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Appendix I

Supplementary materials for Chapter 3

Application of systems biology methods for the identification of novel natural products in *Streptomyces* species

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Table S1 Significantly up or down regulated (with *p*-value less than 0.05) quantified proteins in at least one comparison

Protein IDs	MBT28-30/WT (2log)	*p*-value	MBT28-91/WT (2log)	*p*-value	MBT28-91/30 (2log)	*p*-value	predicted function
NODE_001_gene_001	0.2	0.604	3.1	0.020	2.8	0.008	1 4-alpha-glucan branching enzyme GlgB 2
NODE_001_gene_012	-1.9	0.174	-3.1	0.033	-1.4	0.184	6-phosphofructokinase 2
NODE_001_gene_037	-2.4	0.075	-3.3	0.025	-1.0	0.384	Methylmalonyl-CoA epimerase
NODE_005_gene_007	1.1	0.077	-1.6	0.577	-2.6	0.010	Alanine--tRNA ligase
NODE_009_gene_004	-0.3	0.994	-2.3	0.150	-2.2	0.045	Secreted protease
NODE_012_gene_017	-1.5	0.479	-3.5	0.021	-2.3	0.029	ATP-dependent Clp protease proteolytic subunit 1
NODE_016_gene_001	3.6	0.000	4.3	0.002	0.6	0.576	Secreted protein
NODE_016_gene_019	-1.2	0.658	-3.8	0.010	-2.5	0.014	Ribose-phosphate pyrophosphokinase
NODE_020_gene_023	0.2	0.581	2.8	0.030	2.4	0.026	Secreted protein
NODE_020_gene_034	0.8	0.263	2.8	0.035	2.0	0.064	Flp pilus assembly protein CpaB
NODE_021_gene_028	-2.6	0.068	-3.9	0.007	-1.2	0.272	Cytochrome oxidase subunit I
NODE_021_gene_047	2.4	0.004	3.4	0.012	0.9	0.388	Secreted protein
NODE_021_gene_048	2.5	0.003	4.7	0.001	2.7	0.012	Nuclear export factor GLE1
NODE_025_gene_009	-2.9	0.039	-1.9	0.400	1.0	0.268	Putative PadR-like family transcriptional regulator
NODE_025_gene_015	-1.0	0.532	-3.2	0.029	-2.4	0.029	Ectoine/hydroxyectoine ABC transporter permease EhuC
NODE_025_gene_017	1.3	0.097	3.7	0.006	2.6	0.017	Methyltransferase
NODE_025_gene_022	1.7	0.037	0.6	0.467	-0.9	0.439	Nucleotide-binding protein
NODE_025_gene_023	1.7	0.033	4.5	0.001	2.5	0.021	Peptidoglycan-binding domain 1 protein
NODE_026_gene_007	1.9	0.009	3.7	0.007	1.7	0.072	Secreted protein
NODE_027_gene_001	2.3	0.003	3.4	0.013	1.6	0.088	Conserved hypothetical secreted protein
NODE_029_gene_014	3.2	0.000	2.5	0.051	-0.9	0.411	Secreted protein
NODE_032_gene_004	-1.9	0.174	-3.3	0.025	-1.2	0.254	Membrane protein
NODE_032_gene_009	0.9	0.205	-2.5	0.117	-3.1	0.004	Starvation-induced DNA protecting protein
NODE_033_gene_057	-2.6	0.048	-1.9	0.266	0.7	0.522	Cysteine--tRNA ligase
NODE_035_gene_011	-2.5	0.062	-3.4	0.018	-1.0	0.368	Glycerol-3-phosphate dehydrogenase
NODE_035_gene_012	-2.4	0.073	0.5	0.507	3.2	0.003	Glycerol kinase 1
NODE_035_gene_015	-0.3	0.707	3.0	0.024	2.6	0.007	Methionine synthase
NODE_035_gene_017	3.4	0.000	3.0	0.025	-0.7	0.532	Lipoprotein oligopeptide binding protein
NODE_036_gene_009	0.1	0.429	2.2	0.073	2.1	0.030	Oxidoreductase
NODE_042_gene_025	-1.6	0.262	-3.6	0.013	-1.8	0.089	Nucleotide sugar-1-phosphate transferase
NODE_047_gene_002	-3.8	0.003	-4.4	0.002	-0.5	0.644	Alkylhydroperoxidase like protein AhpD family
NODE_047_gene_007	-3.0	0.022	-2.9	0.056	-0.1	0.958	Alkylhydroperoxidase like protein AhpD family
NODE_048_gene_013	0.9	0.111	3.5	0.011	2.2	0.028	Carboxypeptidase
NODE_048_gene_015	3.9	0.000	3.0	0.025	-0.8	0.493	Metallopeptidase
NODE_051_gene_011	-2.1	0.133	0.2	0.628	2.2	0.039	Monooxygenase
NODE_057_gene_030	-3.3	0.015	-2.5	0.169	0.5	0.585	Putative oxidoreductase
NODE_057_gene_031	-2.7	0.040	-1.6	0.388	1.7	0.105	Putative 6-phospho-3-hexuloisomerase
NODE_057_gene_032	-2.8	0.031	-0.4	0.923	2.3	0.029	Putative triosephosphate isomerase
NODE_058_gene_031	-3.6	0.005	-1.5	0.410	0.8	0.465	Alkylhydroperoxidase AhpD family core domain-containing protein
NODE_062_gene_005	0.0	0.471	-2.4	0.207	-2.3	0.026	DNA-binding protein
NODE_063_gene_013	-3.2	0.013	-2.8	0.064	0.9	0.393	Glutamine synthetase 2
NODE_063_gene_031	2.2	0.007	2.0	0.102	-0.4	0.758	Maltose-binding protein
NODE_064_gene_033	2.5	0.002	1.5	0.202	-1.2	0.286	Secreted protein
NODE_065_gene_019	-2.7	0.040	-2.7	0.078	0.3	0.745	Carboxylesterase
NODE_065_gene_022	1.0	0.163	4.0	0.003	3.1	0.004	Cold shock domain-containing protein CspD
NODE_066_gene_007	-4.0	0.002	-4.0	0.005	-0.2	0.872	Secreted protein
NODE_069_gene_017	4.2	0.000	2.9	0.027	-1.1	0.323	Sugar transporter sugar binding protein
NODE_070_gene_012	2.9	0.000	4.1	0.004	1.0	0.271	Oxidoreductase
NODE_071_gene_024	0.2	0.347	-2.4	0.197	-2.7	0.009	Integral membrane protein
NODE_072_gene_025	1.1	0.134	-0.8	0.798	-2.2	0.043	Succinate-semialdehyde dehydrogenase
NODE_075_gene_003	-0.1	0.555	2.0	0.092	2.7	0.007	Putative methylesterase
NODE_078_gene_010	-2.6	0.049	-3.8	0.008	-1.0	0.376	Putative 3-oxoacyl-ACP synthase II
NODE_079_gene_007	1.0	0.177	-1.8	0.318	-2.3	0.035	Chloride peroxidase
NODE_079_gene_008	0.7	0.290	-1.5	0.444	-2.4	0.029	Alpha/beta hydrolase
NODE_082_gene_003	2.2	0.004	0.5	0.380	-1.3	0.211	Uncharacterized protein
NODE_089_gene_031	-0.5	0.822	2.7	0.038	3.0	0.002	SPFH domain/Band 7 family protein
NODE_090_gene_004	1.8	0.024	0.9	0.369	-1.1	0.333	Integral membrane protein
NODE_091_gene_005	1.2	0.057	-2.2	0.257	-3.6	0.000	Hypothetical cytosolic protein
NODE_092_gene_010	-0.1	0.526	1.9	0.095	1.9	0.046	Redoxin
NODE_092_gene_011	-1.3	0.587	-3.4	0.024	-2.1	0.042	3-phosphoserine phosphatase
NODE_099_gene_033	-0.8	0.665	2.3	0.066	3.1	0.004	NDP-4-keto-6-deoxy-L-hexose 2 3-reductase
NODE_102_gene_017	2.3	0.003	2.1	0.076	-0.1	0.956	ABC-type cobalt transport system
NODE_110_gene_015	-0.4	0.918	2.1	0.096	2.2	0.039	Pseudouridine-5'-phosphate glycosidase

