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Full Paper

Amino Acid Synthesis

Stereoselective Synthesis of the β-Amino Acid Moiety of Fijiolide A

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Abstract: An enantioselective synthesis of the β-amino acid moiety of fijiolide A is described. Starting from eugenol, two sulfamates could be obtained on gram scale as substrates for an enantioselective C–H amination using Rh_2(*R*/*S*-nap)$_4$. Acylation and ring opening of the resulting oxathiazinanes, followed by stepwise oxidation of the corresponding amino alcohol and TES-protection of the catechol gave rise to Cramer's amino acid fragment from the total synthesis of fijiolide A.

Introduction

C-1027 chromophore (**1**) and its cyclization derived counterparts fijiolide A and B (**2**) are highly bioactive compounds which are furthermore intriguing due to their unique geometric complexity. While the biological activity of **1** can be mainly attributed to the DNA-damaging abilities of a biradical intermediate resulting via Bergmann-cyclization,[1] the fijiolides A and B were found to be potent inhibitors of TNF-α-induced NFκB activation.[2] Structurally, they both consist of an enediyne (derived) core, a glycosylated amino sugar and a 3′-chloro-5′-hydroxy-β-tyrosine, while C-1027 also features a benzoxazinone moiety at the diol *ansa*-bridge (Figure 1).

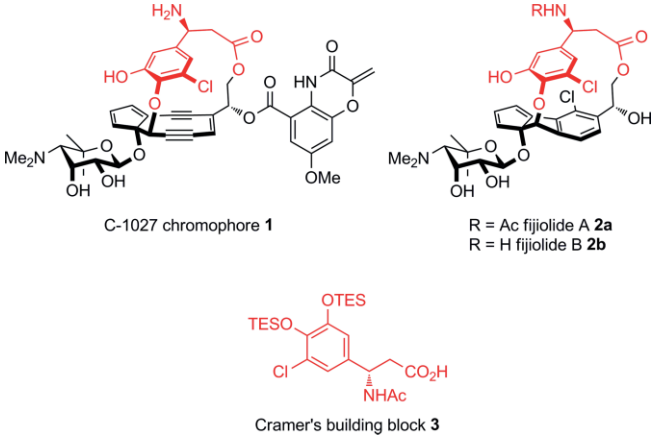
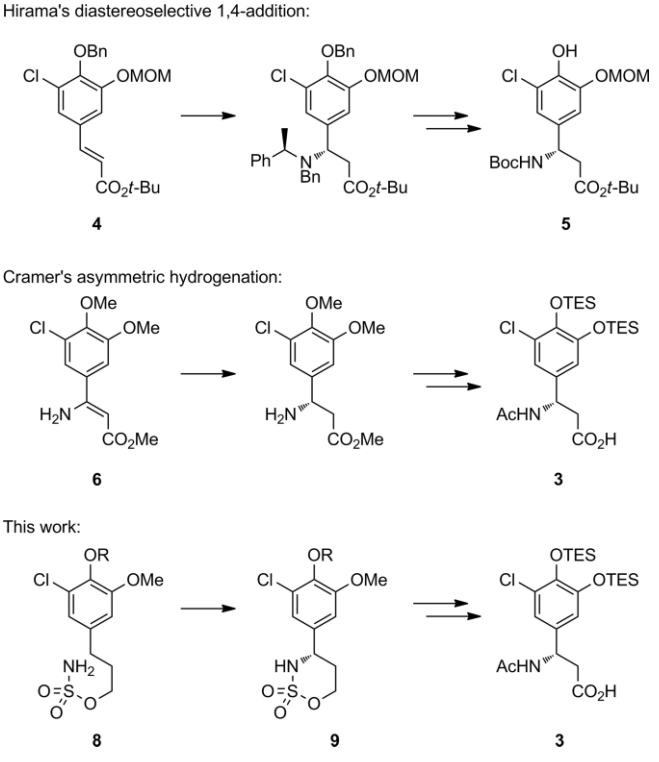


Figure 1. The C-1027 chromophore, the fijiolides and their β-tyrosine unit.

A stereoselective route to the benzodihydropentalene core of the fijiolides was published recently from this laboratory.[3] Here, a stereoselective synthesis of compound **3**, the β-amino acid moiety of fijiolide A is described starting from readily available eugenol.

The stereoselective synthesis of β-amino acids is an intensively studied area.[4] Previous synthetic work by Hirama[5] and Cramer[6] relied on diastereomeric 1,4-addition of Davies lithium amide to cinnamic acid ester **4** to yield **5** or asymmetric hydrogenation of respective enamine **6** which was transformed into amino acid **3** (Scheme 1). Our synthetic plan for amino acid **3** is based on oxidative ring opening of oxathiazinane **9**, which could be obtained by enantioselective C–H amination of sulf-



Scheme 1. Previous synthetic strategies and present approach.

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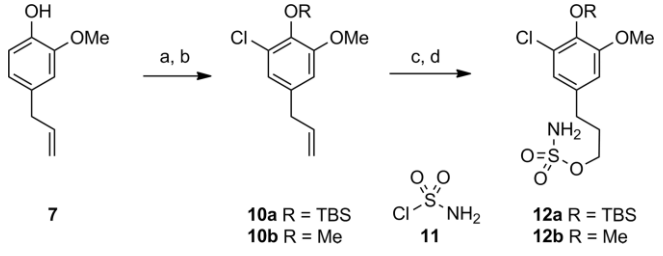
amate **8**. Sulfamate **8** itself origins from eugenol (**7**) via chlorination, hydroboration and subsequent sulfamoylation.

Results and Discussion

Synthesis of the sulfamate started with oxychlorination of eugenol (**7**), following a procedure of Gusevskaya.[7] For the purpose of orthogonal protection of the amino acids' catechol, the remaining phenol was TBS-protected to yield **10a**. Subsequent hydroboration with oxidative work up gave the corresponding alcohol, which was sulfamoylated with in situ formed sulfamoyl chloride[8] **11** to furnish sulfamate **12a** in 49 % yield on gram-scale starting from eugenol (**7**). Cramer's synthesis of fijiolide A (**2a**) demonstrated that the best atropselectivities in the cyclophane formation were obtained with the unprotected catechol.[6] Therefore a second methyl ether was installed onto the chlorinated eugenol for simultaneous catechol deprotection. Analogous transformations **7** → **12b** yielded methylated sulfamate **12b** in 52 % overall yield starting from **7** (Scheme 2).

