl (6.56 g, 43.5 mmol, 1.2 equiv.) were added successively and stirring was continued for 30 min at 0 °C. After warming to rt the reaction mixture was stirred for 2 h before sat. aq. NH_4Cl and H_2O were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (PE:Et_2O 15:1) to afford Methyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (**25**, 8.03 g, 34.6 mmol, 95%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 3.78-3.76 (m, 1H), 3.67-3.63 (m, 4H), 2.65 (m_c, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.04-0.03 (m, 6H) ppm; ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 175.6, 65.4, 51.6, 42.7, 25.9, 18.4, 13.6, −5.4; HRMS (ESI): $C_{11}H_{24}O_3SiNa$ $[M+Na]^+$ calculated: 255.1392, found: 255.1391; R_f = 0.6 (PE:Et_2O 10:1, $KMnO_4$); $[\alpha_D^{20}]$ = −17.8 (*c* 1.0, $CHCl_3$).

Analytical data are in accordance with the literature.[25]

(*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-1-ol (26). Methyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (**25**, 4.00 g, 17.2 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (85 mL) and the resulting solution was cooled to −78 °C. After the addition of D*i*BAl-H (1.0 M in CH_2Cl_2, 43 mL, 43.0 mmol, 2.5 equiv., 0.8 mL/min), the reaction mixture was warmed to −40 °C and stirred at that temperature for 3.5 h. MeOH (8.5 mL) and sat. aq. potassium sodium tartrate (105 mL) were slowly added. After warming to rt, the mixture was stirred vigorously overnight. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-1-ol (**26**, 3.25 g, 15.9 mmol, 92%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 3.74 (m_c, 1H), 3.66-3.58 (m, 2H), 3.54 (m_c, 1H), 2.80 (m_c, 1H), 1.94 (m_c, 1H), 0.90 (s, 9H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 6H) ppm; ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 69.0, 68.5, 37.2, 26.0, 18.3, 13.2, −5.4, −5.5; HRMS (ESI): $C_{10}H_{24}O_2SiNa$ $[M+Na]^+$ calculated: 227.1443, found: 227.1442; R_f = 0.4 (PE:MTBE 10:1, $KMnO_4$); $[\alpha_D^{20}]$ = −8.5 (*c* 1.0, $CHCl_3$).

Analytical data are in accordance with the literature.[25]

Iodide 19. In the darkness, a solution of the obtained (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-1-ol (**26**, 1.50 g, 7.34 mmol, 1.0 equiv.) in CH_2Cl_2 (15.0 mL) was treated with PPh_3 (2.50 g, 9.54 mmol, 1.3 equiv.)

and imidazole (0.75 g, 11.0 mmol, 1.5 equiv.) successively. After cooling to 0 °C, iodine (2.51 g, 9.91 mmol, 1.35 equiv.) was added in eight portions over a period of 30 min. The reaction mixture was warmed to rt and stirred for further 2.5 h before being quenched at 0 °C by the addition of sat. aq. $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with sat. aq. $Na_2S_2O_3$ (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE:Et_2O 95:5) to afford iodide **19** (1.90 g, 6.05 mmol, 82%) as a slightly yellow oil. The iodide was used in the next step without detailed characterization.

(2*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2,4-trimethylpentanamide (27). Lithium chloride (3.08 g, 72.6 mmol, 13.5 equiv.) was flame dried under high vacuum and purged with argon. Then, THF (22.5 mL) and di*iso*propylamine (3.0 mL, 21.5 mmol, 4.0 equiv.) were added. After cooling to −78 °C, *n*BuLi (1.6 M in hexanes, 13.0 mL, 20.4 mmol, 3.8 equiv., 0.5 mL/min) was added and the reaction mixture was stirred for 10 min at −78 °C and then for 5 min at 0 °C. Then, a solution of Myers auxiliary **17**[8] (2.38 g, 10.8 mmol, 2.0 equiv.) in THF (30 mL, 2.0 mL/min) was added at −78 °C. The reaction mixture was stirred for 1 h at this temperature before being warmed to 0 °C and stirred for further 30 min. Finally, the reaction mixture was warmed to rt and stirred for another 5 min. After cooling to 0 °C, a solution of iodide **19** (1.69 g, 5.38 mmol, 1.0 equiv.) in THF (5.4 mL, 1.0 mL/min) was added. The reaction mixture was slowly warmed to rt and stirred overnight at this temperature. Sat. aq. NH_4Cl and EtOAc were added at 0 °C and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (PE:EtOAc 3:1) to afford (2*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2,4-trimethylpentanamide (**27**) as a colorless oil (mixture of amide bond rotamers, 4.5:1, NMR), which was directly used in the next step without further characterization.