NODE_110_gene_016	0.4	0.453	2.0	0.107	2.3	0.032	Dioxygenase
NODE_118_gene_013	1.9	0.011	4.0	0.005	2.0	0.041	Predicted protein
NODE_119_gene_005	0.6	0.347	2.6	0.045	1.8	0.085	Putative secreted extracellular small neutral protease
NODE_126_gene_032	1.0	0.179	-1.4	0.492	-2.3	0.030	Putative calcium binding protein
NODE_131_gene_004	1.5	0.056	2.5	0.050	1.0	0.360	lipoprotein
NODE_131_gene_035	-1.9	0.260	-3.2	0.044	-1.2	0.265	Uncharacterized protein
NODE_136_gene_010	-0.9	0.880	2.5	0.047	3.5	0.000	AdpA
NODE_136_gene_016	0.1	0.397	2.1	0.076	1.9	0.045	B-N-acetylhexosaminidase
NODE_137_gene_015	-2.6	0.048	-1.9	0.258	0.9	0.392	Flavoprotein reductase
NODE_139_gene_026	-1.1	0.726	0.8	0.309	2.5	0.011	Putative uncharacterized protein
NODE_143_gene_007	-1.4	0.322	-3.3	0.025	-1.5	0.176	Succinyl-CoA ligase [ADP-forming] subunit beta-1
NODE_143_gene_008	-4.3	0.001	-3.4	0.028	0.5	0.587	Succinyl-CoA ligase [ADP-forming] subunit alpha
NODE_144_gene_030	2.9	0.000	3.6	0.009	0.5	0.541	Iron transport lipoprotein
NODE_146_gene_013	0.3	0.329	-2.9	0.076	-2.6	0.011	Uncharacterized protein
NODE_146_gene_033	1.6	0.041	-1.2	0.590	-2.6	0.014	Dehydrogenase
NODE_152_gene_033	2.1	0.005	4.4	0.002	2.2	0.023	Amino acid transport integral membrane protein
NODE_153_gene_002	2.7	0.001	3.3	0.014	0.4	0.595	Solute-binding lipoprotein
NODE_154_gene_010	2.1	0.005	3.3	0.015	1.3	0.165	Putative secreted protein
NODE_154_gene_060	NaN	NaN	2.8	0.030	2.8	0.004	Aminotransferase
NODE_154_gene_064	-0.3	0.710	1.9	0.104	2.3	0.018	Oxidoreductase
NODE_155_gene_014	4.6	0.000	5.8	0.000	1.2	0.244	Substrate binding protein
NODE_155_gene_032	1.0	0.161	-1.6	0.372	-2.7	0.011	Mesaconyl-CoA hydratase
NODE_155_gene_040	0.8	0.138	-1.7	0.530	-2.4	0.022	Secreted peptidase
NODE_155_gene_052	-1.2	0.627	0.8	0.299	2.0	0.041	Uncharacterized protein
NODE_159_gene_015	3.8	0.000	4.5	0.002	0.6	0.496	Putative membrane protein
NODE_168_gene_002	0.9	0.190	-1.3	0.538	-2.2	0.045	6-pyruvoyl tetrahydropterin synthase
NODE_171_gene_005	-1.9	0.162	-4.0	0.004	-2.4	0.029	Sugar phosphotransferase
NODE_173_gene_018	1.8	0.022	0.8	0.408	-1.1	0.312	Peptidoglycan-binding domain 1 protein
NODE_175_gene_006	1.0	0.180	-1.5	0.432	-2.3	0.032	Putative lysozyme
NODE_180_gene_024	0.9	0.116	3.0	0.023	2.4	0.016	Aromatic prenyltransferase DMATS type
NODE_180_gene_025	1.6	0.040	2.8	0.031	1.1	0.286	Aromatic amino acid beta-eliminating lyase/threonine aldolase
NODE_188_gene_004	2.4	0.004	-2.4	0.137	-4.7	0.000	Iron sulfur protein (Secreted protein)
NODE_191_gene_023	0.1	0.680	2.0	0.103	2.5	0.018	3-oxoacyl-[acyl-carrier-protein] synthase 2
NODE_196_gene_002	0.6	0.330	3.5	0.010	2.6	0.015	Secreted protein
NODE_198_gene_010	-2.9	0.039	-2.7	0.129	0.5	0.587	Aminoacylase
NODE_207_gene_013	0.9	0.103	3.5	0.011	2.4	0.015	Neutral zinc metalloprotease
NODE_207_gene_015	-1.7	0.226	1.5	0.191	3.5	0.001	Phosphorylase
NODE_207_gene_016	0.6	0.323	3.1	0.020	2.3	0.030	Alpha-amylase
NODE_211_gene_006	3.9	0.000	2.2	0.072	-1.9	0.070	ABC transport system integral membrane protein BldKC
NODE_212_gene_021	-0.1	0.897	-4.5	0.001	-4.3	0.000	Putative signal transduction protein with EFhand domain
NODE_226_gene_007	-1.5	0.434	-3.7	0.012	-2.2	0.030	Exporter
NODE_227_gene_010	1.8	0.028	1.5	0.186	-0.2	0.869	Proteinase
NODE_230_gene_006	-3.0	0.028	-2.2	0.258	0.4	0.637	GCN5-related N-acetyltransferase
NODE_231_gene_019	-2.9	0.030	-3.9	0.006	-0.9	0.393	Peptide transporter
NODE_231_gene_043	-2.7	0.044	-3.1	0.035	-0.7	0.523	FAD-dependent pyridine nucleotide-disulfide oxidoreductase
NODE_244_gene_025	-1.9	0.260	-3.3	0.033	-1.2	0.266	Phosphodiesterase
NODE_245_gene_011	-2.2	0.143	-3.2	0.044	-0.9	0.391	Mycothiol conjugate amidase Mca
NODE_248_gene_003	0.9	0.209	-1.5	0.441	-2.5	0.021	Peptide transport system secreted peptide-binding protein
NODE_249_gene_004	-0.3	1.000	-3.5	0.015	-3.0	0.005	Urease subunit alpha 1
NODE_250_gene_002	-1.3	0.558	1.3	0.188	2.6	0.009	Putative transmembrane transport protein
NODE_250_gene_012	1.4	0.034	2.1	0.076	0.7	0.429	Cationic amino acid transporter
NODE_250_gene_016	-2.2	0.166	-3.2	0.045	-1.1	0.312	Thioredoxin
NODE_251_gene_002	-1.4	0.503	0.8	0.312	2.1	0.033	Sigma 54 modulation protein/SSU ribosomal protein S30P
NODE_259_gene_010	1.7	0.035	1.3	0.242	-0.5	0.659	Subtilisin-like protease
NODE_267_gene_023	3.5	0.000	3.6	0.009	0.1	0.872	Secreted alkaline phosphatase
NODE_271_gene_008	-3.3	0.012	-2.1	0.208	0.1	0.886	UDP-glucose 4-epimerase
NODE_272_gene_009	-0.5	0.854	1.3	0.197	2.0	0.043	WD40 repeat-containing protein
NODE_279_gene_009	1.2	0.113	-1.6	0.378	-2.9	0.007	Putative lipoprotein
NODE_279_gene_082	1.9	0.017	-0.6	0.919	-2.6	0.017	Glyceraldehyde 3-phosphate dehydrogenase
NODE_279_gene_107	0.5	0.236	3.3	0.015	2.7	0.005	Putative cysteine desulphurases SufS
NODE_281_gene_006	-0.1	0.825	-2.6	0.094	-2.6	0.014	3-hydroxyacyl-CoA dehydrogenase PaaC
NODE_282_gene_002	-2.7	0.041	-2.6	0.096	0.1	0.881	Phosphocarrier protein HPr
NODE_286_gene_026	0.7	0.302	-1.7	0.322	-2.4	0.025	Catalase
NODE_288_gene_011	0.7	0.169	-1.6	0.580	-2.1	0.045	Uncharacterized protein
NODE_299_gene_002	-2.8	0.049	-1.4	0.744	1.5	0.127	Bifunctional uroporphyrinogen-III synthetase/response regulator domain protein
NODE_299_gene_014	1.9	0.011	2.2	0.073	0.4	0.616	Sugar transporter sugar-binding protein