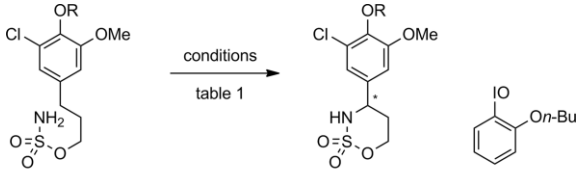


Scheme 2. Synthesis of sulfamates **12a** and **12b** from eugenol (**7**). a) $CuCl_2 \cdot 2H_2O$, LiCl, O_2, AcOH, 80 °C, 6 h, 85 %; b) R = TBS: TBSCl, NEt_3, DMAP, CH_2Cl_2, 0 °C → r.t., 12 h, 97 %; R = Me: NaH, MeI, DMF, 0 °C → r.t., 12 h, 99 %; c) R = TBS, **10a**: i) $BH_3 \cdot SMe_2$, THF, 0 °C → r.t., ii) NaOH, H_2O_2, 0 °C → r.t., 2 h, 74 %; R = Me, **10b**: i) 9-BBN, THF, 0 °C → r.t., 1 h, ii) NaOH, H_2O_2, 0 °C → r.t., 2 h, 87 %; d) **11**, py, CH_2Cl_2, 0 °C → r.t., 12 h, R = TBS, **12a**: 80 %; R = Me, **12b**: 70 %.

The transition metal-catalyzed C–H amination is a powerful method to convert ubiquitous C–H bonds into valuable C-N bonds.[9a] In particular, Du Bois' contributions using carbamates and sulfamates as nitrene sources for intramolecular C–H aminations have received considerable attention.[9b]

With sulfamate **12a** in hand, the rhodium-catalyzed C–H amination using $Rh_2(esp)_2$ gave racemic oxathiazinane **13a** in 90 % yield (Table 1, entry 1). Using $Rh_2(S\text{-nap})_4$,[9c] **13a** was obtained in 82 % with 44 % ee (entry 2). Addition of molecular sieves increased the yield but did not improve the enantioselectivity (entry 3). Using benzene as solvent slightly enhanced the ee to 53 % (entry 4). $Rh_2(S\text{-dosp})_4$ showed only poor enantioinduction with 12 % in favor of the opposite enantiomer (entry 5). Since it was hypothesized that the carboxylate moieties released from the oxidation agent undertook a ligand exchange with the catalyst, iodosobenzene was employed for activation of the substrate, which gave **13a** in 37 % yield with 82 % ee in CH_2Cl_2 and 87 % ee in benzene (entries 6 and 7). By shortening the reaction time to 2 h and using powdered 3 Å molecular sieves the yield of **13a** could be increased to 66 % without a significant loss of enantioselectivity (entries 8 and 9).

Table 1. Optimization of the enantioselective nitrene insertion.



Entry	Catalyst	Oxidating agent	Additive	Yield[a] (ee)[b] [%]
12a → 13a				
1[c]	A	$PhI(OPiv)_2$	MgO	90
2[c]	B	$PhI(OPiv)_2$	MgO	82 (44,R)
3[c]	B	$PhI(OPiv)_2$	MgO, 4 Å MS	98 (37,R)
4[d]	B	$PhI(OPiv)_2$	MgO, 4 Å MS	99 (53,R)
5[d]	C	PhIO	MgO, 4 Å MS	77 (12,S)
6[c]	B	PhIO	MgO, 4 Å MS	37 (82,R)
7[d]	B	PhIO	MgO, 4 Å MS	30 (87,R)
8[c]	B	PhIO	MgO, 3 Å MS (powdered)	66 (84,R)
9[d]	B	PhIO	MgO, 3 Å MS (powdered)	45 (79,R)
12b → 13b				
10[c]	A	$PhI(OPiv)_2$	MgO	99
11[c]	B	PhIO	MgO, 3 Å MS (powdered)	62 (81,R)
12[c,e]	B	PhIO	MgO, 3 Å MS (powdered)	60 (88,R)
13[c]	B	**14**	MgO, 3 Å MS (powdered)	0
14[c,e]	D	PhIO	MgO, 3 Å MS (powdered)	63 (87,S) 52 (> 99,S)[f]

[a] Isolated yields. [b] *ee* was determined by HPLC. [c] Reaction performed in CH_2Cl_2. [d] Reaction performed in benzene; reactions were performed at 25 °C, except. [e] Reaction was performed at 0 °C. [f] After recrystallization from CH_3Cl; catalyst A: $Rh_2(esp)_2$; B: $Rh_2(S\text{-nap})_4$; C: $Rh_2(S\text{-dosp})_4$; D: $Rh_2(R\text{-nap})_4$.

The crystal structure[10] of oxathiazinane **13b** (Figure 2) revealed the (*R*)-enantiomer had been formed which is in contrast to the original paper by Du Bois.[9c] The prediction of enantioselective C–H aminations using $Rh_2(S\text{-nap})_4$ has already been observed and corrected by others.[11] The respective (*S*)-enantiomer could be obtained in similar yield and enantioselectivity by employing $Rh_2(R\text{-nap})_4$.

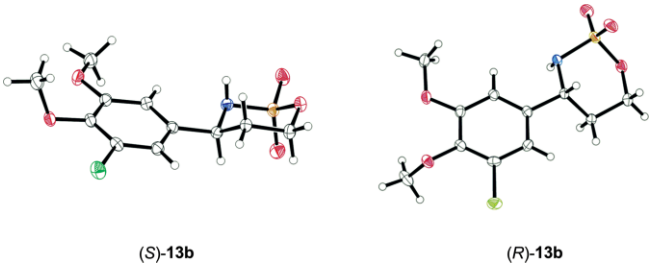
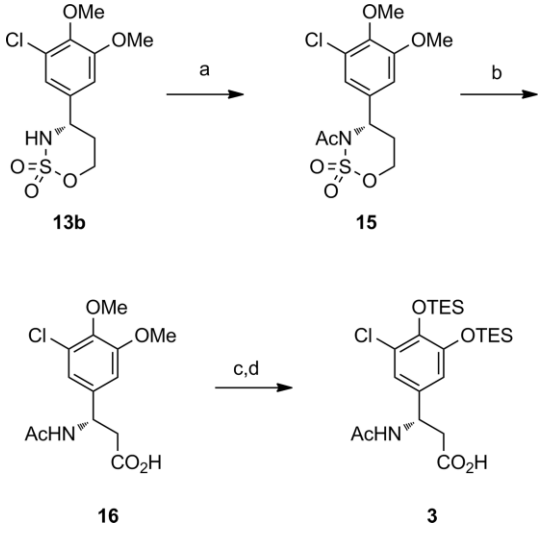


Figure 2. Crystal structures of oxathiazinanes (*S*)- and (*R*)-**13b**.

For sulfamate **12b** using optimized reaction conditions gave oxathiazinane **13b** in 62 % yield with 81 % ee (entry 11); by decreasing the temperature to 0 °C (*R*)-**13b** could be obtained

in 60 % yield with 88 % ee (entry 12). Application of soluble iodine(III) oxidation agent **14** gave no conversion at all (entry 13). Performing the reaction under optimized conditions with Rh_2(*R*-nap)$_4$ gave (*S*)-**13b** in similar yield and enantioselectivity which could be further increased to 99 % ee by recrystallization from $CHCl_3$ (entry 14). The formation of both (*R*) and (*S*)-**13b** could be secured via X-ray crystallography (Figure 2).[11]

With a solution found for the asymmetric C–H amination the conversion of the oxathiazinane into the amino acid was investigated next. Acetylation of **13b** with acetyl chloride under careful adjustment of reaction conditions to prevent deacetylation during the ring opening lead to amino acid **16** in 70 % yield over 2 steps. Employing acetic anhydride as acylation agent resulted in ring opening without acylation, which could prove useful for synthesis of the amino acid moiety of C-1027. Analogous to Cramer's strategy in their synthesis of fijiolide A deprotection of **16** using $AlBr_3$/EtSH followed by double TES-protection yielded the desired amino acid **3** with 61 % yield over two steps (Scheme 3).



