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for

Determination of the Cryptic Stereochemistry of the First PKS Chain Extension Step in Ansamitocin Biosynthesis by *Actinosynnema pretiosum*

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^{1}H-NMR, ^{13}C-NMR and ^{1}H, ^{13}C-COSY as well as NOESY spectra were measured on Avance 200/DPX (Bruker) with 200 MHz (50 MHz), Avance 400/DPX (Bruker) 400 MHz (100 MHz) and Avance 500/DRX (Bruker) spectrometers, respectively, using tetramethylsilane as the internal standard. ^{1}H-multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shift values of ^{13}C NMR spectra are reported in ppm relative to residual $CDCl_3$ (77 ppm) or CD_3OD (49 ppm) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are reported using the following abbreviations: s = singlet (due to quaternary carbon), d =

doublet (methine), t = triplet (methylene), q = quartet (methyl). Mass spectra were recorded on LCT and VG autospec mass spectrometers (Micromass). Ion mass (*m/z*) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensities relative to the base peak (100%). Optical rotations [α] were measured on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. All solvents used were of reagent grade and were further dried. Reactions were monitored by thin layer chromatography (tlc) on silica gel 60 F^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4/4-methoxy-benzaldehyde in methanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt). The starting material **1** was prepared according to reference [1].

3-Hydroxy-5-(2,5-dimethylpyrrol-1-yl)-benzoic acid methyl ester:[2]

The starting material **1** (2.0 g, 12 mmol, 1.0 eq) and 4.2 ml hexane-2,5-dione (36 mmol, 3.0 eq) were dissolved in 50 ml toluene. After adding acetic acid (0.14 ml, 2.4 mmol, 0.2 eq) the mixture was stirred for 5 hours at 90°C to remove water by azeotropic distillation. The resulting mixture was concentrated in vacuo and purified by flash column chromatography (hexanes/ethyl acetate 5:1) to yield the product (2.65 g, 10.8 mmol, 90%).

Colorless crystals, mp: 154°C;

^{1}H-NMR (400 MHz, CD_3OD, CHD_2OD = 3.31 ppm) *d*: 7.47 (m, 1H, H-Ar), 7.26 (m, 1H, H-Ar), 6.84 (m, 1H, H-Ar), 5.80 (s, 2H, CH), 3.89 (s, 3H, OMe), 1.99 (s, 6H, Me).

^{13}C-NMR (100 MHz, CD_3OD, CD_3OD = 49.0 ppm) *d*: 167.8 (s, *C*OOMe), 159.6 (s, C-Ar), 141.8 (s, C_3-Ar), 133.3 (s, C-Ar), 129.3 [s, *C*(Me)], 121.2, 121.0, 116.6 (d, C-Ar), 107.1 (d, CH), 52.8 (q, OMe), 13.0 (q, Me).

HRMS (ESI): calculated for $C_{14}H_{15}NO_3$ $[M+H]^+$ 246.1130, found 246.1126

3-(*tert*-Butyl-diphenyl-silanyloxy)-5-(2,5-dimethylpyrrol-1-yl)-benzoic acid methyl ester:

The material obtained (2.65 g, 10.8 mmol, 1.0 eq) was dissolved in 40 ml dry DMF followed by addition of TBDPS-Cl (4.24 ml, 16.2 mmol, 1.5 eq), imidazole (1.10 g, 16.2 mmol, 1.5 eq) and 4-DMAP (66 mg, 0.54 mmol, 0.05 eq). The mixture was stirred overnight at room temperature, followed by concentration in vacuo. The residue was purified by flash column chromatography (hexanes/ethyl acetate 10:1) to give the desired product (5.03 g, 10.4 mmol, 96%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.71 - 7.66 (m, 4H, H-Ar), 7.64 (dd, 1H, *J* = 2.3, 1.4 Hz, H-Ar), 7.45 - 7.32 (m, 7H, H-Ar), 6.64 (dd, 1H, *J* = 2.2, 2.1 Hz, H-Ar), 5.76 (s, 2H, CH), 3.87 (s, 3H, OMe), 1.74 (s, 6H, Me), 1.11 (s, 9H, *t*-Bu).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 166.1 (s, *C*OOMe), 156.1 (s, C-Ar), 139.7 (s, C-Ar), 135.4 (d, TBDPS), 131.9, 131.8 (s, C-Ar + TBDPS), 130.2 (d, TBDPS), 128.6 [s, *C*(Me)], 127.9 (d, TBDPS), 124.1, 122.3, 120.6 (d, C-Ar), 105.7 (d, CH), 52.3 (q, OMe), 26.3 (q, TBDPS), 19.4 (s, TBDPS), 12.6 (q, Me).

HRMS (ESI): calculated for $C_{30}H_{33}NO_3Si$ $[M+H]^+$ 484.2308, found 484.2307.

3-(*tert*-Butyl-diphenyl-silanyloxy)-5-(2,5-dimethylpyrrol-1-yl)-benzyl alcohol:

The ester (4.84 g, 10.0 mmol, 1.0 eq) described above was dissolved in 40 ml dry THF and cooled to -78°C. After addition of dibal-H [1.2M in toluene] (25 ml, 30.0 mmol, 3.0 eq) the mixture was warmed to 0°C and hydrolyzed by adding 20 ml of a saturated solution of potassium sodium tartrate. Most of the organic solvents were removed under reduced pressure and the residue was extracted twice with ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Further purification by flash column chromatography (hexanes/ethyl acetate 5:1) gave the desired benzyl alcohol (4.10 g, 9.0 mmol, 90%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.70 - 7.67 (m, 4H, H-Ar), 7.42 - 7.32 (m, 6H, H-Ar), 6.93 (m, 1H, H-Ar), 6.69 (m, 1H, H-Ar), 6.41 (m, 1H, H-Ar), 5.75 (s, 2H, CH), 4.59 (d, 2H, *J* = 3.5 Hz, CH_2), 1.77 (s, 6H, Me), 1.64 (bs, 1H, OH), 1.10 (s, 9H, *t*-Bu).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 156.1 (s, C-Ar), 142.9 (s, C-Ar), 139.7 (s, C-Ar), 135.5 (d, C-Ar), 132.2 (s, C-Ar), 130.0 (d, C-Ar), 128.6 [s, *C*(Me)], 127.8 (d, C-Ar), 105.3 (d, CH), 64.6 (t, CH_2), 26.4 (q, *t*-Bu), 19.4 (s, *t*-Bu), 12.7 (q, Me).

HRMS (ESI): calculated for $C_{29}H_{33}NO_2Si$ $[M+H]^+$ 456.2359, found 456.2364.

3-(*tert*-Butyl-diphenyl-silanyloxy)-5-(2,5-dimethylpyrrol-1-yl)-benzyl bromide:

The benzyl alcohol described above (4.10 g, 9.0 mmol, 1.0 eq) was dissolved in 50 ml dry CH_2Cl_2, followed by addition of PPh_3 (3.54 g, 13.5 mmol, 1.5 eq) and slow addition of CBr_4 (4.48 g, 13.5 mmol, 1.5 eq). The reaction mixture was stirred for 30 minutes at room temperature whereupon silica gel (25 g) was added. Dichloromethane was removed by rotary evaporation and

the product was separated by flash column chromatography (hexanes/ethyl acetate, gradient 20:1 to 10:1) to give the desired product (4.56 g, 8.8 mmol, 98%) as a brownish oil.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.70 - 7.67 (m, 4H, H-Ar), 7.42 - 7.32 (m, 6H, H-Ar), 6.94 (m, 1H, H-Ar), 6.73 (m, 1H, H-Ar), 6.42 (m, 1H, H-Ar), 5.75 (s, 2H, CH), 4.35 (s, 2H, CH_2), 1.77 (s, 6H, Me), 1.10 (s, 9H, *t*-Bu).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 156.0 (s, C-Ar), 139.8 (s, C-Ar), 139.4 (s, C-Ar) 135.4 (d, C-Ar), 132.0 (s, C-Ar), 130.1 (d, C-Ar), 128.6 [s, *C*(Me)], 127.9, 121.8, 120.0, 119.7 (d, C-Ar), 105.5 (d, CH), 32.4 (t, CH_2), 26.6 (q, *t*-Bu), 19.4 (s, *t*-Bu), 12.6 (q, Me).

HRMS (ESI): calculated for $C_{29}H_{32}BrNOSi$ $[M+H]^+$ 518.1515, found 518.1514.

3-(*tert*-Butyl-diphenyl-silanyloxy)-5-(2,5-dimethylpyrrol-1-yl)-benzyl iodide (2):

While stirring a solution of the benzyl bromide described above (1.04 g, 2.0 mmol, 1.0 eq) in 15 ml of dry acetone at room temperature, sodium iodide (0.45 g, 3.0 mmol, 1.5 eq) was added. Immediately, sodium bromide precipitated and the mixture was stirred for an additional 15 minutes. Subsequently, 50 ml diethyl ether and 15 ml of a saturated solution of $Na_2S_2O_3$ were added and vigorously stirred for 30 minutes. The organic layer was separated, the aqueous phase extracted twice with diethyl ether and the combined organic phases washed with brine. After drying over anhydrous Na_2SO_4 the organic solvent was removed under reduced pressure to furnish benzyl iodide **1** (1.13 g, 2.0 mmol, quantitative) which was directly processed in the next step.