NODE_300_gene_002	-1.3	0.389	1.0	0.333	2.3	0.031	Adenylosuccinate synthetase
NODE_309_gene_008	-2.1	0.177	-3.1	0.049	-0.7	0.545	Orotate phosphoribosyltransferase
NODE_316_gene_021	1.3	0.050	-0.6	0.821	-1.4	0.172	Secreted hydrolase
NODE_320_gene_035	0.0	0.502	2.1	0.075	2.2	0.025	3-ketosteroid-delta-1-dehydrogenase (Fragment)
NODE_321_gene_026	-3.2	0.013	-2.7	0.081	0.5	0.647	Phosphoribosylaminoimidazole-succinocarboxamide synthase
NODE_330_gene_015	-3.0	0.022	-3.4	0.019	-0.3	0.790	Peptidase M48
NODE_337_gene_001	-2.5	0.093	-3.8	0.009	-0.3	0.830	Putative oxygenase
NODE_340_gene_005	-0.8	0.937	0.9	0.272	1.9	0.049	Pyruvate phosphate dikinase
NODE_346_gene_006	-0.6	0.899	1.1	0.238	2.0	0.038	Translation initiation factor IF-3
NODE_347_gene_004	4.1	0.000	4.4	0.001	0.5	0.642	Lipoprotein
NODE_359_gene_003	-0.9	0.576	-3.0	0.044	-2.0	0.066	Putative secreted protein
NODE_363_gene_001	1.8	0.025	5.3	0.000	4.2	0.000	Putative iron transport lipoprotein
NODE_366_gene_016	4.0	0.000	3.7	0.007	-0.2	0.882	Glutamate binding protein
NODE_366_gene_028	-0.4	0.744	-3.1	0.056	-2.5	0.013	Predicted protein
NODE_366_gene_037	3.4	0.000	3.6	0.010	0.3	0.714	Secreted protein
NODE_395_gene_033	-1.8	0.311	-3.4	0.025	-1.6	0.131	HesB/YadR/YfhF family protein
NODE_395_gene_039	-2.2	0.098	-3.8	0.008	-1.6	0.145	Uncharacterized protein
NODE_399_gene_018	0.8	0.133	-1.7	0.554	-2.1	0.038	Uncharacterized protein
NODE_410_gene_001	1.6	0.041	2.8	0.031	1.1	0.282	Secreted protein
NODE_416_gene_006	1.7	0.030	1.3	0.243	-0.3	0.822	Germacradienol/geosmin synthase
NODE_431_gene_010	0.3	0.545	2.8	0.030	2.3	0.032	Uncharacterized protein
NODE_434_gene_008	-2.0	0.210	-3.9	0.008	-1.2	0.244	Putative polyketide cyclase
NODE_451_gene_001	-1.1	0.474	0.9	0.361	2.4	0.026	NB-ARC domain-containing protein
NODE_453_gene_003	-2.7	0.038	-2.8	0.060	0.4	0.705	Methylmalonyll-CoA mutase
NODE_461_gene_007	1.7	0.038	-1.6	0.397	-3.4	0.002	Protease
NODE_463_gene_011	2.0	0.008	3.0	0.025	1.3	0.173	ABC-type Fe3+-siderophore transporter ATP-binding protein
NODE_463_gene_013	4.1	0.000	5.9	0.000	2.1	0.054	ABC-type Fe3+-siderophore transporter substrate-binding protein
NODE_464_gene_004	0.4	0.282	2.6	0.039	2.1	0.032	Cobalt transport integral membrane protein
NODE_464_gene_005	1.8	0.024	2.5	0.055	1.2	0.248	Putative ABC transporter ATP-binding protein SCO5958
NODE_487_gene_009	1.4	0.042	4.7	0.001	3.5	0.000	Muramoyl-pentapeptide carboxypeptidase
NODE_487_gene_101	3.6	0.000	4.7	0.001	1.6	0.135	Lipoprotein
NODE_487_gene_102	3.7	0.000	5.1	0.001	2.0	0.041	Solute-binding lipoprotein
NODE_487_gene_103	5.3	0.000	6.5	0.000	1.1	0.282	Secreted protein
NODE_491_gene_002	1.8	0.013	1.4	0.168	-0.3	0.854	Secreted alkaline phosphatase
NODE_510_gene_026	-0.3	0.664	-2.1	0.330	-2.1	0.041	Membrane protein
NODE_514_gene_002	-2.2	0.144	-3.8	0.010	-1.6	0.127	Secreted penicillin binding protein
NODE_526_gene_007	-2.8	0.048	-3.3	0.032	-0.3	0.865	Lipoprotein
NODE_528_gene_003	0.8	0.135	3.2	0.018	2.5	0.010	Carrier protein membrane protein (Fragment)
NODE_532_gene_001	1.3	0.096	2.9	0.028	1.9	0.074	Alpha-1 4-glucan:maltose-1-phosphate maltosyltransferase 1
NODE_534_gene_001	-1.7	0.342	1.3	0.196	2.9	0.003	Alpha-1 4-glucan:maltose-1-phosphate maltosyltransferase 1
NODE_585_gene_004	-0.9	0.607	1.6	0.172	2.4	0.023	DUF364 domain-containing protein
NODE_633_gene_002	0.7	0.284	2.7	0.037	1.7	0.116	Nitrogen regulatory protein P-II
NODE_644_gene_008	2.0	0.008	-1.4	0.749	-3.1	0.002	hydrolase
NODE_659_gene_009	-0.6	0.763	2.2	0.080	2.9	0.008	Amidase
NODE_679_gene_001	-1.9	0.169	-3.9	0.006	-2.1	0.052	Phage tail sheath protein
NODE_746_gene_022	0.9	0.202	-2.5	0.113	-3.4	0.002	Lipoprotein
NODE_746_gene_044	0.8	0.263	-1.3	0.543	-2.1	0.050	Putative glyoxalase/bleomycin resistance family protein
NODE_746_gene_047	0.5	0.230	-2.7	0.119	-3.1	0.003	Phytanoyl-CoA dioxygenase