(2*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (28). To a stirred solution of di*iso*propylamine (3.1 mL, 22.2 mmol, 4.3 equiv.) in THF (21.0 mL) was added *n*BuLi (1.6 M in hexanes, 13.0 mL, 20.6 mmol, 4.0 equiv.) at −78 °C. After stirring for 10 min at this temperature, the solution was warmed to 0 °C and stirred for further 10 min. Then borane-ammonia complex (0.72 g, 23.2 mmol, 4.5 equiv.) was added in three portions over a period of 5 min and the reaction mixture was allowed to stir for 15 min at 0 °C before being warmed to rt and stirred for further 15 min. After cooling to 0 °C a solution of the obtained (2*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2,4-trimethylpentanamide (**27**, 1.0 equiv.) in THF (26 mL) was added. The reaction mixture was slowly warmed to rt and stirred for 4.5 h at that temperature before being cooled to 0 °C. Sat. aq. NH_4Cl and MTBE were added. The organic layer was separated and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with sat. aq. NH_4Cl (1x) and sat. aq. NaCl (1x), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude material by flash column chromatography (PE:Et_2O 4:1) afforded (2*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (**28**, 1.07 g, 4.34 mmol, 81% o2s, *dr* ≥ 95:5) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.50-3.37 (m, 4H), 1.81-1.66 (m, 2H), 1.48 (bs, 1H), 1.27-1.10 (m, 2H), 0.90-0.88 (m, 12H), 0.86 (d, J = 6.7 Hz, 3H), 0.04 (s, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 69.18, 69.16, 37.0, 33.2, 33.1, 26.1, 18.5, 16.8, 16.6, −5.2 ppm; HRMS (ESI): $C_{13}H_{30}O_2SiNa$ $[M+Na]^+$ calculated: 269.1913, found: 269.1913; R_f = 0.3 (PE:EtOAc 3:1, $KMnO_4$); $[\alpha_D^{20}]$ = −16.3 (*c* 1.0, $CHCl_3$).

Analytical data are in accordance with the literature.[26]

TIB ester 13. (2*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (**28**, 1.06 g, 4.30 mmol, 1.0 equiv.) was dissolved in anhydrous THF (14.5 mL) and PPh_3 (1.13 g, 4.30 mmol, 1.0 equiv.) and TIBOH (**6**, 1.17 g, 4.73 mmol, 1.1 equiv.) were added successively. After cooling to 0 °C, DIAD (0.93 mL, 4.73 mmol, 1.1 equiv., 0.12 mL/min) was added, the reaction mixture was slowly warmed to rt and stirred overnight at that temperature. Et_2O and sat. aq. $NaHCO_3$ were added and the phases were separated. The aqueous phase was extracted with Et_2O (3x), the combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* to leave a crude oil which was then triturated with PE. The white suspension was filtered through a short plug of silica using PE:EtOAc (9:1) as eluent. The solvent was removed under reduced pressure and the crude material was further purified by flash column chromatography (PE:EtOAc 99:1) to afford TIB ester **13** (1.79 g, 3.75 mmol, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.00 (s, 2H), 4.13 (dd, *J* = 6.3, 2.4 Hz, 2H), 3.40 (m_c, 2H), 2.94-2.80 (m, 3H), 2.02-1.94 (m, 1H), 1.75-1.67 (m, 1H), 1.31-1.14 (m, 20H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): *δ* = 171.3, 150.1, 144.9, 130.9, 121.0, 70.8, 68.9, 37.1, 34.6, 33.1, 31.7, 30.1, 26.1, 24.4, 24.1, 18.5, 16.9, 16.5, −5.2 ppm; HRMS (ESI): $C_{29}H_{52}O_3SiNa$ $[M+Na]^+$ calculated: 499.3583, found: 499.3582; R_f = 0.6 (PE:EtOAc 95:5, UV, $KMnO_4$); $[\alpha_D^{20}]$ = −13.3 (*c* 0.5, $CHCl_3$).