Scheme 3. Conversion of oxathiazinane **13b** into amino acid **16** and synthesis of amino acid building block **3**. a) KO*t*Bu, AcCl, THF, r.t., 8 h, 74 %; b) i) MeCN/H_2O, 50 °C, 4 h; ii) TEMPO, NaOCl, $NaClO_2$, 35 °C, 16 h, 64 %; c) $AlBr_3$, EtSH, 0 °C → r.t., 24 h; d) TESCl, NEt_3, DMAP, DMF, r.t., 8 h, 61 %, 2 steps.

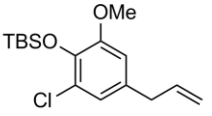
Conclusions

In summary, a stereoselective synthesis of the β-amino acid moiety of the fijiolides was achieved. The stereocenter was controlled via Du Bois' asymmetric C–H amination of a sulfamate using Rh_2(*S*-nap)$_4$ and Rh_2(*R*-nap)$_4$ respectively. Ring opening of the resulting oxathiazinane led to the target β-amino acid substructure in protected form that corresponds to Cramer's intermediate. In combination with earlier synthesis of the dihydrobenzopentalene core[3] this work paves the way for a total synthesis of the fijiolides and structurally related natural products.

Experimental Section

General Methods: All nonaqueous reactions were carried out by using Schlenk technique with freshly dried and distilled solvents. Other solvents were distilled by rotary evaporation prior to use. ^{1}H-NMR spectra were recorded at 300 or 500 MHz, ^{13}C-NMR at 75 or 125 MHz, the solvent residue signals were used as internal standard and all spectra are reported in ppm. Mass spectra were recorded with a LTQ-FT or AccuTOF-GCv mass spectrometer. Melting points were recorded with a Mettler Toledo MP70 by using one side open capillary tubes. More details regarding experimental procedures are specified in the Supporting Information.

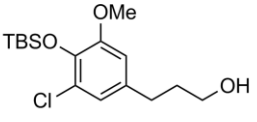
(4-Allyl-2-chloro-6-methoxyphenoxy)(*tert*-butyl)dimethylsilane (10a): Under Ar-atmosphere 6-chloroeugenol (**17**, 4.88 g, 24.6 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (100 mL). At 0 °C DMAP (1.50 g, 12.3 mmol, 0.50 equiv.), NEt_3 (4.26 mL, 31.9 mmol, 1.30 equiv.) and TBSCl (4.42 g, 29.5 mmol, 1.20 equiv.) were added and the mixture was stirred at r.t. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (50 mL), brine (50 mL) and dried with Na_2SO_4. All volatiles were removed in vacuo. After column chromatography (*n*-pentane/EtOAc, 40:1) TBS-protected chloroeugenol **10a** (7.43 g, 23.7 mmol, 97 %) was obtained as colorless oil.



10a

TLC: R_f = 0.65 (*n*-pentane/EtOAc, 40:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 6 H, TBS), 1.04 (s, 9 H, TBS), 3.29 (d, J = 6.7 Hz, 2 H, 1-H), 3.78 (s, 3 H, OMe), 5.04–5.13 (m, 2 H, 3-H), 5.93 (ddt, J = 6.7, 9.6, 17.4 Hz, 1 H, 2-H), 6.56 (d, J = 2.0 Hz, 1 H, Ar), 6.77 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –4.0 (TBS), 19.0 (TBS), 26.1 (TBS), 39.8 (C1), 55.5 (OMe), 110.7 (Ar), 116.4 (C3), 122.0 (Ar), 125.7 (Ar), 133.4 (Ar), 137.1 (C2), 140.1 (Ar), 151.5 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{16}H_{25}ClO_2Na$ $[M - Na]^+$ 564.1244, found 564.1249. FT-IR: (neat): $\tilde{\nu}$ = 2937 (w), 1598 (w), 1572 (m), 1490 (s), 1461 (w), 1415 (m), 1273 (m), 1235 (m), 1181 (w), 1140 (m), 1051 (s), 1001 (s), 968 (w), 913 (m), 837 (m), 778 (m), 686 (m), 598 (w), 3078 (w), 3002 (w), 2830 (w), 1639 (w) cm^{-1}.

3-{4′-[(*tert*-Butyldimethylsilyl)oxy]-3′-chloro-5′-methoxyphenyl}propanol (18): Under Ar-atmosphere olefin **10a** (7.43 g, 23.7 mmol, 1.00 equiv.) was dissolved in THF (120 mL). At 0 °C BH_3•SMe_2 (2.25 mL, 23.7 mmol, 1.00 equiv.) was added, the mixture was stirred at this temperature for 10 min and at r.t. for 1 h. Aq. NaOH (8.20 mL, 35.6 mmol, 15wt.-%, 1.50 equiv.) and aq. H_2O_2 (4.90 mL, 47.4 mmol, 30 %, 2.00 equiv.) were added at 0 °C and the reaction mixture was stirred for 2 h at r.t. The reaction was quenched with brine (100 mL), extracted with Et_2O (3 × 50 mL), dried with $MgSO_4$ and concentrated in vacuo. After column chromatography (*n*-pentane/EtOAc, 1:1) the alcohol (5.82 g, 17.6 mmol, 74 %) was obtained as colorless oil.

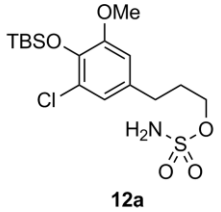


18

TLC: R_f = 0.65 (EtOAc). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.18 (s, 6 H, TBS), 1.03 (s, 9 H, TBS), 1.71 (s, 1 H, OH), 1.84 (dt, J = 6.4, 13.5 Hz, 2 H, 2-H), 2.60 (dd, J = 6.8, 8.6 Hz, 2 H, 3-H), 3.65 (t, J = 6.4 Hz, 2 H, 1-H), 3.77 (s, 3 H, OMe), 6.58 (d, J = 2.0 Hz, 1 H, Ar), 6.77 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –4.0 (TBS), 19.1 (TBS), 26.1 (TBS), 31.8 (C2), 34.2 (C3), 55.5 (OMe), 62.2 (C1), 110.6 (Ar), 121.7 (Ar), 125.7 (Ar), 135.1 (Ar), 139.9 (Ar), 151.5 (Ar) ppm.

HR-MS: (ESI+): m/z calc. for $C_{16}H_{28}ClO_3Si$ $[M - H]^+$ 331.1491, found 331.1502. FT-IR: (neat): $\tilde{\nu}$ = 3337 (w), 2931 (m), 2885 (w), 2857 (w), 1571 (w), 1495 (s), 1466 (w), 1415 (w), 1391 (w), 1361 (w), 1321 (w), 1249 (s), 1187 (w), 1149 (m), 1055 (s), 1010 (w), 906 (s), 837 (s), 804 (w), 782 (m), 738 (w), 695 (w), 660 (w), 600 (w) cm^{-1}.