Table S2. Oligo nucleotides used in this study

Name	Sequence
*rpsL*_For	CGGCACACAGAAACCGGAGAAG
*rpsL*_Rev	GTCGATGATGACCGGGCGCTTCG
*rsmG*_For	TGACGAATTCGTCAGCCTGATAGTTCTGGTGG
*rsmG*_Rev	TCAGTAAGCTTGCCGTGCAGCAGTGAGCGACG
SC06_0044_F_EcoRI	CGATGAATTCCGTCCGGCGCTTCGTGTG
SC06_0044_R_EcoRI_NdeI	CGATGAATTCGCACCCGGTACAGGAGTGTGTCATATGCGATTCAACCTCATC

Appendix II

Supplementary materials for Chapter 4

Unravelling the response of *Streptomyces roseifaciens* to challenge with small molecules by genome-wide proteomics

Chao Du, Somayah Elsayed, Marta del Rio, Bogdan I. Florea, Jos Raaijmakers, Gilles P. van Wezel

Table S1 Differentially expressed proteins (DEPs) for all small molecule treatments

ID	predicted function	Ctr Mean	HyC			…
			Mean	log2 Fold change	log10 p-Value	…
sc01_0047	Uncharacterized protein	5942.667	18992.33	1.676235	0.743147	…
sc01_0194	transferase	14004.33	9288.667	-0.59233	1.59673	…
sc01_0208	Putative Uncharacterized 50.6 kDa protein in the 5'region of gyrA and gyrB	10565.67	**51839.67**	**2.294673**	**3.189379**	**…**
sc01_0222	Pyruvate dehydrogenase E1 component	28681.67	**2925.333**	**-3.29346**	**2.101675**	**…**
sc01_0228	Methyltransferase domain-containing protein	3432.667	**8844.333**	**1.365424**	**1.816476**	**…**
sc01_0243	ERCC4 domain protein	52936.67	**7105.333**	**-2.89729**	**1.455557**	**…**
sc01_0253	Glyoxalase	10574.33	**27181**	**1.362032**	**1.453402**	**…**
sc02_0182	Putative transcriptional regulatory protein	3132	**6385.333**	**1.027678**	**1.603741**	**…**
…	…	…	**…**	**…**	**…**	**…**

Bold numbers indicating the protein in that specific treatment passed the threshold for DEPs (*p*-value < 0.05, fold change ≧2 or ≦-2)

Complete table can be accessed via:
https://osf.io/hx9vc/?view_only=fdbe5749fe6c49e8a6665e29ee2b6cb0

Table S2. DEPs[†] induced by short-term JA treatment

Protein ID	0 h		15 min				30 min				1 h				2 h				4 h				Log$_2$ ratios of JA/Control				
	Control		Control		JA*		Control		JA		Control		JA		Control		JA		Control		JA						
	Mean	SEM**	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	0.25 h	0.5 h	1 h	2 h	4 h
sc01_0033	171.73	18.41	130.50	10.95	143.14	32.71	235.09	21.68	114.50	2.76	180.46	13.77	174.29	22.10	187.25	37.58	172.51	11.96	240.22	60.22	200.53	14.25	0.13	-1.04	-0.05	-0.12	-0.26
sc03_1246	814.23	41.74	754.06	35.54	806.78	68.77	967.86	38.72	856.13	5.85	1681.0	270.38	1169.0	56.73	6645.9	1239.0	2649.0	364.60	5927.2	199.25	4058.8	189.29	0.10	-0.18	-0.52	-1.33	-0.55
sc03_1247	235.94	34.89	245.00	23.42	211.93	16.71	158.31	43.87	167.48	25.81	189.04	34.06	189.24	78.33	861.62	143.00	315.85	37.29	908.33	137.78	666.82	80.93	-0.21	0.08	0.00	-1.45	-0.45
sc03_1249	129.32	13.64	102.77	8.65	115.03	4.20	177.19	10.03	112.76	5.61	366.57	60.46	201.99	26.79	3561.0	824.60	1091.8	171.33	3787.5	88.17	2374.1	133.60	0.16	-0.65	-0.86	-1.71	-0.67
sc03_2100	500.37	158.39	545.66	282.49	492.02	299.45	105.20	32.83	225.20	27.32	201.93	38.33	246.89	143.51	124.81	29.63	164.69	58.50	111.68	48.88	117.98	51.65	-0.15	1.10	0.29	0.40	0.08
sc04_0002	319.68	68.39	301.95	125.37	306.08	104.41	205.99	24.51	207.12	80.48	239.13	78.37	290.35	89.24	233.63	12.53	206.34	94.98	104.11	47.02	313.34	63.97	0.02	0.01	0.28	-0.18	1.59
sc04_0750	396.84	15.64	401.30	16.82	408.36	26.00	410.10	19.62	402.35	20.99	388.51	10.25	354.26	34.80	287.18	26.24	206.13	25.78	107.33	32.13	248.03	43.24	0.03	-0.03	-0.13	-0.48	1.21
sc04_1170	394.22	46.27	425.35	133.40	377.12	165.35	361.41	78.41	466.88	117.53	658.66	24.38	301.28	56.60	318.30	84.40	331.86	94.43	110.65	37.54	282.80	169.83	-0.17	0.37	-1.13	0.06	1.35
sc04_1502	96.83	10.97	88.91	28.93	207.91	26.07	114.09	16.79	259.42	30.44	56.95	19.36	215.97	12.85	102.05	31.08	308.75	7.84	76.14	4.39	275.32	15.28	1.23	1.19	1.92	1.60	1.85
sc04_1633	323.46	27.50	300.17	33.55	384.81	75.34	269.77	52.56	266.76	14.40	162.78	41.38	261.29	66.32	195.44	51.06	235.02	49.42	144.89	23.07	299.26	45.04	0.36	-0.02	0.68	0.27	1.05
sc04_1686	78.77	6.66	83.35	19.95	71.16	35.30	72.62	6.94	80.64	6.91	66.46	15.07	74.07	9.64	56.04	4.28	64.07	24.25	11.97	3.26	33.90	4.77	-0.23	0.15	0.16	0.19	1.50
sc04_1826	350.02	52.46	447.19	127.62	493.15	128.74	316.14	84.27	318.42	103.59	460.82	53.67	390.43	96.70	263.19	90.38	364.63	113.34	224.35	64.68	510.72	98.56	0.14	0.01	-0.24	0.47	1.19
sc04_2087	104.53	20.67	44.41	19.40	74.01	42.92	119.96	27.04	71.47	19.81	182.20	61.89	145.37	35.15	124.57	33.11	114.39	47.34	221.71	42.75	77.86	25.69	0.74	-0.75	-0.33	-0.12	-1.51
sc04_2763	106.39	10.70	101.77	27.63	150.29	37.40	98.12	21.00	124.19	22.43	111.66	4.11	127.48	3.06	88.21	22.37	86.78	30.58	42.08	5.93	158.01	29.02	0.56	0.34	0.19	-0.02	1.91
sc05_0038	234.86	20.28	234.63	47.23	161.05	25.86	225.17	40.44	168.51	20.40	122.24	35.87	251.23	29.70	164.85	43.53	235.10	34.19	161.65	26.11	131.90	12.09	-0.54	-0.42	1.04	0.51	-0.29
sc06_0231	396.04	76.39	451.81	256.57	353.99	222.27	393.23	33.27	510.93	201.85	637.06	103.70	262.52	100.55	342.28	188.36	423.92	154.72	157.03	36.62	307.99	183.65	-0.35	0.38	-1.28	0.31	0.97
sc07_0079	39.60	8.61	30.99	15.59	32.40	12.54	45.13	23.22	52.11	14.86	54.75	38.49	47.64	24.58	433.02	69.70	102.58	34.91	364.71	25.66	240.48	50.47	0.06	0.21	-0.20	-2.08	-0.60