^{1}H-NMR (200 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.72 - 7.65 (m, 4H, TBDPS), 7.42 - 7.31 (m, 6H, TBDPS), 6.90 (m, 1H, H-Ar), 6.71 (m, 1H, H-Ar), 6.38 (m, 1H, H-Ar), 5.76 (s, 2H, CH), 4.30 (s, 2H, CH_2), 1.78 (s, 6H, CH_3), 1.10 (s, 9H, TBDPS).

HRMS (ESI): calculated for $C_{29}H_{32}INOSi$ $[M+H]^+$ 566.1376, found 566.1383.

[4*S*, (2*R*)]-4-Benzyl-3-{3-[3-(*tert*-butyl-diphenyl-silanyloxy]-5-(2,5-dimethyl-pyrrol-1-yl)-phenyl]-2-methyl-propionyl}-oxazolidin-2-one:

(4*S*)-4-Benzyl-3-propionyl-oxazolidin-2-one **6** (825 mg, 3.54 mmol, 2.0 eq; 99% *ee*) was dissolved in 15 ml dry THF and cooled to -78°C. This solution was treated with 1.77 ml LDA [2M in THF/n-heptane] (3.54 mmol, 2.0 eq) and stirred for 20 minutes, while maintaining the temperature at -78°C. Then, iodide **2** (1.0 g, 1.77 mmol, 1.0 eq) (as a solution in 5 ml dry THF) was added slowly via syringe pump, while the temperature

was raised to -40°C within one hour. Stirring was continued until complete conversion was detected by TLC (approx. 3 hours). The reaction mixture was hydrolyzed by slow addition of 25 ml saturated NH_4Cl solution and warmed to room temperature. The majority of THF was removed under reduced pressure and the resulting aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (hexanes/ethyl acetate, gradient 9:1 to 5:1) afforded the pure title compound (608 mg, 0.92 mmol, 52%, d.r. > 99:1). The enantiomer was prepared according to this procedure using the corresponding (*R*)-configured Evans auxiliary.

Orange crystals;[3] mp: 64-66°C; $[a]_D^{20} = +3.0$ (*c* = 1.0 in $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.70 - 7.63 (m, 4H, H-Ar), 7.40 - 7.24 (m, 9H, H-Ar), 7.15 - 7.10 (m, 2H, H-Ar), 6.86 (m, 1H, H-Ar), 6.63 (m, 1H, H-Ar), 6.36 (m, 1H, H-Ar), 5.74 (s, 2H, CH-pyrrole), 4.66 (m, 1H, 4-H), 4.15 (m, 2H, 5-H), 3.96 (m, 1H, C*H*CH_3), 3.16 (dd, 1H, *J* = 13.3, 3.3 Hz, NCHC*H*$_2$), 3.08 [dd, 1H, *J* = 13.2, 6.3 Hz, CH(CH_3)C*H*$_2$], 2.60 (dd, 1H, *J* = 13.3, 9.6 Hz, NCHC*H*$_2$), 2.52 [dd, 1H, *J* = 13.2, 8.3 Hz, CH(CH_3)C*H*$_2$], 1.76 (s, 6H, CH_3-pyrrole), 1.08 (s, 9H, *t*Bu), 1.07 [d, 3H, *J* = 6.7 Hz, CH(C*H*$_3$)CH_2].

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 176.1 (s, NCOCH), 155.9 (s, C-Ar), 152.9 (s, N*C*OO), 141.0, 139.4 (s, C-Ar), 135.5 (d, C-Ar), 135.2 (s, C-Ar), 132.4 (s, TBDPS), 129.9 (d, C-Ar), 129.4, 128.9 (d, C-Ar), 128.6 (s, C-pyrrole), 127.8, 127.3, 122.3, 120.4, 117.9 (d, C-Ar), 105.3 (d, CH-pyrrole), 66.0 (t, C-5), 55.2 (d, C-4), 39.4 (d, *C*HCH_3), 39.2 [t, CH(CH_3)*C*H$_2$], 37.9 (t, NCH*C*H$_2$), 26.4 (q, TBDPS), 19.4 (s, TBDPS), 16.3 (q, CH*C*H$_3$), 12.7 (q, CH_3-pyrrole).

HRMS (ESI): calculated for $C_{42}H_{46}N_2O_4Si$ $[M+H]^+$ 671.3305, found 671.3311

Selective analytical data for enantiomer: mp: 66°C; $[a]_D^{20} = -3.0$ (*c* = 1.0 in $CHCl_3$); HRMS (ESI): calculated for $C_{42}H_{46}N_2O_4Si$ $[M+H]^+$ 671.3305, found 671.3291.

[4*S*, (2*R*)]-4-Benzyl-3-{3-[3-hydroxy-5-(2,5-dimethylpyrrol-1-yl)-phenyl]-2-methyl- propionyl}-oxazolidin-2-one:

The alkylation product described above (500 mg, 0.75 mmol, 1.0 eq) was dissolved in 10 ml THF, cooled to 0°C and treated with TBAF * 3 H_2O (235 mg, as 1M solution in THF, 0.75 mmol, 1.0 eq). After ten minutes the mixture was hydrolyzed by adding 5 ml saturated NH_4Cl solution and warmed to room temperature. The organic layer was separated and the remaining aqueous phase extracted three times with ethyl acetate. After washing with brine, the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl

acetate, gradient 4:1 to 2:1) to yield the title compound (164 mg, 0.38 mmol, 51%).

Faint yellow foam; mp: 55-62°C; $[a]_D^{20}$ = + 8.7 (*c* = 1.0 in $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.32 - 7.23 (m, 3H, H-Ar), 7.11 - 7.07 (m, 2H, H-Ar), 6.86 (dd, 1H, *J* = 2.2, 1.5 Hz, H-Ar), 6.68 (dd, 1H, *J* = 1.5, 1.5 Hz, H-Ar), 6.56 (dd, 1H, *J* = 2.2, 2.2 Hz, H-Ar), 5.95 (bs, 1H, OH), 5.86 (s, 2H, CH-pyrrole), 4.68 (m, 1H, 4-H), 4.14 (m, 3H, 5-H, CH), 3.14 (m, 2H, $PhCH_2$, $ArCH_2$), 2.65 (dd, 1H, *J* = 13.4, 9.3 Hz, $PhCH_2$), 2.61 (dd, 1H, J = 13.3, 8.0 Hz, $ArCH_2$), 2.02 (s, 6H, CH_3-pyrrole), 1.17 (d, 3H, *J* = 6.8 Hz, CHC*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 176.3 (s, NCO), 156.3 (s, C-Ar), 153.3 (s, NCOO), 141.5, 140.0, 135.0 (s, C-Ar), 129.4, 128.9 (d, C-Ar), 128.7 (s, C-Ar), 127.4, 121.7, 115.2, 113.6 (d, C-Ar), 105.6 (d, CH-pyrrole), 66.1 (t, C-5), 55.2 (d, C-4), 39.5 (t, CH_2), 39.4 (d, *C*H-CH_3), 37.8 (t, CH_2Ph), 16.4 (q, 2-CH_3), 13.0 (q, CH_3-pyrrole).

HRMS (ESI): calculated for $C_{26}H_{28}N_2O_4$ $[M-H]^-$ 431.1971, found 431.1973.
For related benzylation protocols refer to reference [4]. Benzylation products which are structurally very similar to the above mentioned alkylation product have been reported by B. L. Feringa et al.[4a] with [α]= + 15.4 (*c*= 4.05, $CHCl_3$) and by Angus et al.[4b] with [α]= + 19.4 (c= 0.24, $CHCl_3$).

Selected analytical data for enantiomer: mp: 56-60°C; $[a]_D^{20}$ = - 8.8 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): calculated for $C_{26}H_{28}N_2O_4$ $[M-H]^-$ 431.1971, found 431.1973.

(2*R*)-3-[5-Hydroxy-3-(2,5-dimethylpyrrol-1-yl)-phenyl]-2-methyl-propionic acid:

A solution of the above mentioned phenol (160 mg, 0.37 mmol, 1.0 eq) in 6 ml THF/H_2O (3:1) was cooled to 0°C and H_2O_2 (0.24 ml, 30% wgt., 2.22 mmol, 6.0 eq) was added. After treating the mixture with LiOH * H_2O (as aqueous solution, 31 mg, 0.74 mmol, 2.0 eq) it was stirred for 1.5 hours at 0°C, then 3 ml of an aqueous Na_2SO_3 solution was added and stirring was continued for 30 minutes. The major part of the organic layer was removed under reduced pressure and the remaining aqueous phase extracted twice with dichloromethane. Then, the aqueous phase was acidified with HCl (1M) to pH 4 and extracted four times with ethyl acetate. Ethyl acetate layers were combined, dried over $MgSO_4$ and concentrated in vacuo to afford the product (88 mg, 0.32 mmol, 87%) as a faint red oil, which was directly converted in the next reaction.