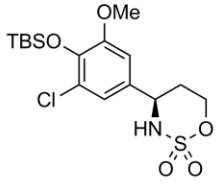
3-{4′-[(*tert*-Butyldimethylsilyl)oxy]-3′-chloro-5′-methoxyphenyl}propyl sulfamate (12a): Under Ar-atmosphere formic acid (0.99 mL, 26.4 mmol, 1.50 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (2.29 mL, 26.4 mmol, 1.50 equiv.) at 0 °C. After 5 min of vigorous stirring, CH_2Cl_2 (15 mL) was added and the mixture was stirred at 0 °C for 1 h and at r.t. for 8 h. At 0 °C the alcohol (5.82 g, 17.6 mmol, 1.00 equiv.) and pyridine (2.13 mL, 26.4 mmol, 1.50 equiv.) in CH_2Cl_2 (15 mL) were added dropwise. The reaction mixture was slowly warmed to r.t. and stirred for 12 h. The mixture was diluted with EtOAc (60 mL), quenched with H_2O (60 mL) and the layers were separated. The aq. layer was extracted with EtOAc (2 × 30 mL) and the combined org. layers were washed with brine (2 × 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. After column chromatography (*n*-pentane/EtOAc, 2:1) sulfamate **12a** (5.80 g, 14.2 mmol, 80 %) was isolated as colorless solid.



12a

TLC: R_f = 0.48 (*n*-pentane/EtOAc, 1:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.18 (s, 6 H, TBS), 1.02 (s, 9 H, TBS), 2.01 (ddt, *J* = 4.9, 7.3, 8.4 Hz, 2 H, 2-H), 2.63 (dd, *J* = 6.7, 8.4 Hz, 2 H, 3-H), 3.78 (s, 3 H, OMe), 4.18 (t, *J* = 6.2 Hz, 2 H, 1-H), 6.58 (s, 1 H, Ar), 6.76 (s, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –4.0 (TBS), 19.0 (TBS), 26.0 (TBS), 30.4 (C2), 31.1 (C3), 55.5 (OMe), 70.4 (C1), 110.8 (Ar), 121.6 (Ar), 125.7 (Ar), 133.7 (Ar), 140.1 (Ar), 151.5 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{16}H_{28}ClNO_5SSiNa$ $[M - Na]^+$ 432.1038, found 432.1049. FT-IR: (neat): $\tilde{\nu}$ = 3282 (w), 2931 (m), 2895 (w), 2857 (w), 1570 (w), 1495 (s), 1466 (w), 1416 (w), 1360 (m), 1324 (w), 1272 (w), 1249 (s), 1179 (s), 1149 (w), 1054 (m), 1010 (w), 905 (m), 836 (m), 804 (w), 781 (s), 740 (w), 694 (w), 662 (w), 593 (w), 662 (w) cm^{-1}. m.p.: 46 °C (EtOAc).

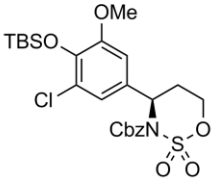
(*R*)-4-{4′-[(*tert*-Butyldimethylsilyl)oxy]-3′-chloro-5′-methoxyphenyl}-1,2,3-oxathiazinane 2,2-dioxide (13a): Under Ar-atmosphere sulfamate **12a** (96.3 mg, 235 µmol, 1.00 equiv.), MgO (19.0 mg, 470 µmol, 2.00 equiv.), 3 Å molecular sieves (40.0 mg) and Rh_2(*S*-nap)$_4$ (6.00 mg, 4.70 µmol, 0.02 equiv.) were dissolved in CH_2Cl_2 (1 mL). Iodosobenzene (67.2 mg, 306 µmol, 1.30 equiv.) was added and the mixture was stirred at r.t. for 2 h. CH_2Cl_2 (3 mL) was added and the reaction mixture was filtered through a pad of Celite. The crude product was concentrated in vacuo. After column chromatography (*n*-pentane/EtOAc, 4:1) oxathiazinane **13a** (63.2 mg, 155 µmol, 66 %, 84 % *ee*) was isolated as colorless solid.



13a

TLC: R_f = 0.33 (*n*-pentane/EtOAc, 4:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 6 H, TBS), 1.02 (s, 9 H, TBS), 1.99 (ddd, *J* = 2.3, 4.2, 14.3 Hz, 1 H, 5-H_A), 2.22 (dtd, *J* = 5.0, 12.4, 14.3 Hz, 1 H, 5-H_B), 3.82 (s, 3 H, OMe), 4.39 (d, *J* = 9.6 Hz, 1 H, NH), 4.64 (ddd, *J* = 1.7, 5.0, 11.7 Hz, 1 H, 6-H_A), 4.75 (ddd, *J* = 2.5, 9.0, 12.4 Hz, 1 H, 4-H), 4.85 (dd, *J* = 2.3, 11.7 Hz, 1 H, 6-H_B), 6.78 (d, *J* = 2.2 Hz, 1 H, Ar), 6.91 (d, *J* = 2.2 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –3.9 (TBS), 19.0 (TBS), 26.0 (TBS), 30.1 (C5), 55.7 (OMe), 58.6 (C4), 71.9 (C6), 108.6 (Ar), 119.7 (Ar), 126.2 (Ar), 131.1 (Ar), 142.4 (Ar), 152.1 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{24}H_{32}ClNO_7SSiNa$ $[M - Na]^+$ 564.1249, found 564.1248. FT-IR: (neat): $\tilde{\nu}$ = 3262 (w), 2931 (w), 2896 (w), 2857 (w), 1573 (w), 1500 (m), 1467 (w), 1420 (w), 1360 (w), 1333 (w), 1306 (w), 1251 (m), 1188 (s), 1155 (w), 1055 (m), 1022 (w), 988 (w), 909 (w), 884 (w), 870 (w), 840 (m), 782 (s), 742 (w), 714 (w), 742 (w), 714 (w), 681 (w), 600 (w), 579 (w) cm^{-1}. m.p.: 169 °C (EtOAc). HPLC: (Chiralpac IC, *n*-hexane/EtOAc, 9:1, 0.7 mL/min, 254 nm) t_R(major) = 31.1 min, t_R(minor) = 21.9 min. $[\alpha]_D^{23}$: –7.3 (c 0.5, EtOAc, for a sample with 84 %*ee*).

***rac*-Benzyl-4-{4′-[(*tert*-butyldimethylsilyl)oxy]-3′-chloro-5′-methoxy-phenyl}-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide (19):** Under Ar-atmosphere oxathiazinane 13a (36.7 mg, 90.0 µmol, 1.00 equiv.) was dissolved in THF (1.5 mL). KO*t*Bu (15.1 mg, 135 µmol, 1.50 equiv.) was added and the mixture was stirred at r.t. for 1.5 h. Benzyl chloroformate (32.0 µL, 225 µmol. 2.50 equiv.) was added and the mixture was stirred at r.t. for 12 h. H_2O (3 mL) was added to quench the reaction, it was extracted with EtOAc (3 × 2 mL), washed with brine (2 mL), dried with $MgSO_4$ and filtered. All volatiles were removed under reduced pressure. After column chromatography (*n*-pentane/CH_2Cl_2, 1:1) Cbz-*N*-protected oxathiazinane (45.0 mg, 83.0 µmol, 92 %) was isolated as colorless oil.