[†] *p*-value < 0.1, fold change ≧ 2

* Jasmonic acid treatment

** Standard error of mean

Table S3. Oligonucleotides used in this study

Purpose	No.	Name	Sequence 5'-3'
jarA knockout	1	jaraSpCRko	CATGCCATGGACAGGTCCTCCAGCATGAAGGTTTTAGAGCTAGAAATAGC
	2	jaraUp_GF	TCGTCGAAGGCACTAGAAGGGATGCCAACCTCGTACAGATCG
	3	jaraUp_GR	GTAGTGGCTGGGGATTCCCGTCAGGACCTCCCGGATGACTTC
	4	jaraDown_GF	CGGGAATCCCCAGCCACTAC
	5	jaraDown_GR	GGTCGATCCCCGCATATAGGCGGGCGGGTTGATGATGAC
jarA knockout genotype check	6	03.1245_KOCK_F	GGCCGTGAGCCACCTCACC
	7	03.1245_KOCK_R	CCGGCTCCAGCGCCTGTATC
SC04_1502 knockout	8	04.1502up_F	AGGAAGCTTTCCTTGGCCCTACCTTTACCC
	9	04.1502up_R	AGGTCTAGAATGAGCGTGCCGGTGTTCTG
	10	04.1502down_F	ACATCTAGAGCAGGGCGGCTGACAGAC
	11	04.1502down_R	ACAGAATTCATGGGCATGGCCCATCGG
SC04_1502 knockout genotype check	12	04.1502_KOCK_F	AGTGGGCGGAGAGCTACCAG
	13	04.1502_KOCK_R	GCCACACTCGCACCGCAAAG

Table S4. Plasmids and constructs used in this study

Plasmid and construct	Description	reference/vendor reference
pWHM3-oriT	*E. coli/Streptomyces* shuttle vector, high copy number and unstable in Streptomyces	Modified from Vara *et al.* (1989)
pUWL-Cre	*E. coli/Streptomyces* shuttle vector expressing the Cre recombinase in Streptomyces	Fedoryshyn *et al.* (2008)
pCRISPR-Cas9	*E. coli/Streptomyces* shuttle vector, harbouring codon optimised *cas9*, designed for easy inserting spacer sequences. Recombination template is designed to be inserted through in-vitro assembly to *Stu*I site	Tong *et al.* (2015b)
pGWS1460	pCRISPR-Cas9 harbouring spacer and HDR region to knockout *jarA*	This study
pGWS1461	pWHM3-oriT harboring apramycin resistant cassette flanked by *loxP* sites and flanking regions of SC04_1502 to knockout SC04_1502	This study

Table S5 – CAS number and supplier of the small molecules used in this study

Abbreviations	Compound name	CAS number	Provider, catalog numbers, notes
`JA`	Jasmonic acid	77026-92-7	Cayman Chemical, 88300
`SA`	Salicylic acid	69-72-7	Alfa Aesar, A12253
`IAA`	Indole-3-acetic acid	6505-45-9	Sigma-Aldrich, I5148
`NAA`	Naphthalene acetic acid	86-87-3	Duchefa, N0903
`HyC`	Hydroxycoumarine	93-35-6	Alfa Aesar, L04082, 7-Hydroxycoumarine
`GlcNAc`	N-acetylglucosamine	7512-17-6	Sigma-Aldrich, A3286
`CB`	Cellobiose	528-50-7	Sigma-Aldrich, C7252
`CS`	Chitosan	9012-76-4	Sigma-Aldrich, C3646, ≧75% deacetylated
`CA`	Cinnamic acid	621-82-9	Honeywell, 63185H
`FA`	Ferulic acid	537-98-4	Sigma-Aldrich, W518301
`BA`	Benzoic acid	65-85-0	Supelco, 1.00136.0100
`BR`	Sodium butyrate	156-54-7	Sigma-Aldrich, 303410

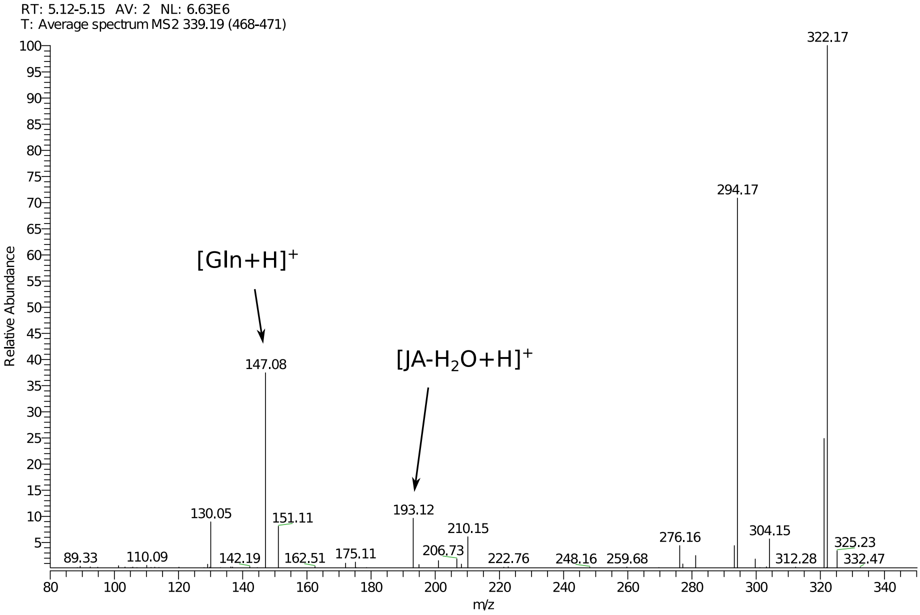

Figure S1. MS2 spectrum of jasmonoyl-glutamine (JA-Gln). Main fragments are annotated by arrows.