$[a]_D^{20}$ = - 15.0 (*c* = 1.0 in MeOH);

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.0 ppm) *d*: 6.70 (dd, 1H, *J* = 2.2, 1.7 Hz, H-Ar), 6.50 (m, 1H, H-Ar), 6.45 (m, 1H, H-Ar), 5.75 (s, 2H, CH-pyrrole), 2.94 (dd, 1H, *J* = 12.4, 6.5 Hz, 3-H), 2.70 (m, 2H, 2-H, 3-H'), 1.98 (s, 6H, CH_3-pyrrole), 1.16 (d, 3H, *J* = 6.8 Hz, 2-Me).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 179.7 (s, C-1), 159.2, 143.2, 141.3 (s, C-Ar), 129.3 (s, C-pyrrole), 121.2, 116.4, 114.3 (d, C-Ar), 106.4 (d, CH-pyrrole), 42.6 (d, C-2), 40.5 (t, C-3), 17.3 (q, 2-Me), 13.0 (q, CH_3-pyrrole).

HRMS (ESI): calculated for $C_{16}H_{19}NO_3$ $[M-H]^-$ 272.1287, found 272.1287.
In reference [4a] the authors also described the free acid and like in the present case noted a reversal of sign for [α]= -15.0 (*c* = 1.0 in MeOH).

Selected analytical data for enantiomer: $[a]_D^{20}$ = + 14.8 (*c* = 0.5 in MeOH); HRMS (ESI): calculated for $C_{16}H_{19}NO_3$ $[M-H]^-$ 272.1287, found 272.1283.

(2*R*)-3-(3-Amino-5-hydroxy-phenyl)-2-methyl-propionic acid:

The carboxylic acid described above (88 mg, 0.32 mmol, 1.0 eq) was dissolved in 4 ml MeOH/H_2O (3:1), and NH_2OH * HCl (111 mg, 1.6 mmol, 5.0 eq) and KOH (36 mg, 0.64 mmol, 2.0 eq) were added. The mixture was stirred for 60 hours at 60°C and subsequently neutralized by adding 0.1 M HCl. The mixture was evaporated to dryness under reduced pressure. Purification by flash column chromatography (ethyl acetate/methanol 10:1) yielded the amino acid (39 mg, 0.20 mmol, 63%).

Faint yellow crystals; mp: 48-52°C; $[a]_D^{20}$ = - 11.0 (*c* = 1.4 in MeOH);

^{1}H-NMR (400 MHz, CD_3OD, CHD_2OD = 3.31 ppm) *d*: 6.12 (m, 1H, H-Ar), 6.04 (m, 2H, H-Ar), 2.83 (dd, 1H, *J* = 13.3, 6.7 Hz, 3-H), 2.63 (m, 1H, 2-H), 2.42 (dd, 1H, *J* = 13.3, 7.9 Hz, 3-H'), 1.10 (d, 3H, *J* = 6.9 Hz, 2-Me).

^{13}C-NMR (100 MHz, CD_3OD, CD_3OD = 49.0 ppm) *d*: 180.7 (s, C-1), 159.1, 149.5, 143.0 (s, C-Ar), 109.4, 107.5, 101.9 (d, C-Ar), 42.8 (d, C-2), 40.9 (t, C-3), 17.3 (q, 2-Me).

HRMS (ESI): calculated for $C_{10}H_{13}NO_3$ $[M-H]^-$ 194.0817, found 194.0817.

Selected analytical data for enantiomer: mp: 49-52°C; $[a]_D^{20}$ = + 10.4 (*c* = 0.8 in MeOH); HRMS (ESI): calculated for $C_{10}H_{13}NO_3$ $[M-H]^-$ 194.0817, found 194.0824.

(2*R*)-3-(3-Amino-5-hydroxy-phenyl)-2-methyl-thiopropionic acid *S*-(2-acetylamino-ethyl)-ester (3a):

To a solution of the amino acid described above (39 mg, 0.2 mmol, 1.0 eq) in 2 ml acetonitrile was added *N*-acetylcysteamine (28 µl, 0.26 mmol, 1.3 eq). Subsequently, DCC (54 mg, 0.26 mmol, 1.3 eq) and 4-DMAP (2.4 mg, 0.02 mmol, 0.1 eq) were added and the reaction mixture was stirred overnight at room temperature. The precipitated dicyclohexyl urea was filtered off and the remaining solution was concentrated under reduced pressure. Flash column chromatography of the crude product (gradient, hexanes/ethyl acetate 1:1 to pure ethyl acetate to ethyl acetate/methanol 10:1; $CuSO_4$ impregnated silica gel on top of silica gel column) afforded the title compound **3a** (38.5 mg, 0.13 mmol, 65%) as a sticky yellow solid.

$[a]_D^{20}$ = - 10.1 (*c* = 1.0 in MeOH);

^{1}H-NMR (400 MHz, CD_3OD, CHD_2OD = 3.31 ppm) *d*: 6.08 (m, 2H, H-Ar), 6.00 (m, 1H, H-Ar), 3.30 (m, 2H, SCH_2CH_2), 2.98 (m, 2H, SCH_2CH_2), 2.92 (m, 2H, 2-H, 3-H), 2.47 (dd, 1H, *J* = 13.1, 7.1 Hz, 3-H'), 1.92 (s, 3H, $COCH_3$), 1.14 (d, 3H, *J* = 6.8 Hz, 2-CH_3).

^{13}C-NMR (100 MHz, CD_3OD, CD_3OD = 49.0 ppm) *d*: 204.5 (s, SCO), 173.4 (s, NCO), 159.2, 149.8, 142.3 (s, C-Ar), 109.3, 107.3, 101.9 (d, C-Ar), 51.5 (d, C-2), 41.2 (t, C-3), 40.1 (t, SCH_2CH_2), 29.0 (t, SCH_2CH_2), 22.5 (q, $COCH_3$), 17.8 (q, 2-CH_3).

HRMS (ESI): calculated for $C_{14}H_{20}N_2O_3S$ $[M-H]^-$ 295.1116, found 295.1116.

Selected analytical data for enantiomer **3b**: $[a]_D^{20}$ = + 10.0 (*c* = 0.6 in MeOH); HRMS (ESI): calculated for $C_{14}H_{20}N_2O_3S$ $[M-H]^-$ 295.1116, found 295.1123.

3-(*tert*-Butoxycarbonylamino)-5-hydroxybenzoic acid methylester:

The starting material[1] (5.0 g, 29.9 mmol, 1.0 eq) was dissolved in 30 ml THF, 115 ml of a saturated $NaHCO_3$ solution was added and the mixture was treated with Boc_2O (6.53 g, 29.9 mmol, 1.0 eq, as 1M solution in THF). After 2 hours 3.0 g of solid $NaHCO_3$ were added and stirring was continued for an additional 36 hours at room temperature. The organic layer was removed under reduced pressure and the remaining aqueous phase extracted 3x with ethyl acetate. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. Recrystallization from $CHCl_3$ afforded 7.59 g (28.4 mmol, 95%).

Colorless crystals: mp: 146°C;

^{1}H-NMR (400 MHz, acetone-d_6, acetone-d_5 = 2.05 ppm) *d*: 8.67 (bs, 1H), 8.53 (bs, 1H), 7.73 (m, 1H, H-Ar), 7.40 (m, 1H, H-Ar), 7.13 (m, 1H, H-Ar), 3.84 (s, 3H, OCH_3), 1.48 (s, 9H, *t*Bu).

^{13}C-NMR (100 MHz, acetone-d_6, acetone-d_6 = 29.3 ppm) *d*: 166.6 (s, *C*OOMe), 158.2, 153.1 (2x s, C-Ar, N*C*OO), 141.5, 132.1 (s, C-Ar), 110.9, 110.4, 110.0 (d, C-Ar), 79.7 (s, *t*Bu), 51.7 (q, OCH_3), 28.0 (q, *t*Bu).

HRMS (ESI): calculated for $C_{13}H_{17}NO_5$ $[M-H]^-$ 266.1028, found 266.1038.