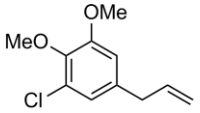


19

TLC: R_f = 0.10 (*n*-pentane/CH_2Cl_2, 1:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.19 (s, 6 H, TBS), 1.03 (s, 9 H, TBS), 2.40 (dddd, *J* = 2.3, 3.5, 6.2, 14.7 Hz, 1 H, 5-H_A), 2.90 (dddd, *J* = 4.9, 7.4, 10.8, 14.7 Hz, 1 H, 5-H_B), 3.71 (s, 3 H, OMe), 4.46 (td, *J* = 6.2, 10.8 Hz, 1 H, 6-H_A), 4.70 (ddd, *J* = 2.3, 7.4, 10.8 Hz, 1 H, 6-H_B), 5.32 (s, 2 H, Cbz), 5.64 (t, *J* = 5.6 Hz, 1 H, 4-H), 6.78 (d, *J* = 2.2 Hz, 1 H, Ar), 6.91 (dd, *J* = 0.7, 2.2 Hz, 1 H, Ar), 7.31–7.38 (m, 5 H, Ph) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = –3.9 (TBS), 19.0 (TBS), 26.0 (TBS), 28.5 (C5), 55.5 (OMe), 60.4 (ArCN), 69.8 (C4), 70.1 (C6), 107.8 (Ar), 119.1 (Ar), 126.3 (Ar), 128.0 (Ph), 128.7 (Ph), 128.8 (Ph), 130. 9 (Ar), 134.8 (Ph), 151.8 (Ar), 152.2 (NCO_2) ppm. HR-MS: (ESI+): m/z calc. for $C_{24}H_{32}ClNO_7SSiNa$ $[M - Na]^+$ 564.1249, found 564.1248. FT-IR: (neat): $\tilde{\nu}$ = 3246 (s), 2943 (s), 2836 (m), 1601 (m), 1576 (s), 1496 (s), 1461 (s), 1423 (s), 1362 (m), 1305 (m), 1286 (m), 1241 (s), 1187 (s), 1147 (s), 1053 (m), 1023 (m), 993 (s), 922 (s), 871 (w), 785 (w), 618 (w), 573 (w), 549 (w), 522 (w) cm^{-1}. The Cbz-protected oxathiazinane was synthesized using racemic oxathiazinane **13a**, therefore no measurement of optical rotation was performed.

5-Allyl-1-chloro-2,3-dimethoxybenzene (10b): Under Ar-atmosphere 6-chloroeugenol (1.05 g, 5.28 mmol, 1.00 equiv.) was dissolved in DMF (100 mL). At 0 °C NaH (290 mg, 6.34 mmol, 1.20 equiv.) was added. After 15 min MeI (1.50 mL, 21.1 mmol, 4.00 equiv.) was added and the mixture was stirred at r.t. for 16 h. The reaction was quenched with H_2O (150 mL) and extracted with cyclohexane (3 × 40 mL), dried with Na_2SO_4, filtered and concen-

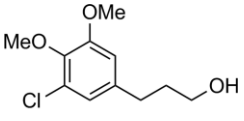
trated in vacuo. After column chromatography (*n*-pentane/EtOAc, 8:1) 5-allyl chloro-2,3-dimethoxybenzene **10b** (1.12 g, 5.26 mmol, 99 %) was isolated as colorless oil.



10b

TLC: R_f = 0.55 (*n*-pentane/EtOAc, 8:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 3.31 (dd, J = 1.4, 6.8 Hz, 2 H, 1-H), 3.84 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 5.07–5.14 (m, 2 H, 3-H), 5.92 (ddt, J = 6.8, 9.6, 17.4 Hz, 1 H, 2-H), 6.63 (d, J = 1.9 Hz, 1 H, Ar), 6.81 (d, J = 1.9 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 39.9 (C1), 56.2 (OMe), 60.8 (OMe), 111.6 (Ar), 116.6 (C3), 121.9 (Ar), 128.2 (Ar), 136.7 (C2), 143.9 (Ar), 153.8 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{11}H_{13}ClO_2Na$ [M – Na]$^+$ 235.0496, found 235.0497. FT-IR: (neat): $\tilde{\nu}$ = 3078 (w), 3001 (w), 2934 (w), 2832 (w), 1681 (w), 1639 (w), 1598 (w), 1572 (m), 1490 (s), 1459 (w), 1415 (m), 1273 (m), 1235 (m), 1182 (w), 1140 (m), 1051 (s), 1001 (m), 968 (w), 913 (m), 837 (m), 777 (w), 745 (w), 686 (w), 598 (w), 548 (w) cm^{-1}.

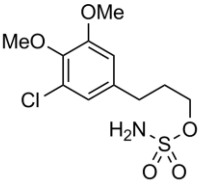
3-(3′-Chloro-4′,5′-dimethoxyphenyl) propanol (20): Under Ar-atmosphere 5-allyl-1-chloro-2,3-dimethoxybenzene (**10b**) (1.12 g, 5.27 mmol, 1.00 equiv.) was dissolved in THF (20 mL). At 0 °C 9-BBN (11.1 mL, 5.53 mmol, 0.5 M in THF, 1.05 equiv.) was added and the mixture was stirred at 0 °C for 10 min and at r.t. for 1 h. 15 % aq. NaOH (1.80 mL, 7.90 mmol, 1.50 equiv.) and aq. H_2O_2 (1.08 mL, 10.5 mmol, 30 %, 2.00 equiv.) were added at 0 °C and the reaction mixture was stirred at r.t. for 2 h. The reaction was quenched with brine (40 mL), extracted with Et_2O (3 × 20 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. After column chromatography (*n*-pentane/EtOAc, 1:1) the respective alcohol (1.05 g, 4.56 mmol, 87 %) was obtained as colorless oil.



20

TLC: R_f = 0.30 (EtOAc). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 1.82–1.91 (m, 2 H, 2-H), 2.65 (dd, J = 6.7, 8.7 Hz, 2 H, 3-H), 3.67 (t, J = 6.4 Hz, 2 H, 1-H), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 6.58 (d, J = 2.0 Hz, 1 H, Ar), 6.77 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 31.0 (C2), 34.1 (C3), 56.3 (OMe), 60.8 (OMe), 62.2 (C1), 111.5 (Ar), 121.7 (Ar), 128.2 (Ar), 138.6 (Ar), 143.8 (Ar), 153.8 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{11}H_{15}ClO_3Na$ [M – Na]$^+$ 253.0602, found 253.0603. FT-IR: (neat): $\tilde{\nu}$ = 3387 (w), 3054 (w), 2939 (w), 2877 (w), 1599 (w), 1572 (m), 1491 (m), 1457 (w), 1414 (m), 1307 (w), 1270 (m), 1234 (m), 1183 (w), 1141 (m), 1049 (s), 1001 (m), 963 (w), 916 (w), 852 (m), 774 (w), 733 (s), 702 (w), 655 (w), 610 (w), 573 (w), 512 (w), 472 (w) cm^{-1}.