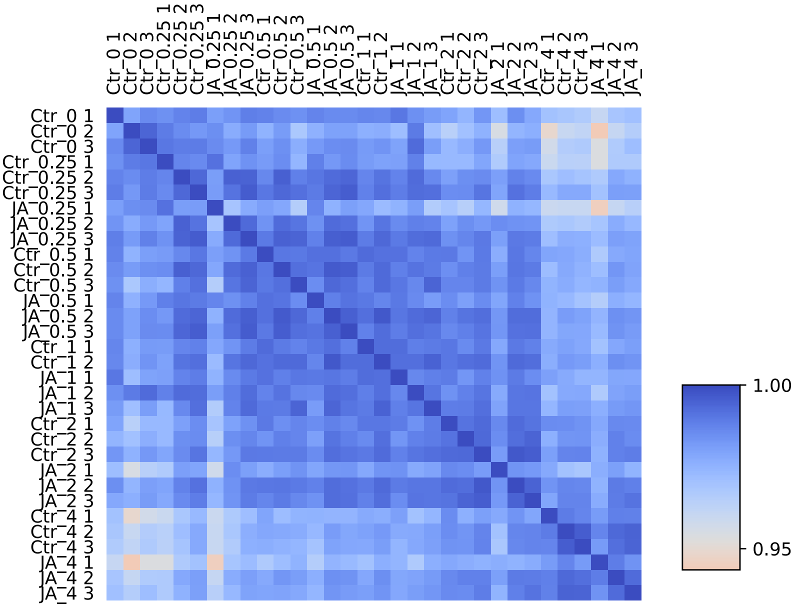

Figure S2. Correlation plot of proteomics data of all samples in short-term JA response experiment. Ctr: control sample; JA, jasmonic acid treatment; the numbers directly after underline indicating hours after jasmonic acid induction; the last number indicates the replicate number.

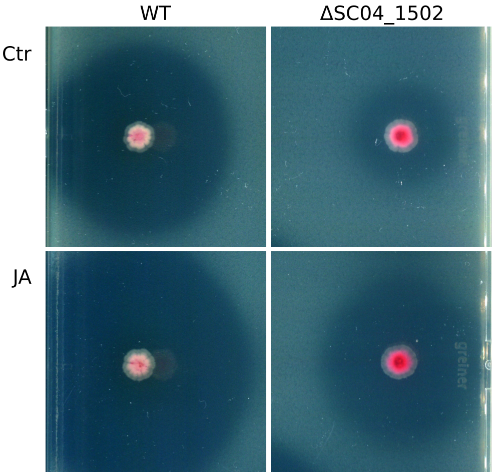

Figure S3. Antimicrobial activity test of the ΔSC04_1502 strain compare with wildtype strain under JA treatment. Spores of *S. roseifaciens* were grown for 5 days on MM medium supplemented with mannitol. *E. coli* ASD19 was overlaid on top as indicator.

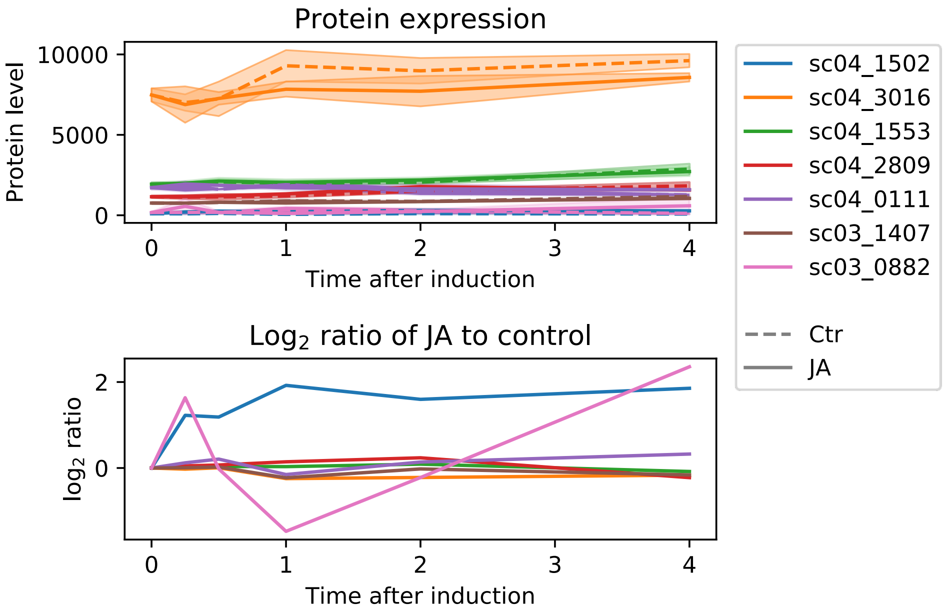

Figure S4. Abundance pattern of all detected MFS family proteins found in *S. roseifaciens* genome. Note that SCO03_0882 (pink line) did not pass the threshold as DEP.

Appendix III

Supplementary materials for Chapter 5

Analysis of the background-reduced antibiotic production host *Streptomyces coelicolor* M1152 using quantitative proteomics

Chao Du, Dino van Dissel, Alexander Wentzel, Gilles P. van Wezel

Table S1. Protein levels in each sample

Strain	M145	M145	M145	…
Fermenter	F516	F516	F516	…
Aligned time point	1	2	3	…
Time after inoculation (h)	21	29	33	…
Total quantiified	1732	1836	1873	…
SCO0006	1573	ND	ND	…
SCO0018	2086	2013	2045	…
SCO0020	ND	1513	ND	…
SCO0033	3356	2353	3924	…
SCO0070	ND	2638	3283	…
SCO0072	10821	7661	5601	…
SCO0075	2456	2637	1328	…
…	…	…	…	…

ISOQuant output using Top3 quantification method
ND - None detected
Complete table can be accessed via:
https://osf.io/e352b/?view_only=ac6b5126cb5e4523b56bd55231365a51

Table S2. DEPs for aligned time comparison between M1152 and M145

Aligned time point	1		2		3		…
Time after inoculation (h, M1152)	33		41		45		…
Time after inoculation (h, M145)	21		29		33		…
Number of DEPs	171		126		105		…
Protein ID (name)	$\log_2$ fold change	*p*-value	$\log_2$ fold change	*p*-value	$\log_2$ fold change	*p*-value	…
SCO2198 (GlnA)	-1.800	0.000	-0.842	0.010	-0.613	0.105	…
SCO2210 (GlnII)	-2.111	0.000	-2.575	0.002	-2.565	0.030	…
SCO2286 (PhoA)	NA	NA	NA	NA	NA	NA	…
SCO2878	NA	NA	1.688	0.024	1.221	0.005	…
SCO4141 (PstC)	NA	NA	NA	NA	NA	NA	…
SCO4159 (GlnR)	-1.137	0.002	NA	NA	NA	NA	…
SCO4228	0.816	0.285	1.672	0.001	1.716	0.000	…
SCO0888	-1.266	0.031	NA	NA	-3.117	0.013	…
SCO1865 (EctB)	-0.656	0.170	0.685	0.014	0.472	0.138	…
SCO1867 (EctD)	0.558	0.000	1.195	0.002	1.396	0.000	…
SCO4683 (GdhA)	2.344	0.000	1.130	0.009	0.570	0.073	…
SCO5584 (GlnK)	-2.339	0.042	-3.136	0.062	-2.298	0.003	…
SCO5585 (GlnD)	-2.304	0.000	NA	NA	NA	NA	…
…	…	…	…	…	…	…	…