3-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-benzoic acid methylester:

The procedure for the silylation of phenols described above was employed except that CH_2Cl_2 was used as solvent, which afforded the title compound (5.41 g 10.7 mmol, 99%) as a colorless, sticky foam.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.73 - 7.68 (m, 4H, H-Ar), 7.63 (m, 1H, H-Ar), 7.45 - 7.35 (m, 6H, H-Ar), 7.09 (m, 1H, H-Ar), 6.95 (m, 1H, H-Ar), 6.36 (bs, 1H, NH), 3.78 (s, 3H, OCH_3), 1.47 (s, 9H, *t*Bu), 1.10 (s, 9H, *t*Bu).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 166.6 (s, *C*OOMe), 156.1, 152.3 (s, C-Ar, N*C*OO), 139.3 (s, C-Ar), 135.5 (d, C-Ar), 132.4, 131.6 (s, C-Ar), 130.0, 127.8, 115.5, 114.2, 112.4 (d, C-Ar), 80.8 (s, *t*Bu), 52.0 (q, OCH_3), 28.2 (q, *t*Bu), 26.5 (q, *t*Bu), 19.5 (s, *t*Bu).

HRMS (ESI): calculated for $C_{29}H_{35}NO_5Si$ $[M-H]^-$ 504.2206, found 504.2209.

3-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-benzyl alcohol:

The procedure for the reduction of methyl esters described above was employed here, which afforded the title compound (4.73 g, 9.9 mmol, 99%) as a colorless foam.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.72 - 7.68 (m, 4H, H-Ar), 7.44 - 7.33 (m, 6H, H-Ar), 7.06 (m, 1H, H-Ar), 6.58 (m, 1H, H-Ar), 6.39 (m, 1H, H-Ar), 6.31 (bs, 1H, NH), 4.41 (s, 2H, CH_2), 1.59 (bs, 1H, OH), 1.46 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$= 77.0 ppm) *d*: 156.2, 152.5 (s, N*C*OO, C-Ar), 142.9, 139.3 (s, C-Ar), 135.5 (d, C-Ar), 132.7 (s, C-Ar), 129.9, 127.8 (d, C-Ar), 112.8, 109.7, 109.0 (d, C-Ar), 80.5 (s, *t*Bu), 65.0 (t, CH_2), 28.3 (q, *t*Bu), 26.5 (q, *t*Bu), 19.4 (s, *t*Bu).

HRMS (ESI): calculated for $C_{28}H_{35}NO_4Si$ $[M+Na]^+$ 500.2233, found 500.2235.

3-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-benzyl bromide:

The procedure for the bromination of benzylic alcohols described above was employed here again, which afforded the title compound (4.33 g, 8.0 mmol, 89%) as a colorless, sticky foam.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.73 - 7.68 (m, 4H, H-Ar), 7.45 - 7.35 (m, 6H, H-Ar), 7.15 (m, 1H, H-Ar), 6.56 (m, 1H, H-Ar), 6.43 (m, 1H, H-Ar), 6.28 (bs, 1H, NH), 4.22 (s, 2H, CH_2), 1.47 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 156.1, 152.3 (s, C-Ar, NHCOO), 139.4, 139.3 (s, C-Ar), 135.5 (d, C-Ar), 132.5 (s, C-Ar), 130.0 (d, C-Ar), 127.8 (d, C-Ar), 115.2, 111.8, 109.7 (d, C-Ar), 80.7 (s, *t*Bu), 33.3 (t, CH_2), 28.3 (q, *t*Bu), 26.4 (q, *t*Bu), 19.4 (s, *t*Bu).

HRMS (ESI): calculated for $C_{28}H_{34}BrNO_3Si$ $[M-H]^-$ 538.1413, found 538.1397.

3-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-benzyl iodide (4):

The procedure for the Finkelstein reaction described above was employed here, which afforded the title compound **4** (1.10 g 1.88 mmol, 94%) as a yellowish foam after additional filtration with dichloromethane over silica gel.

^{1}H-NMR (200 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.74 - 7.67 (m, 4H, H-Ar), 7.47 - 7.33 (m, 6H, H-Ar), 7.12 (m, 1H, H-Ar), 6.53 (m, 1H, H-Ar), 6.40 (m, 1H, H-Ar), 6.23 (bs, 1H, NH), 4.18 (s, 2H, CH_2), 1.47 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu).

^{13}C-NMR (50 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 156.1, 152.3 (s, C-Ar, NHCOO), 140.8, 139.4 (s, C-Ar), 135.5 (d, C-Ar), 132.6 (s, C-Ar), 130.0 (d, C-Ar), 127.9 (d, C-Ar), 115.0, 111.5, 109.4 (d, C-Ar), 80.6 (s, *t*Bu), 28.3 (q, *t*Bu), 26.5 (q, *t*Bu), 19.4 (s, *t*Bu), 5.3 (t, CH_2).

(*2RS*)-2-Methyl-3-[3-(*tert*-butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-phenyl]-propionic acid *tert*-butylester:

Propionic acid *tert*-butyl ester (0.88 g, 6.75 mmol, 3.0 eq) was dissolved in 15 ml dry THF and cooled to -78°C. After addition of LDA (3.38 ml, 6.75 mmol, as a 2M solution in THF/n-heptane) the mixture was stirred for 30 minutes with dropwise addition of benzyl iodide **4** (1.30 g, 2.25 mmol, 1.0 eq, as 0.5M solution in THF). Upon further stirring for 30 minutes the mixture was hydrolyzed by adding 20 ml aqueous NH_4Cl-solution and warmed to room temperature. The organic layer was separated and the aqueous phase extracted twice with ethyl acetate. The combined organic phases were washed with

brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (hexanes/ethyl acetate 25:1) to furnish the product (1.2 g, 2.03 mmol, 90%) as a highly viscous compound.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.73 - 7.68 (m, 4 H, H-Ar), 7.44 - 7.33 (m, 6H, H-Ar), 6.86 (bs, 1H, H-Ar), 6.57 (m, 1H, H-Ar), 6.23 (bs, 1H, NH), 6.18 (m, 1H, H-Ar), 2.76 (m, 1H, 3-H), 2.31 (m, 2H, 2-H, 3-H'), 1.47 (s, 9H, *t*Bu), 1.38 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu), 0.86 (d, 3H, *J* = 6.7 Hz, 2-Me).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 175.5 (s, *C*OO*t*Bu), 155.8, 152.4 (s, NHCO, C-Ar), 141.5, 139.0 (s, C-Ar), 135.5 (d, C-Ar), 132.9 (s, C-Ar), 129.8, 127.7, 115.4, 111.9, 107.8 (d, C-Ar), 80.3 (s, *t*Bu), 79.9 (s, *t*Bu), 41.8 (d, C-2), 39.5 (t, C-3), 28.3 (q, *t*Bu), 28.0 (q, *t*Bu), 26.5 (q, *t*Bu), 19.4 (s, *t*Bu), 16.4 (q, 2-Me).

(*2RS*)-2-Methyl-3-[3-(*tert*-butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-phenyl]-propanol:

The procedure for the reduction of the ester derived from the alkylation described above was employed here, which afforded the title compound **4** (0.79 g, 1.52 mmol, 75%) as a colorless foam after chromatographic purification with hexanes/ethyl acetate 3:1.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.73 - 7.69 (m, 4H, H-Ar), 7.44 - 7.33 (m, 6H, H-Ar), 6.81 (bs, 1H, H-Ar), 6.68 (m, 1H, H-Ar), 6.32 (bs, 1H, NH), 6.10 (m, 1H, H-Ar), 3.22 (m, 2H, 1-H, 1-H'), 2.40 (dd, 1H, *J* = 13.3, 6.8 Hz, 3-H), 2.15 (dd, 1H, *J* = 13.3, 7.7 Hz, 3-H'), 1.65 (bs, 1H, OH), 1.62 (m, 1H, 2-H), 1.48 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu), 0.70 (d, 3H, *J* = 6.8 Hz, 2-Me).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 155.8, 152.5 (s, C-Ar, NHCO), 142.3, 139.1 (s, C-Ar), 135.5 (d, C-Ar), 132.9 (s, C-Ar), 129.8, 127.7, 115.3, 112.0, 107.6 (d, C-Ar), 80.3 (s, *t*Bu), 67.1 (t, C-1), 39.5 (t, C-3), 37.3 (d, C-2), 28.3 (q, *t*Bu), 26.4 (q, *t*Bu), 19.4 (s, *t*Bu), 16.4 (q, 2-Me).

HRMS (ESI): calculated for $C_{31}H_{41}NO_4Si$ $[M+Na]^+$ 542.2703, found 542.2714.