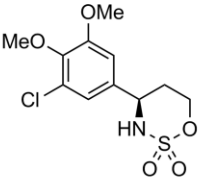
3-(3′-Chloro-4′,5′-dimethoxyphenyl) propyl sulfamate (12b): Under Ar-atmosphere formic acid (0.75 mL, 19.8 mmol, 2.50 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (1.72 mL, 19.8 mmol, 2.50 equiv.) at 0 °C. After 5 min of vigorous stirring, CH_2Cl_2 (8 mL) was added and the mixture was stirred at 0 °C for 1 h and at r.t. for 8 h. At 0 °C the alcohol (1.82 g, 7.90 mmol, 1.00 equiv.) and pyridine (1.59 mL, 19.8 mmol, 2.50 equiv.) in CH_2Cl_2 (10 mL) were added dropwise. The reaction mixture was slowly warmed to r.t. and stirred for 12 h. The mixture was diluted with EtOAc (100 mL), quenched with H_2O (100 mL) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 50 mL) and the combined org. layers were washed with brine (2 × 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. After column chromatography (*n*-pentane/EtOAc, 2:1) sulfamate **12b** (1.65 g, 5.40 mmol, 70 %) was isolated as colorless oil.



12b

TLC: R_f = 0.33 (*n*-pentane/EtOAc, 2:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.00–2.09 (m, 2 H, 2-H), 2.68 (t, J = 7.5 Hz, 2 H, 3-H), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.21 (t, J = 6.2 Hz, 2 H, 1-H), 4.74 (s_{br}, 1 H, NH), 6.65 (d, J = 1.8 Hz, 1 H, Ar), 6.80 (d, J = 1.8 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 30.4 (C2), 31.4 (C3), 56.3 (OMe), 60.8 (OMe), 70.4 (C1), 111.7 (Ar), 121.7 (Ar), 128.3 (Ar), 137.2 (Ar), 144.1 (Ar), 154.0 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{11}H_{16}ClNO_5SNa$ [M – Na]$^+$ 332.0330, found 332.0333. FT-IR: (neat): $\tilde{\nu}$ = 3361 (w), 3270 (w), 3106 (w), 2940 (w), 1599 (w), 1572 (m), 1492 (m), 1459 (w), 1416 (w), 1360 (s), 1309 (w), 1277 (w), 1234 (w), 1176 (s), 1141 (m), 1083 (w), 1048 (m), 996 (w), 927 (s), 818 (m), 777 (w), 734 (w), 657 (w), 590 (w), 552 (s) cm^{-1}. m.p.: 66 °C (EtOAc).

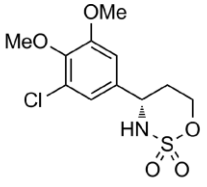
(*R*)-4-(3′-Chloro-4′,5′-dimethoxyphenyl)-1,2,3-oxathiazinane 2,2-dioxide (*R*-13b): Under Ar-atmosphere sulfamate **12b** (200 mg, 646 μmol, 1.00 equiv.), MgO (52.1 mg, 1.29 mmol, 2.00 equiv.), 3 Å molecular sieves (120 mg) and $Rh_2(S\text{-nap})_4$ (16.5 mg, 12.9 μmol, 0.02 equiv.) were dissolved in CH_2Cl_2 (5 mL). Iodosobenzene (156 mg, 710 μmol, 1.10 equiv.) was added and the mixture was stirred at 0 °C for 3 h. CH_2Cl_2 (10 mL) was added and the reaction mixture was filtered through a pad of Celite. The crude product was concentrated in vacuo. After column chromatography (*n*-pentane/EtOAc, 2:1) oxathiazinane (*R*)-**13b** (119 mg, 387 μmol, 60 %, 88 % *ee*) was isolated as colorless solid.



(*R*)-13b

TLC: R_f = 0.28 (*n*-pentane/EtOAc, 2:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.02 (ddd, J = 2.3, 2.5, 14.4 Hz, 1 H, 5-H_A), 2.22 (ddt, J = 5.0, 12.5, 14.4 Hz, 1 H, 5-H_B), 3.86 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 4.40 (d, J = 9.3 Hz, 1 H, NH), 4.66 (ddd, J = 1.7, 5.0, 11.7 Hz, 1 H, 6-H_A), 4.78 (ddd, J = 2.5, 9.3, 12.5 Hz, 1 H, 4-H), 4.85 (dd, J = 2.3, 11.7 Hz, 1 H, 6-H_B), 6.82 (d, J = 2.0 Hz, 1 H, Ar), 6.93 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 29.9 (C5), 56.4 (OMe), 58.3 (C4), 60.9 (OMe), 71.8 (C6), 109.5 (Ar), 119.6 (Ar), 128.8 (Ar), 134.6 (Ar), 145.7 (Ar), 154.3 (Ar) ppm. HR-MS: (ESI+): m/z calc. for $C_{11}H_{14}ClNO_5SNa$ [M – Na]$^+$ 330.0173, found 330.0171. FT-IR: (neat): $\tilde{\nu}$ = 3246 (w), 2943 (w), 2836 (w), 1601 (w), 1576 (w), 1496 (w), 1461 (w), 1423 (m), 1362 (m), 1305 (w), 1286 (w), 1241 (w), 1187 (s), 1147 (w), 1053 (m), 1023 (w), 993 (m), 922 (w), 871 (w), 785 (m), 618 (w), 573 (w), 549 (w), 522 (w) cm^{-1}. HPLC: (Chiralpac IC, *n*-hexane/EtOAc, 3:2, 0.7 mL/min, 277 nm) t_R(major) = 8.357, t_R(minor) = 7.127 min. $[\alpha]_D^{23}$: –6.4 (c 0.6, EtOAc, for a sample with 88 % *ee*). m.p.: 66 °C (EtOAc).

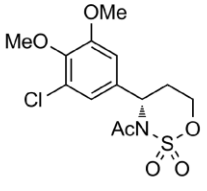
(*S*)-4-(3′-Chloro-4′,5′-dimethoxyphenyl)-1,2,3-oxathiazinane 2,2-dioxide (*S*-13b): Under Ar-atmosphere sulfamate **12b** (1.27 g, 4.10 mmol, 1.00 equiv.), MgO (328 mg, 8.20 mmol, 2.00 equiv.), 3 Å molecular sieves (300 mg) and $Rh_2(R\text{-nap})_4$ (105 mg, 82.0 μmol, 0.02 equiv.) were dissolved in CH_2Cl_2 (40 mL). Iodosobenzene (992 mg, 4.51 mmol, 1.10 equiv.) was added and the mixture was stirred at 0 °C for 3 h. CH_2Cl_2 (40 mL) was added and the reaction mixture was filtered through a pad of Celite. The crude product was concentrated in vacuo. After column chromatography (*n*-pentane/EtOAc, 2:1) oxathiazinane **13b** (794 mg, 2.58 mmol, 63 %, 87 % *ee*) was isolated as colorless solid. Recrystallization from $CHCl_3$ gave (*S*)-**13b** with 52 % yield and 99 % *ee*.