Showing only comparisons between aligned time points
p-values are calculated from student's T-test
None-significant ($p \geqq 0.05$, $-1 < \log2$ fold change < 1) are greyed out
NA - No data
Complete table can be accessed via:
https://osf.io/e352b/?view_only=ac6b5126cb5e4523b56bd55231365a51

Table S3. DEPs before and after phosphate depletion

Strain	M145		M1152				
tp6/tp2	45/29 h		57/41 h		Belong to protein group		
Protein ID (name)	$\log_2$ fold change	*p*-value	$\log_2$ fold change	*p*-value	glycolysis	TCA	PPP
SCO0617	3.14	0.01	0.85	0.08	-	-	Yes
SCO2627	1.28	0.04	-0.37	0.24	-	-	Yes
SCO4979	3.41	0.01	0.15	0.26	Yes	Yes	-
SCO0169	-1.73	0.01	-0.72	0.38	-	-	-
SCO0186(CrtI)	1.87	0.02	0.70	0.17	-	-	-
SCO0203	-2.07	0.00	-2.35	0.06	-	-	-
SCO0392	3.43	0.02	0.89	0.00	-	-	-
SCO0393	NA	NA	1.13	0.01	-	-	-
SCO0395	3.28	0.02	0.63	0.02	-	-	-
SCO0498(CchB)	-1.16	0.01	2.24	0.00	-	-	-
...	...	...	...	...	...	...	...

Tp2 and tp6 was chosen as representative aligned time points before and after phosphate depletion, respectively.

p-values are calculated from student's T-test

None-significant ($p \geqq 0.05$, $-1 < \log2$ fold change < 1) are greyed out

NA - No data

Complete table can be accessed via:
https://osf.io/e352b/?view_only=ac6b5126cb5e4523b56bd55231365a51

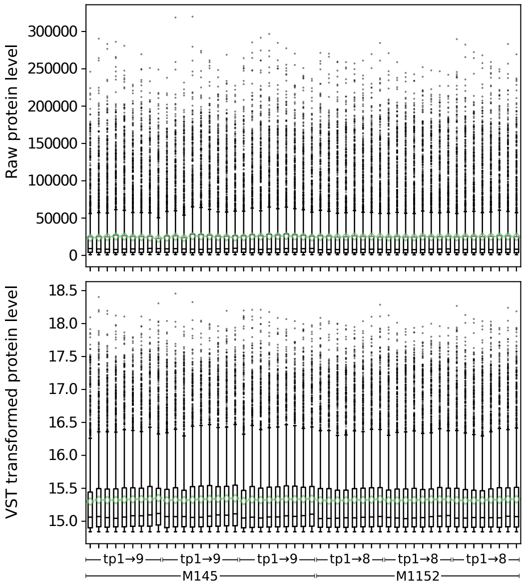

Figure S1. Boxplot of protein levels in each sample before and after VST data transformation. Outliers are indicated by black dots, the overall means of all proteins in each sample are indicated by green diamonds.

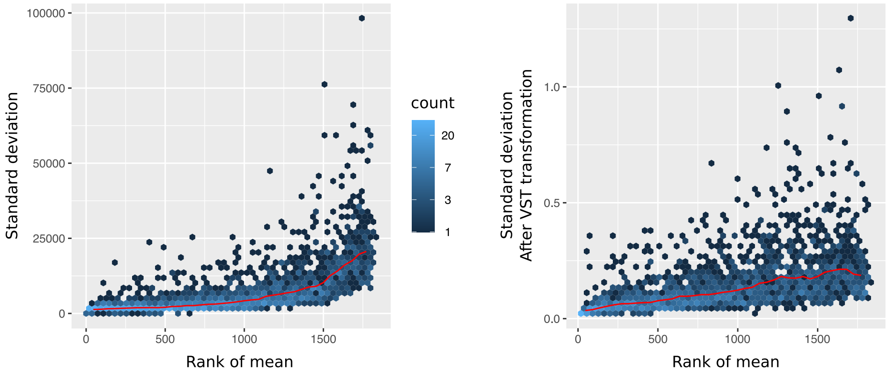

Figure S2. Mean – standard deviation plot of protein levels in each sample before and after VST data transformation. The red line depicts the running median estimator (window-width 10%).

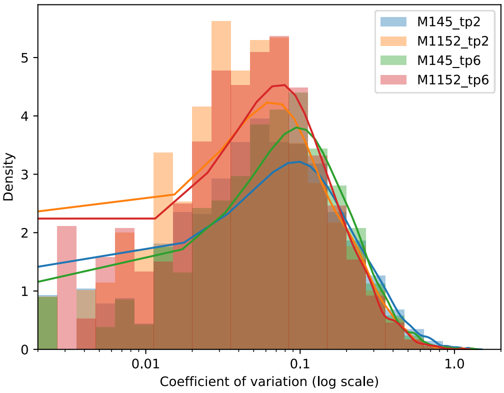

Figure S3. Distribution plot of coefficient of variation (ratio of SD to mean) of each quantified protein.

Appendix IV

Supplementary materials for Chapter 6

A novel nucleoid-associated protein specific to Actinobacteria that binds to GATC sequences

Chao Du, Joost Willemse, Victor J. Carrion, and Gilles P. van Wezel

Table S1. SCO1839 binding regions that overlap with promoter regions

Gene	Product	Translation start site on genome	Strand	25h peak fold enrichment	48h peak fold enrichment	25h peak summit position	25h peak width	48h peak summit position	48h peak width	…
SCO0002	ttrA (hypothetical protein)	1251	+	24.53	18.63	-5	304	+3	306	…
SCO0003	DNA-binding protein	3868	+	7.93	6.83	-167	234	-167	255	…
SCO0008	hypothetical protein	11360	-	10.32	4.37	-93	361	-139	285	…
SCO0019	hypothetical protein	19771	-	4.17	5.97	-148	260	-136	533	…
SCO0020	transposase	19973	+	4.17	5.97	-54	260	-66	533	…
SCO0021	hypothetical protein	21616	+	4.91	7.22	+3	205	+5	266	…
SCO0026	hypothetical protein	23315	+	3.68	6.33	-9	172	-6	228	…
SCO0044	Oxidore-ductase	36674	-	5.23	4.32	-27	214	-27	230	…
…	…	…	…	…	…	…	…	…	…	…

-350 to +50 relative to translation start site was considered as promoter region

"Peak" in this table refers to "binding region"

An "overlap" represents > 50% of the peak region overlaps with the promoter region

Complete table can be accessed via:
https://osf.io/8ds2m/?view_only=8710562f6e4043da8d2bfc4a31dab7d8

Table S2. AtrA binding motif used to predict the binding site in PREDetector

Name	**Sequence**	**Ref**
nagE2_AtrAMotif	GGAATCACGGGTTCC	Nothaft *et al.* (2010)
actII-ORF4_AtrAMotif	GGAATGCCAGATTCT	Uguru *et al.* (2005)
predicted	GGAACCACCGGTTCC	Hiard *et al.* (2007)
strR_AtrAMotif	GGAGGGGGCCGTTCC	Hirano *et al.* (2008)