(*2RS*)-2-Methyl-3-[3-(*tert*-butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-phenyl]-propionaldehyde:

Benzyl alcohol (240 mg, 0.46 mmol, 1.0 eq) was dissolved in dry dichloromethane and $NaHCO_3$ (155 mg, 1.84 mmol, 4.0 eq) and Dess-Martin-periodinan (234 mg, 0.55 mmol, 1.2 eq) were added. The reaction mixture was stirred for 30 minutes before it was hydrolyzed by adding 155 mg of $NaHCO_3$, 4 ml of saturated $Na_2S_2O_3$-solution and 4 ml water. The mixture was vigorously stirred for 30 minutes, the organic layer was separated and

the aqueous phase was extracted 3x with dichloromethane. The combined organic phases were washed twice with a 1:1 mixture of $NaHCO_3$/$Na_2S_2O_3$-solution, followed by a washing with brine. The dried organic layer ($MgSO_4$) was concentrated under reduced pressure to yield the crude aldehyde (217 mg, 0.42 mmol, 91%), which was used in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 9.50 (d, 1H, *J* = 1.3 Hz, 1-H), 7.73 - 7.66 (m, 4H, H-Ar), 7.47 - 7.31 (m, 6H, H-Ar), 6.85 (bs, 1H, H-Ar), 6.65 (dd, 1H, *J* = 2.1, 2.1 Hz, H-Ar), 6.28 (bs, 1H, NH), 6.10 (dd, 1H, *J* = 2.1, 1.6 Hz, H-Ar), 2.79 (m, 1H, 3-H), 2.30 (m, 2H, 2-H, 3-H'), 1.48 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu), 0.82 (d, 3H, *J* = 6.8 Hz, 2-Me).

(2*E*, 4*RS*)-4-Methyl-5-[3-(*tert*-butoxycarbonylamino)-5-(*tert*-butyl-diphenyl-silanyloxy)-phenyl]-thiopent-2-enoic acid *S*-(2-acetylamino-ethyl)-ester:

The aldehyde described above (200 mg, 0.386 mmol, 1.0 eq) was dissolved in 2 ml $CHCl_3$ and the ylide **7** (325 mg, 0.772 mmol, 2.0 eq) was added (a high concentration of the reactants is essential for complete conversion).[5] After stirring for 48 hours at 60°C the product was purified by flash column chromatography (hexanes/ethyl acetate 1:1) to yield the SNAC ester (207 mg, 0.313 mmol, 81%).

Colorless, sticky solid; mp: 60-75°C.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.72 – 7.69 (m, 4H, H-Ar), 7.44 - 7.34 (m, 6H, H-Ar), 6.81 (bs, 1H, H-Ar), 6.75 (dd, 1H, *J* = 15.6, 6.9 Hz, 3-H), 6.64 (m, 1H, H-Ar), 6.35 (bs, 1H, NH), 6.09 (m, 1H, H-Ar), 5.94 (bs, 1H, NH), 5.93 (dd, 1H, *J* = 15.6, 0.9 Hz, 2-H), 3.44 (dt, 2H, *J* = 6.4, 6.1 Hz, C*H*$_2$NH), 3.07 (t, 2H, *J* = 6.1 Hz, CH_2S), 2.49 (m, 1H, 5-H), 2.26 (m, 2H, 4-H, 5-H'), 1.95 (s, 3H, $COCH_3$), 1.48 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu), 0.80 (d, 3H, J = 6.2 Hz, 4-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$= 77.0 ppm) *d*: 190.4 (s, C-1), 170.2 (s, NH*C*OCH$_3$), 156.0, 152.5 (s, C-Ar, NH*C*OOtBu), 150.7 (d, C-3), 141.0, 139.2 (s, C-Ar), 135.5 (d, C-Ar), 132.8 (s, C-Ar), 129.9 (d, C-Ar), 126.7 (d, C-2), 115.2, 111.9, 108.0 (d, C-Ar), 80.4 (s, *t*Bu), 42.0 (t, C-5), 39.8 (t, CH_2NH), 37.9 (d, C-4), 28.3 (t, CH_2S), 28.3 (q, *t*Bu), 26.5 (q, *t*Bu), 23.2 (q, CO*C*H$_3$), 19.4 (s, *t*Bu), 18.3 (q, 4-CH_3).

HRMS (ESI): calculated for $C_{87}H_{48}N_2O_5SSi$ $[M-H]^-$ 659.2975, found 659.3000.

(2*E*, 4*RS*)-4-Methyl-5-[3-(*tert*-butoxycarbonylamino)-5-hydroxy-phenyl]-thiopent-2-enoic acid *S*-(2-acetylamino-ethyl)-ester:

The procedure for the desilylation described above (except that only 0.5 eq TBAF * $3H_2O$ were necessary for complete conversion) was employed here, which afforded the title phenol

(123 mg, 0.291 mmol, 93%) as a sticky solid after chromatographic purification with hexanes/ethyl acetate 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.73 (bs, 1H, OH), 6.87 (dd, 1H, *J* = 15.7, 6.7 Hz, 3-H), 6.77 (m, 2H, H-Ar), 6.72 (bs, NH), 6.30 (m, 1H, H-Ar), 6.25 (t, 1H, *J* = 6.0 Hz, NH), 6.00 (d, 1H, *J* = 15.7 Hz, 2-H), 3.47 (dt, 2H, *J* = 6.1, 6.0 Hz, C*H*$_2$NH), 3.06 (m, 2H, CH_2S), 2.56 (m, 3H, 4-H, 5-H, 5-H′), 1.97 (s, 3H, $COCH_3$), 1.50 (s, 9H, *t*Bu), 1.05 (d, 3H, *J* = 6.0 Hz, 4-Me).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 190.7 (s, C-1), 171.2 (s, NH*C*OCH_3), 156.9, 152.8 (s, C-Ar, NH*C*O*O*t*Bu), 151.0 (d, C-3), 141.3 (s, C-Ar), 139.4 (s, C-Ar), 127.1 (d, C-2), 111.2, 111.0, 104.0 (d, C-Ar), 80.4 (s, *t*Bu), 42.5 (t, C-5), 39.6 (t, CH_2NH), 38.0 (d, C-4), 28.4 (t, CH_2S), 28.3 (q, *t*Bu), 23.0 (q, CO*C*H_3), 18.8 (q, 4-Me).

HRMS (ESI): calculated for $C_{21}H_{30}N_2O_5S$ $[M-H]^-$ 421.1797, found 421.1799.

(2*E*, 4*RS*)-4-Methyl-5-[3-amino-5-hydroxy-phenyl]-thiopent-2-enoic acid *S*-(2-acetylamino-ethyl)-ester (5):

Four ml of dry dichloromethane were poured into a flask containing the phenol described above (100 mg, 0.237 mmol, 1.0 eq). While stirring at room temperature, 0.90 ml CF_3COOH (11.8 mmol, ~ 50 eq.) were added whereupon the phenol completely dissolved. After complete conversion (12 hours) the mixture was hydrolyzed by adding a $NaHCO_3$ solution and finally adjusted to pH 7 with phosphate buffer. The organic layer was separated and the remaining aqueous phase extracted 3x with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 93% of the crude product. Final purification by flash column chromatography (pure ethyl acetate) afforded the title compound **5** (48 mg, 0.149 mmol, 63%).

^{1}H-NMR (400 MHz, CD_3OD, CHD_2OD = 3.31 ppm) *d*: 6.87 (dd, 1H, *J* = 15.6, 7.2 Hz, 3-H), 6.09 - 6.04 (m, 3H, 2x H-Ar, 2-H), 6.00 (m, 1H, H-Ar), 3.33 (m, 2H, NHC*H*$_2$), 3.04 (t, 2H, *J* = 6.7 Hz, CH_2S), 2.58 (m, 1H, 4-H), 2.53 (dd, 1H, *J* = 12.9, 6.9 Hz, 5-H), 2.44 (dd, 1H, *J* = 12.9, 7.2 Hz, 5-H′), 1.91 (s, 3H, $COCH_3$), 1.04 (d, 3H, *J* = 6.5 Hz, 4-CH_3).

^{13}C-NMR (100 MHz, CD_3OD, CD_3OD = 49.0 ppm) *d*: 191.3 (s, C-1), 173.4 (s, *C*OCH_3), 159.1 (s, C-Ar), 152.0 (d, C-3), 149.7, 142.8 (s, C-Ar), 127.9 (d, C-2), 109.4, 107.5, 101.8 (d, C-Ar), 43.5 (t, C-5), 40.2 (t, $NHCH_2$), 39.3 (d, C-4), 28.9 (t, CH_2S), 22.5 (q, CO*C*H_3), 19.2 (q, 4-CH_3).

HRMS (ESI): calculated for $C_{16}H_{22}N_2O_3S$ $[M+Na]^+$ 345.1249, found 345.1254.

(2-Acetylamino-ethylsulfanyl-carbonylmethyl)-triphenylphosphonium bromide:

Bromo-thioacetic acid *S*-(2-acetylamino-ethyl)-ester[6] (2.64 g, 11.0 mmol, 1.0 eq) was dissolved in 50 ml toluene, heated up to 80°C and subsequently treated with 2.89 g PPh_3 (11.0 mmol, 1.0 eq). The mixture was further stirred for 12 hours whereupon a white solid precipitated. Filtration and washing (toluene) of this solid yielded (4.86 g, 9.68 mmol, 88%) of the Wittig salt after drying in vacuo.