(*S*)-13b

TLC: R_f = 0.27 (*n*-pentane/EtOAc, 2:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.03 (ddd, J = 2.4, 4.2, 14.4 Hz, 1 H, 5-H_A), 2.22 (dtd, J = 5.0, 12.6, 17.4 Hz, 1 H, 5-H_B), 3.87 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.30 (d, J = 9.2 Hz, 1 H, NH), 4.67 (ddd, J = 1.5, 5.0, 11.7 Hz, 1 H, 6-H_A), 4.87 (ddd, J = 2.9, 7.3, 12.1 Hz, 1 H, 4-H), 4.87 (dd, J = 2.4, 11.8 Hz, 1 H, 6-H_B), 6.83 (d, J = 1.9 Hz, 1 H, Ar), 6.93 (d, J = 1.6 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 29.9 (C5), 56.4 (OMe), 58.4 (C4), 60.9 (OMe), 71.8 (C6), 109.5 (Ar), 119.5 (Ar), 128.9 (Ar), 134.5 (Ar), 145.9 (Ar), 154.4 (Ar) ppm. HR-MS: (ESI–): m/z calc. for $C_{11}H_{13}ClNO_5S$ [M – H] 306.0208, found 306.0210. FT-IR: (neat): $\tilde{\nu}$ = 3248 (w), 2943 (w), 2836 (w), 1601 (w), 1576 (w), 1496 (w), 1462 (w), 1423 (m), 1362 (m), 1306 (w), 1286 (w), 1241 (w), 1187 (s), 1147 (w), 1053 (m), 1023 (w), 992 (m), 922 (w), 890 (w), 871 (w), 786 (m), 732 (w), 618 (w), 574 (w), 549 (w), 523 (w) cm^{-1}. HPLC: (Chiralpac IC, *n*-hexane/EtOAc, 3:2, 0.7 mL/min, 277 nm) t_R(major) = 7.212 min, t_R(minor) = 8.555 min. $[\alpha]_D^{23}$: +17.5 (c 0.1, EtOAc, for a sample with 99 %*ee*). m.p.: 194 °C ($CHCl_3$).

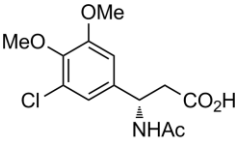
(*S*)-1-[4-(3′-Chloro-4′,5′-dimethoxyphenyl)-2,2-dioxido-1,2,3-oxathiazinan-3-yl]ethan-1-one (*S*-15): Under Ar-atmosphere oxathiazinane **13b** (64.0 mg, 208 μmol, 1.00 equiv.) was dissolved in THF (6 mL). KO*t*Bu (46.7 mg, 416 μmol, 2.00 equiv.) was added and the mixture was stirred at r.t. for 2 h. Acetyl chloride (37.7 μL, 520 μmol, 2.50 equiv.) was added and the mixture was stirred at r.t. for 10 h. H_2O (6 mL) was added to quench the reaction, it was extracted with EtOAc (2 × 10 mL), dried with Na_2SO_4 and all volatile compounds were removed under reduced pressure. After column chromatography (*n*-pentane/EtOAc, 2:1) *N*-acylated oxathiazinane **15** (54.0 mg, 154 μmol, 74 %) was isolated as colorless solid.



15

TLC: R_f = 0.20 (*n*-pentane/CH_2Cl_2, 2:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 2.47 (dddd, J = 2.3, 3.5, 6.2, 14.7 Hz, 1 H, 5-H_A), 2.59 (s, 3 H, Me), 2.87 (dddd, J = 4.6, 7.4, 10.8, 14.7 Hz, 1 H, 5-H_B), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.51 (td, J = 6.2, 10.8 Hz, 1 H, 6-H_A), 4.73 (ddd, J = 2.3, 7.4, 10.8 Hz, 1 H, 6-H_B), 5.89 (t, J = 4.6 Hz, 1 H, 4-H). 6.80 (d, J = 2.1 Hz, 1 H, Ar), 6.94 (dd, J = 0.8, 2.1 Hz, 1 H, Ar) ppm. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 24.8 (Me), 28.2 (C5), 56.3 (OMe), 57.7 (C4), 60.8 (OMe), 70.9 (C6), 108.9 (Ar), 119.3 (Ar), 128.9 (Ar), 134.3 (Ar), 145.2 (Ar), 154.2 (Ar), 168.6 (CO) ppm. HR-MS: (ESI+): m/z calc. for $C_{13}H_{16}ClNO_6SNa$ [M – Na]$^+$ 372.0279, found 372.0276. FT-IR: (neat): $\tilde{\nu}$ = 2937 (w), 1705 (m), 1601 (w), 1574 (w), 1495 (m), 1463 (w), 1414 (w), 1370 (s), 1261 (s), 1176 (s), 1144 (m), 1112 (w), 1047 (m), 988 (s), 958 (w), 925 (m), 888 (m), 790 (s), 755 (w), 731 (w), 583 (s), 544 (w), 506 (w), 479 (w) cm^{-1}. m.p.: 95 °C (EtOAc). $[\alpha]_D^{23}$: –13.8 (c 0.1, EtOAc, for a sample with 99 %*ee*).

(*S*)-3-Acetamido-3-(3′-chloro-4′,5′-dimethoxyphenyl)propanoic Acid (*S*-16b): Acylated oxathiazinane **15b** (277 mg, 792 mmol, 1.00 equiv.) was dissolved in MeCN/H_2O (4.8 mL, 4:3) and the mixture was stirred at 50 °C for 4 h. The mixture was cooled to 35 °C and Na_2HPO_4·12H_2O (397 mg, 1.11 mmol, 1.40 equiv.) was added to reach pH ≈ 4. TEMPO (11.0 mg, 71.3 μmol, 0.09 equiv.) was added, aq. NaOCl (8.00 μL, 15.8 μmol, 12wt.-%, 0.02 equiv.) and $NaClO_2$ (143 mg, 1.58 mmol, 2.00 equiv.) were added in 7 portions over 3 h and the mixture was stirred at this temperature for 16 h. Aq. NaOH (2.0 M) was added to reach pH ≈ 8, aq. Na_2SO_3 (240 mg, 1.90 mmol, 2.40 equiv.) was added and stirring was continued at r.t. for 30 min. The reaction mixture was washed with EtOAc (20 mL), the pH was adjusted to ≈ 3 by addition of HCl (1.0 M) and the layers were separated. The aq. layer was extracted with EtOAc (3 × 20 mL), the combined org. layers were dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was recrystallized from Et_2O to yield clean **16** (152 mg, 0.504 mmol, 64 %) as colorless solid.