Alcohol 20. To a stirred solution of TIB ester **13** (450 mg, 0.94 mmol, 1.0 equiv.) and (+)-sparteine (0.35 mL, 1.51 mmol, 1.6 equiv.) in Et_2O (3.8 mL) at −78 °C was added *s*BuLi (1.3 M in hexanes, 1.1 mL, 1.42 mmol, 1.5 equiv., 0.5 mL/min). The brown reaction mixture was stirred for 5 h at that temperature before a solution of mono-Zweifel product **14** (296 mg, 1.32 mmol, 1.4 equiv.) in THF (2.6 mL, 0.5 mL/min) was added. After stirring for further 2 h at −78 °C, the yellow reaction mixture was warmed to 40 °C and stirred overnight. The reaction mixture was cooled to rt, aq. 5% H_3PO_4 was added and the biphasic mixture was stirred for 20 min. The phases were separated, the organic layer was washed with aq. 5% H_3PO_4 (3x) and the combined aqueous phases were extracted with MTBE (3x). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The orange residue was dissolved in THF (4.8 mL) and cooled to −20 °C. A premixed solution of NaOH (2.0 M)/H_2O_2 (35%, 2/1 v/v, 3.8 mL) was added dropwise. The reaction mixture was stirred for 2 h at rt before being quenched by the addition of sat. aq. $Na_2S_2O_3$ at 0 °C. The solution was diluted with MTBE, the phases were separated and the aqueous phase was extracted with MTBE (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE:EtOAc 97:3 → 95:5) to afford alcohol **20** (207 mg, 0.60 mmol, 64% o2s, *dr* ≥ 95:5) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 5.68 (m_c, 1H), 4.97-4.89 (m, 2H), 3.41 (d, *J* = 6.5 Hz, 2H), 3.17-3.15 (m, 1H), 2.24 (m_c, 1H), 1.78-1.59 (m, 3H), 1.50 (bs, 1H), 1.41-1.32 (m, 2H), 1.25-1.17 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.86-0.80 (m, 9H), 0.05 (s, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): *δ* = 145.3, 112.5, 78.6, 69.7, 41.2, 36.5, 35.3, 33.7, 33.2, 32.2, 26.1, 20.4, 18.6, 16.7, 16.1, 13.3, −5.2 ppm; HRMS (ESI): $C_{20}H_{42}O_2SiNa$ $[M+Na]^+$ calculated: 365.2852, found: 365.2849; R_f = 0.3 (PE:EtOAc 95:5, vanillin); $[\alpha_D^{20}]$ = −19.2 (*c* 0.5, $CHCl_3$).

Alcohol 21. Through a solution of Wilkinson's catalyst (108 mg, 0.12 mmol, 20 mol%) in benzene (3.0 mL) were bubbled three balloons of H_2. The dark red solution was stirred for 1.5 h at rt under an atmosphere of H_2 while the solution turned orange to yellow. After the addition of alcohol **20** (200 mg, 0.58 mmol, 1.0 equiv.) in PhH (3.0 mL), the reaction mixture was stirred overnight. The solvent was removed and the crude residue was purified by flash column chromatography (PE:EtOAc 98:2) to give alcohol **21** (190 mg, 0.55 mmol, 95%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 3.40 (dd, *J* = 6.4, 1.1 Hz, 2H), 3.10 (m_c, 1H), 1.78-1.62 (m, 3H), 1.48-1.05 (m, 8H), 0.90 (s, 9H), 0.87-0.83 (m, 15H), 0.04 (s, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): *δ* = 80.6, 69.7, 41.5, 35.7, 33.4, 33.3, 32.3, 31.7, 30.5, 26.1, 19.1, 18.5, 16.5, 16.4, 13.1, 11.5, −5.2 ppm; HRMS (ESI): $C_{20}H_{44}O_2SiNa$ $[M+Na]^+$ calculated: 367.3008, found: 367.3008; R_f = 0.3 (PE:EtOAc 95:5, vanillin); $[\alpha_D^{20}]$ = −38.2 (*c* 0.6, $CHCl_3$).

(6*S*,8*S*,9*R*)-11,11-diisopropyl-2,2,3,3,6,8,12-heptamethyl-9-((2*S*,4*R*)-4-methylhexan-2-yl)-4,10-dioxa-3,11-disilatridecane (29). Alcohol **21** (90 mg, 0.26 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2.4 mL) and the solution was cooled to −78 °C. 2,6-Lutidine (0.18 mL, 1.57 mmol, 6.0 equiv.) and TIPSOTf (0.28 mL, 1.04 mmol, 4.0 equiv.) were added successively and the reaction mixture was warmed to rt and stirred at that temperature overnight. Sat. aq. $NaHCO_3$ and MTBE were added, the phases separated and the aqueous phase was extracted with MTBE (3x). The combined organic phases were washed with sat. aq. $NaHSO_4$ and sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. Further Purification of the crude material by flash column chromatography (PE) afforded (6*S*,8*S*,9*R*)-11,11-di*iso*propyl-2,2,3,3,6,8,12-heptamethyl-9-((2*S*,4*R*)-4-methylhexan-2-yl)-4,10-dioxa-3,11-disilatridecane (**29**, 128 mg, 0.26 mmol, ≥ 95%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.53-3.51 (m, 1H), 3.39-3.38 (m, 2H), 1.79-1.60 (m, 3H), 1.40-1.22 (m, 5H), 1.19-1.12 (m, 2H), 1.08 (s, 21H), 0.89-0.81 (m, 24H), 0.03 (s, 6H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 81.6, 69.5, 43.0, 36.9, 36.2, 33.5, 32.9, 31.9, 30.8, 26.1, 18.9, 18.61, 18.57, 18.5, 16.2, 15.6, 15.0, 13.5, 11.6, −5.2 ppm; HRMS (ESI): $C_{26}H_{57}O_2Si_2Na$ $[M-C_3H_7+Na]^+$ calculated: 457.3897, found: 457.3893; R_f = 0.5 (PE, $KMnO_4$); $[\alpha_D^{20}]$ = −18.0 (*c* 0.5, $CHCl_3$).