Colorless crystals; mp: 182-184°C

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 8.12 (t, 1H, *J* = 5.9 Hz, NH), 7.87 - 7.76 (m, 9H, H-Ar), 7.71 - 7.64 (m, 6H, H-Ar), 5.85 (d, 2H, J_{P-H} = 12.3 Hz, CH_2P), 3.32 (dt, 2H, *J* = 5.9, 5.7 Hz, CH_2N), 3.01 (t, 2H, *J* = 5.7 Hz, CH_2S), 1.94 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 190.4 (s, J_{P-C} = 6.7 Hz, COS), 171.4 (s, CONH), 135.1 (d, J_{P-C} = 3.1 Hz, C-Ar), 133.9 (d, J_{P-C} = 10.7 Hz, C-Ar), 130.2 (d, J_{P-C} = 13.2 Hz, C-Ar), 117.9 (s, J_{P-C} = 88.7 Hz, C-Ar), 40.5 (t, J_{P-C} = 55.0 Hz, CH_2P), 37.9 (t, CH_2N), 30.6 (t, CH_2S), 23.1 (q, CH_3).

HRMS (ESI): calculated for $C_{24}H_{25}BrNO_2PS$ $[M-Br]^+$ 422.1344, found 422.1358.

(Triphenyl-λ^5-phosphaneylidene)-thioacetic acid S-(2-acetylamino-ethyl) ester:

The Wittig salt described above (2.01 g, 4 mmol, 1.0 eq) was dissolved in 20 ml water and treated with 0.5 *N* aqueous NaOH to pH 10 whereupon a white solid precipitated. The mixture was stirred for ten minutes and extracted 5x with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure, whereupon the ylide crystallized (1.68 g, 3.986 mmol, >99%).

Colorless crystals; mp: 170-172°C (decomposition)

^{1}H-NMR (400 MHz, $CDCl_3$, TMS = 0.00 ppm) *d*: 7.66 - 7.57 (m, 9H, H-Ar), 7.52 - 7.47 (m, 6H, H-Ar), 7.32 (bs, 1H, NH), 3.82 (d, 1H, J_{P-H} = 22.0 Hz, CH=P), 3.37 (m, 2H, CH_2N), 2.99 (m, 2H, CH_2S), 1.69 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77.0 ppm) *d*: 181.5 (s, J_{P-C} = 5.0 Hz, COS), 170.3 (s, CONH), 132.9 (d, J_{P-C} = 10.4 Hz, C-Ar), 132.5 (d, J_{P-C} = 2.9 Hz, C-Ar), 129.0 (d, J_{P-C} = 12.5 Hz, C-Ar), 126.1 (s, J_{P-C} = 91.4 Hz, C-Ar), 48.7 (d, J_{P-C} = 110.0 Hz, CH=P), 42.8 (t, CH_2N), 27.5 (t, J_{P-C} = 2.5 Hz, CH_2S), 23.0 (q, CH_3).

HRMS (ESI): calculated for $C_{24}H_{24}NO_2PS$ $[M+H]^+$ 422.1344, found 422.1339.

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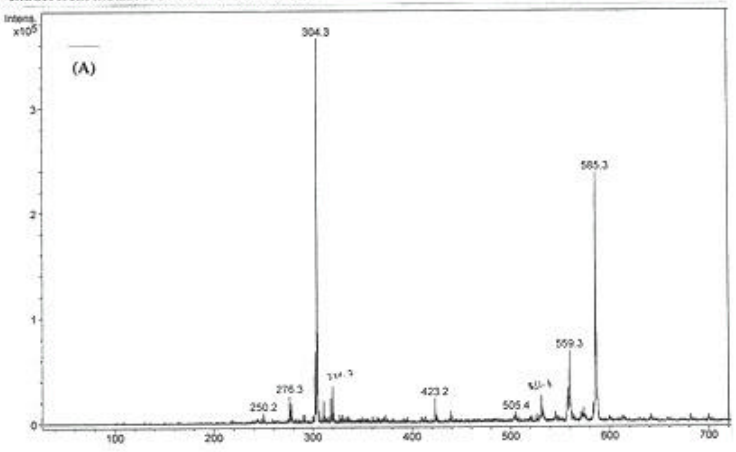
Figure S 1. ESI-MS (A) and daughter ion spectrum of mass 657 $(M+Na)^+$ (B) of extract from mutant HGF073 without addition.



Acquisition Parameter

Ion Source Type	ESI	Mass Range Mode	Std/Normal	Ion Polarity	Positive
Scan Begin	30.00 m/z	Capillary Exit	100.0 Volt	Averages	4 Spectra
Scan End	1000.00 m/z	Skim 1	30.0 Volt	Trap Drive	55.0

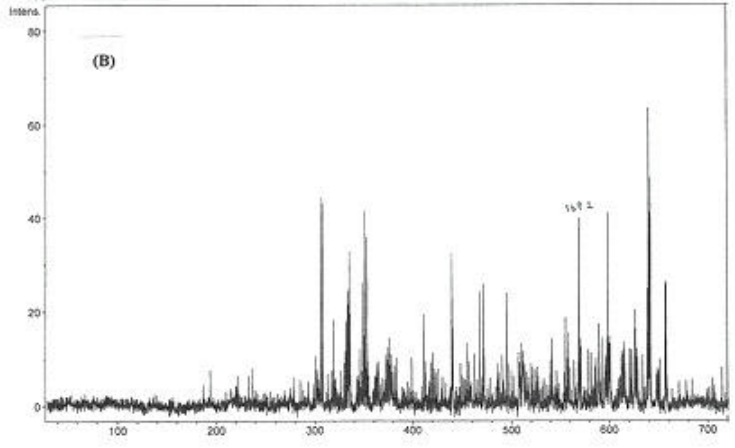
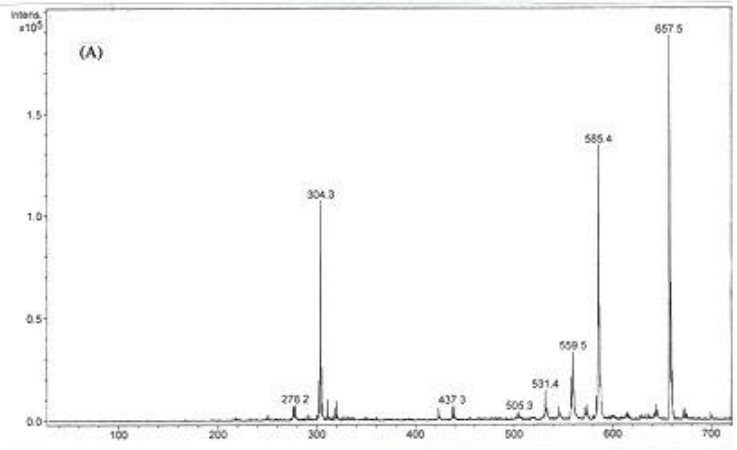


Figure S 2. ESI-MS (A) and daughter ion spectrum of mass 657 $(M+Na)^+$ (B) of extract from mutant HGF073 with addition of AHBA.



Acquisition Parameter

Ion Source Type	ESI	Mass Range Mode	Std/Normal	Ion Polarity	Positive
Scan Begin	30.00 m/z	Capillary Exit	100.0 Volt	Averages	4 Spectra
Scan End	1000.00 m/z	Skim 1	30.0 Volt	Trap Drive	55.0

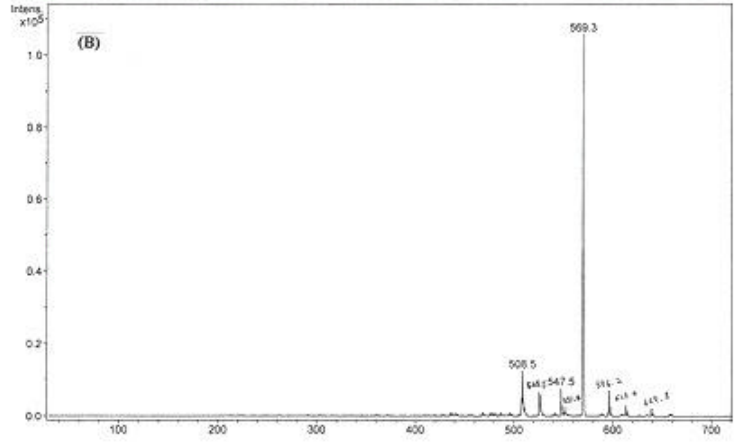


Figure S 3. ESI-MS (A) and daughter ion spectrum of mass 657 (M+Na)⁺ (B) of extract from mutant HGF073 with addition of (*R*)-diketide SNAC **3a**.