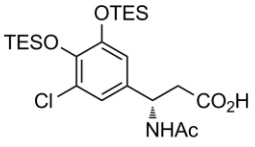
16

TLC: R_f = 0.29 (CH_2Cl_2/MeOH/AcOH, 100:20:1). ^{1}H-NMR: 300 MHz, [D_4]DMSO; δ = 1.82 (s, 3 H, Me), 2.65 (d, J = 7.5 Hz, 2 H, 2-H), 3.71 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 5.11 (q, J = 7.5 Hz, 1 H, 3-H), 6.93 (d, J = 2.0 Hz, 1 H, Ar), 6.99 (d, J = 2.0 Hz, 1 H, Ar), 8.34 (d, J = 8.4 Hz, 1 H, NH), 12.17 (s_{br}, 1 H, CO_2H) ppm. 300 MHz, [D_4]MeOD; δ = 1.96 (s, 3 H, Me), 2.76 (dd, J = 4.6, 7.4 Hz, 2 H, 2-H), 3.78 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 5.25 (t, J = 7.4 Hz, 1 H, 3-H), 6.96 (s_{br}, 2 H, Ar) ppm. ^{13}C-NMR: 75 MHz, [D_4]MeOD; δ = 22.6 (Me), 41.4 (C2), 51.2 (C3), 56.7 (OMe), 60.9 (OMe), 111.3 (Ar), 120.7 (Ar), 129.0 (Ar), 139.9 (Ar), 145.8 (Ar), 155.2 (Ar), 171.4 (Ac), 173.8 (CO_2H) ppm. HR-MS: (ESI+): m/z calc. for $C_{13}H_{16}ClNO_5Na$ [M – Na]$^+$ 324.0609, found 324.0605. FT-IR: (neat); $\tilde{\nu}$ = 3313 (w), 2937 (w), 2828 (w), 2567 (w), 2504 (w), 1692 (s), 1612 (m), 1555 (s), 1493 (m), 1451 (w), 1428 (w), 1408 (m), 1377 (w), 1340 (w), 1272 (m), 1235 (s), 1214 (w), 1184 (m), 1141 (m), 1114 (w), 1069 (w), 1048 (m), 991 (s), 909 (m), 856 (m), 833 (w), 793 (w), 716 (w), 631 (w), 613 (s), 517 (m), 481 (w), 442 (w) cm^{-1}. m.p.: 154 °C (Et_2O). $[\alpha]_D^{23}$: –29.9 (c 0.1, MeOH, for a sample with 99 %*ee*).

(*S*)-3-Acetamido-3-{3′-chloro-4′,5′-bis[(triethylsilyl)oxy]-phenyl}propanoic Acid (3): Under Ar-atmosphere amino acid **16** (33.0 mg, 109.0 μmol, 1.00 equiv.) was suspended in CH_2Cl_2 (0.5 mL) and added to a solution of $AlBr_3$ (233 mg, 875 μmol, 8.00 equiv.) in EtSH (580 μL, 7.65 mmol, 70.0 equiv.) at 0 °C. The mixture was warmed to r.t. and stirred for 18 h at this temperature. The reaction was quenched by addition of 1.0 M HCl (1.0 mL) and diluted with EtOAc (1.0 mL). NaCl was added to saturate the aq. layer and it was extracted with EtOAc (4 × 3.0 mL). The combined org. layers were

dried with Na_2SO_4, filtered and all volatile compounds were removed in vacuo to yield the crude deprotected catechol (30.0 mg), which was directly used for the next step without further purification.

Under Ar-atmosphere crude amino acid, NEt_3 (0.12 mL, 887 μmol, 8.00 equiv.) and DMAP (2.00 mg, 16.0 μmol, 0.15 equiv.) were dissolved in DMF (1.0 mL). At 0 °C TESCl (138.0 μL, 822 μmol, 7.50 equiv.) was added and the mixture was stirred at r.t. for 7 h. Sat. aq. NH_4Cl (3.0 mL) was added to quench the reaction, it was extracted with Et_2O (3 × 7 mL), the combined layers were dried with Na_2SO_4 and all volatile compounds were removed in vacuo. After column chromatography (CH_2Cl_2/MeOH/AcOH, 100:2:1) TES-protected amino acid **3** (33.6 mg, 66.9 μmol, 61 %) was isolated as colorless oil.



3

TLC: R_f = 0.11 (CH_2Cl_2/MeOH/AcOH, 100:2:1). ^{1}H-NMR: 300 MHz, $CDCl_3$; δ = 0.72–0.80 (m, 12 H, TES), 0.96 (td, J = 6.0, 7.8 Hz, 1 H, TES), 2.03 (s, 3 H, Me), 2.80 (dd, J = 5.8, 16.1 Hz, 1 H, 2-H_A), 2.91 (dd, J = 5.8, 16.1 Hz, 1 H, 2-H_B), 5.30 (dt, J = 5.8, 8.5 Hz, 1 H, 3-H), 6.48 (d, J = 8.5 Hz, 1 H, NH), 6.67 (d, J = 2.3 Hz, 1 H, Ar), 6.86 (d, J = 2.3 Hz, 1 H, Ar) ppm. The carboxylic acid proton could not be detected. ^{13}C-NMR: 75 MHz, $CDCl_3$; δ = 5.2 (TES), 5.6 (TES), 6.7 (TES), 6.8 (TES), 23.4 (Me), 39.5 (C2), 48.8 (C3), 116.6 (Ar), 120.0 (Ar), 126.8 (Ar), 133.4 (Ar), 143.6 (Ar), 148.4 (Ar), 170.1 (Ac), 174.8 (CO_2H) ppm. HR-MS: (ESI+): m/z calc. for $C_{23}H_{40}ClNO_5Si_2H$ $[M - H]^+$ 502.2212, found 502.2206. FT-IR: (neat); $\tilde{\nu}$ = 3246 (s), 2943 (m), 2836 (s), 1601 (s), 1576 (s), 1496 (s), 1461 (m), 1423 (m), 1362 (m), 1305 (s), 1286 (m), 1241 (m), 1187 (s), 1147 (s), 1053 (m), 1023 (m), 993 (m), 922 (s), 871 (s), 785 (w), 618 (s), 573 (s), 549 (s), 522 (w) cm^{-1}. $[\alpha]_D^{23}$: –56.5 (c 1.0, $CHCl_3$, for a sample with 99 %*ee*).

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Keywords: C–H Amination · Nitrene insertion · Fijiolide A · Amino acids

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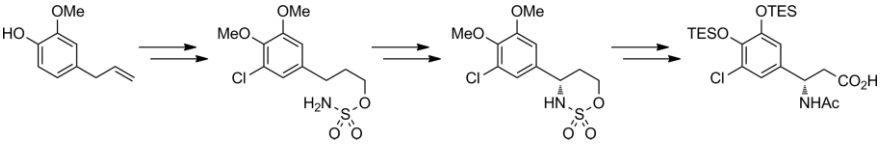
Amino Acid Synthesis



A stereoselective synthesis of the β-amino acid moiety of the fijiolides was achieved using an intramolecular Du Bois' asymmetric C–H amination of a sulfamate.

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