Alcohol 22. To a stirred solution of (6*S*,8*S*,9*R*)-11,11-di*iso*propyl-2,2,3,3,6,8,12-heptamethyl-9-((2*S*,4*R*)-4-methylhexan-2-yl)-4,10-dioxa-3,11-disilatridecane (**29**, 120 mg, 0.24 mmol, 1.0 equiv.) in CH_2Cl_2/MeOH (1/1, v/v, 2.4 mL) was added PPTS (66 mg, 0.26 mmol, 1.1 equiv.). The reaction mixture was heated to 45 °C and stirred at that temperature for 1 h. Sat. aq. $NaHCO_3$ and EtOAc were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was further purified by flash column chromatography (PE:EtOAc 93:7) to afford primary alcohol **22** (80 mg, 0.21 mmol, 88%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.53 (m_c, 1H), 3.45 (m_c, 2H), 1.83-1.63 (m, 3H), 1.40-1.03 (m, 28H), 0.92-0.81 (m, 15H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 81.6, 69.6, 42.9, 36.8, 36.1, 33.6, 33.0, 32.0, 30.8, 18.9, 18.61, 18.56, 16.1, 15.7, 15.0, 13.5, 11.6 ppm; HRMS (ESI): $C_{23}H_{50}O_2SiNa$ $[M+Na]^+$ calculated: 409.3478, found: 409.3480; R_f = 0.3 (PE:EtOAc 93:7, CAN); $[\alpha_D^{20}]$ = −20.0 (*c* 0.6, $CHCl_3$).

TIB ester 23. Alcohol **22** (50 mg, 0.13 mmol, 1.0 equiv.) was dissolved in anhydrous THF (0.43 mL) and PPh_3 (34 mg, 0.13 mmol, 1.0 equiv.) and TIBOH (**6**, 32 mg, 0.13 mmol, 1.0 equiv.) were added successively. After cooling to 0 °C, DIAD (28 µL, 0.14 mmol, 1.1 equiv.) was added, the reaction mixture was slowly warmed to rt and stirred for 3 d at that temperature. Et_2O and sat. aq. $NaHCO_3$ were added and the phases separated. The aqueous phase was extracted with Et_2O (3x), the organic layers combined and dried over Na_2SO_4. The solvent was removed *in vacuo* to leave a crude oil which was then triturated with PE. The white suspension was filtered through a short plug of silica using PE:EtOAc (9:1) as eluent. The solvent was removed under reduced pressure and the crude material was further purified by flash column chromatography (PE:EtOAc 98:2) to afford TIB ester **23** (25 mg, 0.04 mmol, 31%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 2H), 4.13 (m_c, 2H), 3.54 (m_c, 1H), 2.94-2.80 (m, 3H), 2.00-1.89 (m, 1H), 1.85-1.66 (m, 2H), 1.41-1.12 (m, 24H), 1.08-1.04 (m, 22H), 0.97-0.79 (m, 15H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.3, 150.1, 144.9, 130.9, 121.0, 81.4, 71.2, 43.0, 37.2, 36.2, 34.6, 32.9, 31.9, 31.7, 30.7, 30.3, 24.3, 24.1, 18.9, 18.6, 18.5, 16.5, 15.6, 14.9, 13.5, 11.6 ppm; HRMS (ESI): $C_{39}H_{72}O_3SiNa$ $[M+Na]^+$ calculated: 639.5148, found: 639.5148; R_f = 0.3 (PE:EtOAc 95:5, UV, $KMnO_4$); $[\alpha_D^{20}]$ = −18.0 (*c* 0.9, $CHCl_3$).

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Supplementary Material

^{1}H-NMR and ^{13}C-NMR spectra associated with this article are available as supplementary data.

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