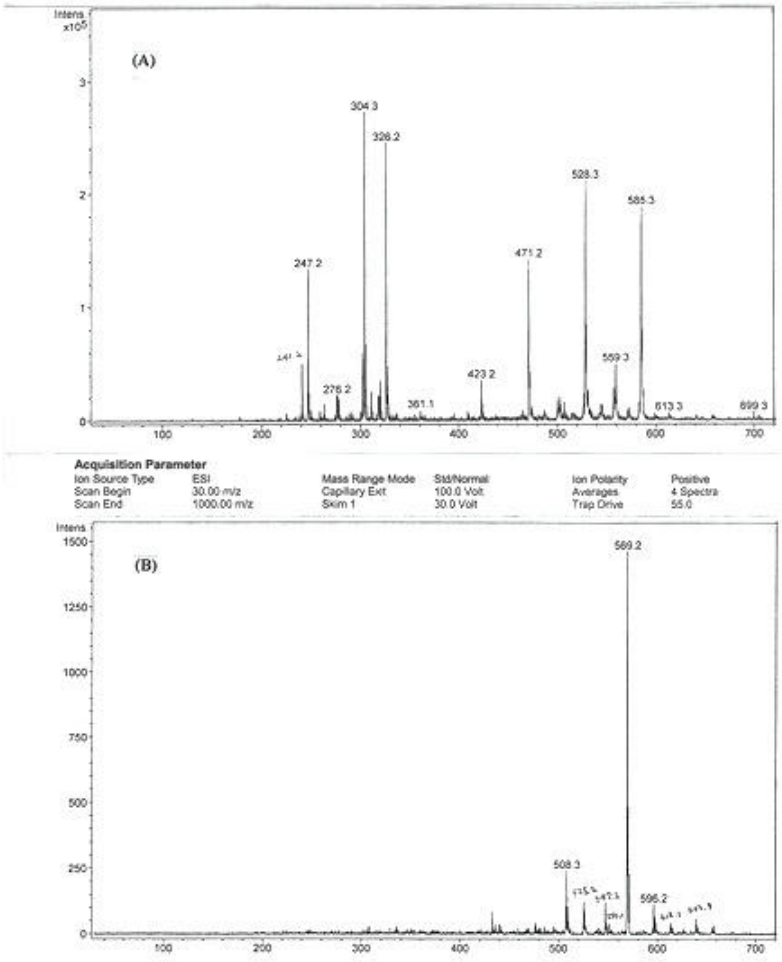


Figure S 4. ESI-MS (A) and daughter ion spectrum of mass 657 (M+Na)⁺ (B) of extract from mutant HGF073 with addition of (*S*)-diketide SNAC **3b**.

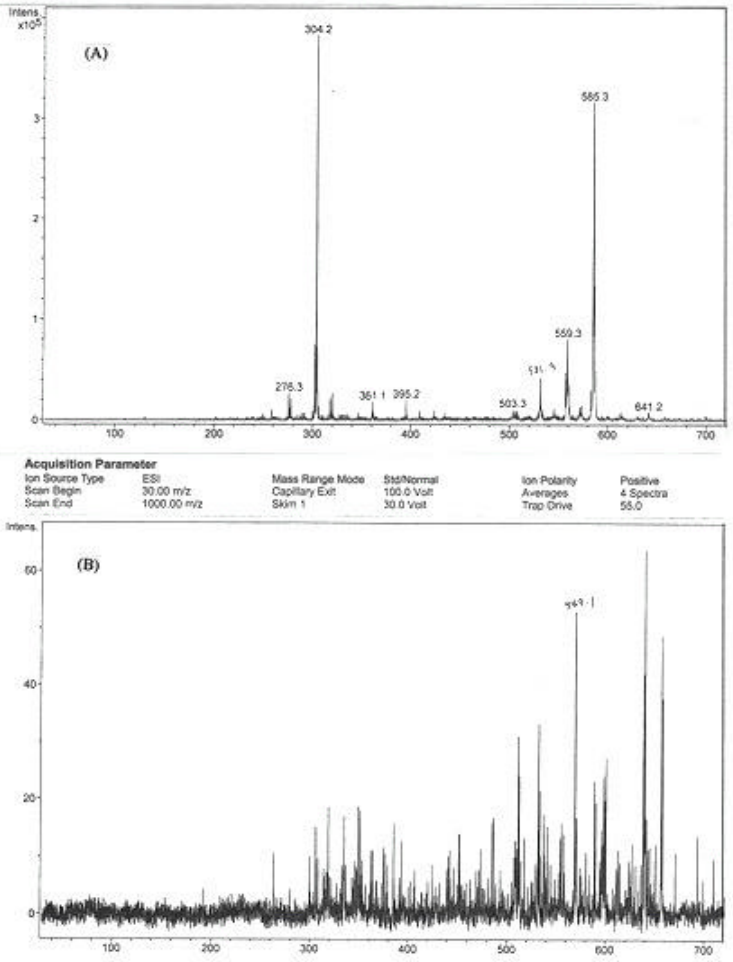
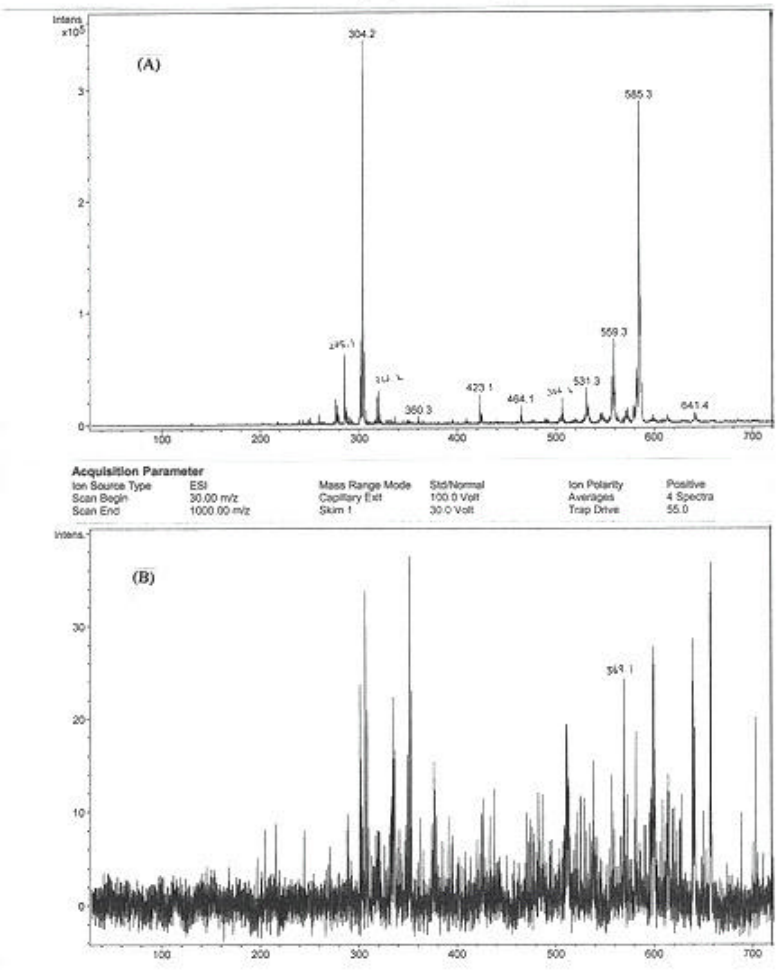
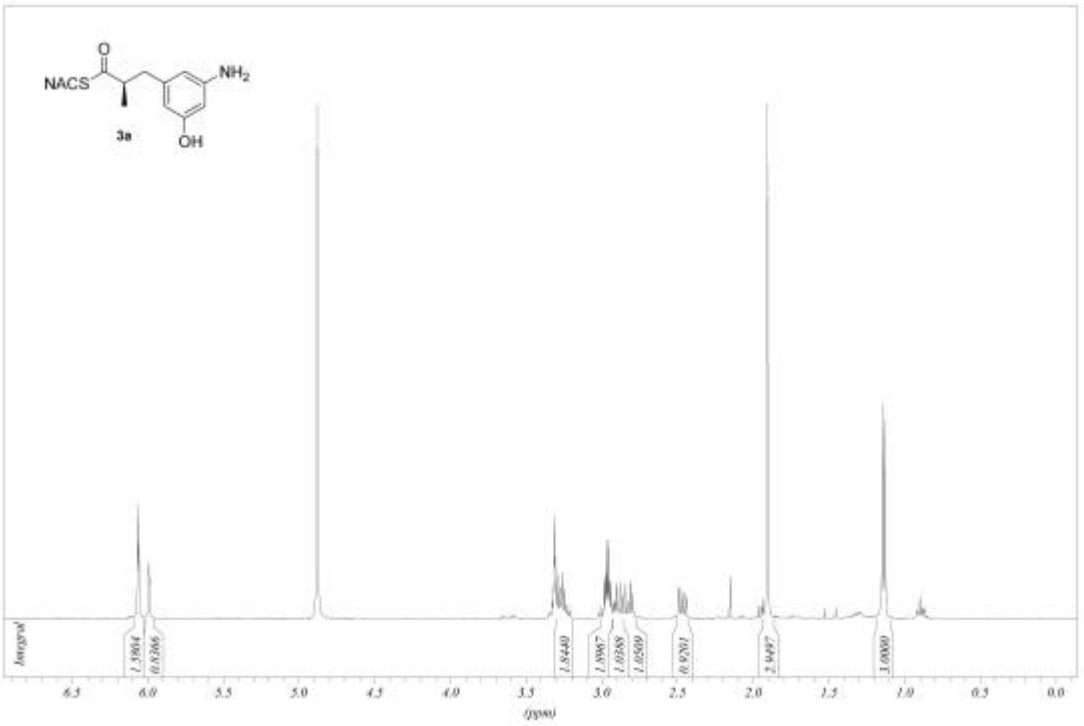
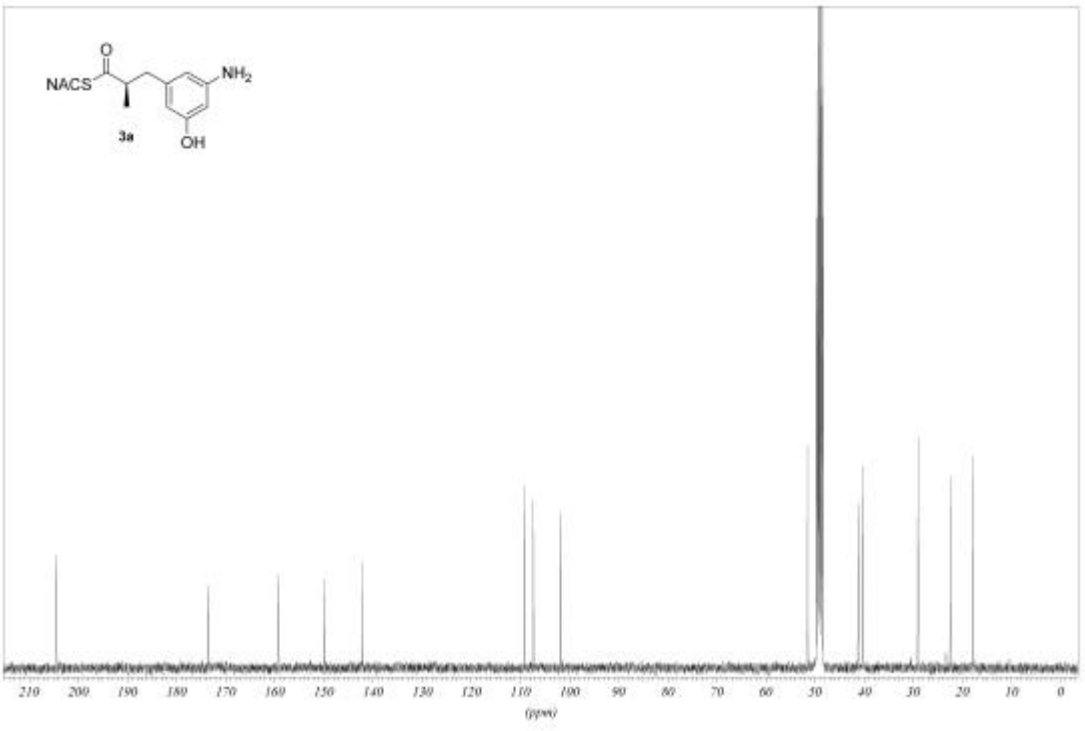
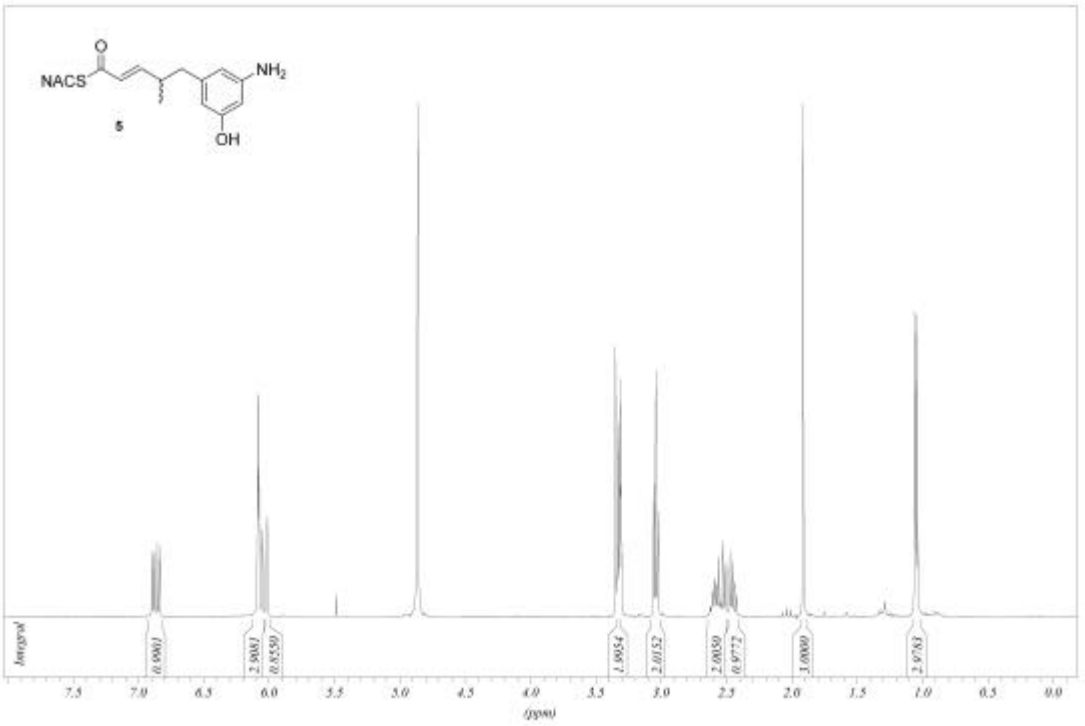


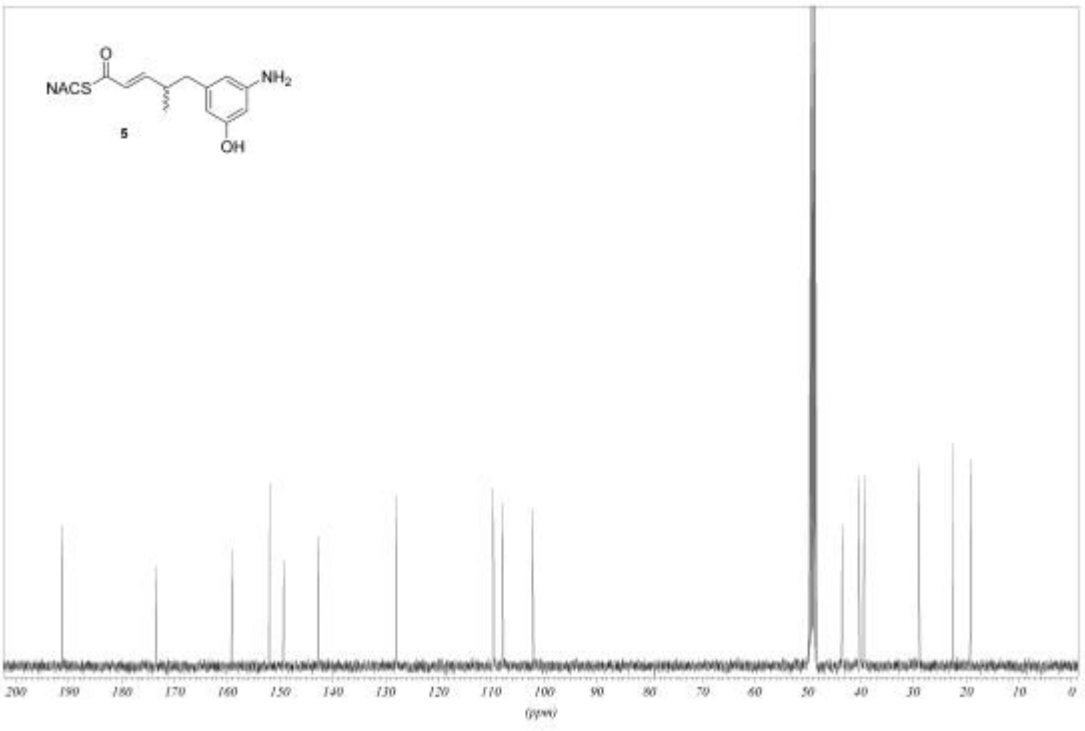
Figure S 5. ESI-MS (A) and daughter ion spectrum of mass 657 $(M+Na)^+$ (B) of extract from mutant HGF073 with addition of (*rac*)-triketide SNAC 5.




NACS
O
NH2
OH
3a
Integral
1.5904
0.5366
4.4410
1.8967
1.0369
1.0509
0.9201
2.4497
3.0000
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


NACS
O
NH2
OH
3a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


NACS
O
NH2
OH
5
Integral
0.9981
2.9081
0.8559
1.9554
2.0152
2.0059
0.9772
3.0000
2.9763
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


NACS
O
NH2
OH
5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)