Table S3. Bacterial strains used in this study

Strain	Genotype/description	Reference/vendor reference
E. coli JM109	See reference	Sambrook *et al.* (1989)
E. coli ET12567	See reference	MacNeil *et al.* (1992)
E. coli ET12567/pUZ8002	See reference	Flett *et al.* (1997)
E. coli BL21 CodonPlus (DE3)-RIPL	See reference	Agilent 230280
S. coelicolor A3(2) M145	See reference	Kieser *et al.* (2000)
S. coelicolor M512	See reference	van Wezel *et al.* (2000b)
GAD003	M145ΔSCO1839	This study
GAD014	M145ΔSCO1839 + pGWS1260	This study
GAD039	Part of SCO1839 promoter replaced by PermE	This study
GAD043	3×FLAG fused to SCO1839 C-term	This study
GAD099	eGFP fused to SCO1839 C-term	This study
GAD075	M145ΔatrA	This study
GAD078	M145ΔatrAΔSCO1839	This study
GAD105	M512 + pGWS1454	This study
GAD093	M512ΔatrA	This study
GAD107	M512ΔatrA + pGWS1454	This study

Table S4. Plasmids and constructs used in this study

Plasmid and construct	Description	reference/vendor ID
pWHM3	*E. coli*/*Streptomyces* shuttle vector, high copy number and unstable in *Streptomyces*	Vara *et al.* (1989)
pUWL-Cre	*E. coli*/*Streptomyces* shuttle vector expressing the Cre recombinase in *Streptomyces*	Fedoryshyn *et al.* (2008)
pHJL401	*E. coli*/*Streptomyces* shuttle vector, 5-10 copies per chromosome in *Streptomyces*	Larson and Hershberger (1986)
pHM10a	*E. coli*/*Streptomyces* shuttle vector, designed for gene over-expression using consecutive promoter P*ermE*	Motamedi *et al.* (1995)
pCRISPomyces-2	*E. coli*/*Streptomyces* shuttle vector, harbouring codon optimised *cas9*, designed for easy inserting spacer sequences. Recombination template is designed to be inserted at *Xba*I site.	Cobb *et al.* (2015)
pCRISPR-Cas9	*E. coli*/*Streptomyces* shuttle vector, harbouring codon optimised *cas9*, designed for easy inserting spacer sequences. Recombination template is designed to be inserted through in-vitro assembly to *Stu*I site	Tong *et al.* (2015a)
pIJ2587	*E. coli*/*Streptomyces* shuttle vector, harbouring *redD* with multiple cloning sites in front for inserting external promoter sequence	van Wezel *et al.* (2000b)
pGWS526	pHJL401 expressing SsgA-eGFP	Zhang *et al.* (2016)
pGWS728	Construct harbouring *aac(3)IV*	Zhang *et al.* (2018)
pET28a	*E. coli* vector, designed to build His-tag fusion protein expression construct	Novagene 69864-3
pUC19	*E. coli* vector with multi-copy origin of replication	NEB N3041
pGWS1255	pWHM3 containing flanking regions of SCO1839 with apramycin resistance cassette with *loxP* sites inserted as *Xba*I fragment between flanking regions	This study
pGWS1260	pHJL401 harbouring SCO1839 and its own promoter region	This study
pGWS1298	pCRISPomyces-2 with spacer sequence from near the end of SCO1839, containing recombination template for 3×FLAG tag knock-in	This study
pGWS1299	pCRISPomyces-2 with spacer sequence from near the end of SCO1839, containing recombination template for eGFP knock-in	This study
pGWS1295	pCRISPomyces-2 with spacer sequence from near the beginning of SCO1839, containing recombination template for P*ermE* knock-in	This study
pGWS1286	pET28a with SCO1839 coding sequence built-in, for 6His-SCO1839 fusion protein expression	This study
pGWS1300	pUC19 harbouring partial SCO1839 promoter region for EMSA experiment	This study
pGWS1451	pUC19 harbouring random SCO1839 non-binding region for EMSA experiment	This study
pGWS1452	pCRISPR-Cas9 with spacer sequence from near the beginning of *atrA*, containing recombination template for atrA knock-out	This study
pGWS1454	pIJ2587 with the promoter region of SCO1839	This study

Table S5. Primers used in this study

Purpose	No.	Name	Sequence 5'-3'	Note
SCO1839 knock-out and complementation	1	SCO1839FU_F	CGATGGATCCGACGCCGACTCGATCATCTG	
	2	SCO1839FU_R	CGATTCTAGACCGTGCCTCCTCATGGGAAG	
	3	SCO1839FD_F	CGATTCTAGAGCCACTTCGGCCTGACGTCC	
	4	SCO1839FD_R	CGATAAGCTTCCGGCCTGCTCGACGAAAC	
	5	SCO1839CM_F	ACTGAAGCTTGGGACGTCAGGCCGAAGTG	
	6	SCO1839CM_R	ACTGGGATCCGGTCTCCTCGGCCAACGTG	
SCO1839 over-expression	7	1839_Ukp_F	CCGATCTAGACGACGCCGACTCGATCATCTG	No.1 changed to XbaI
	8	1839_Ukp_R	CAGTGAGCTCTCCGCCGAACGAGTTTCTCC	
	9	SCO1839OP_F	CAGTCATATGGCCGAGACTCTGAAGAAGGG	
	10	SCO1839FD_R_XbaI	CGATTCTAGACCGGCCTGCTCGACGAAAC	No.4 changed to XbaI
	11	Sp_1839U_F	ACGCTCGGCAAGGCTGATGAGACA	Spacer assembly
	12	Sp_1839U_R	AAACTGTCTCATCAGCCTTGCCGA	
3×FLAG tag knock-in	13	1839sp_down_F	ACGCGCCACTTCGGCCTGACGTCC	Spacer assembly, also used in eGFP knock-in
	14	1839sp_down_R	AAACGGACGTCAGGCCGAAGTGGC	
	15	1839flagFL_UR	AGTCGCCGTCGTGGTCCTTGTAGTCGGCCGAAGTGGCCTTCTTGC	
	16	3xFLAG+1839ending	GACTACAAGGACCACGACGGCGACTACAAGGACCACGACATCGACTACAAGGACGACGACGACAAGTGACGTCCCGGGCGGCCCCCGGCTCCGAAAGTGACGGTGGCCACCCGGT	
	17	1839flagCR_DR	GCGGCCTTTTTACGGTTCCTGGCCTCCTCGTAGTCCCGCGTCTGG	
	18	1839flagCR_UF_xbal	CGATTCTAGATGGTCTCCTCGGCCAACGTG	
	19	1839flagCR_DR_xbal	CGATTCTAGACCTCGTAGTCCCGCGTCTGG	
eGFP knock-in	20	1839GFPF_UR_BamHI	CGATGGATCCGCCGAAGTGGCCTTCTTGC	
	21	1839GFPF_DF_HindIII	ATCGAAGCTTGCTCCGAAAGTGACGGTGGC	
	22	eGFP(ftsZ)_F	TGGACGTGCCGGACTTCCTG	BamHI locates inside PCR product
	23	eGFP_R_HindIII	ATCGAAGCTTGGCCGCTTTACTTGTACAGCTC	
50 bp EMSA fragments	24	p1839_50Single_strong	CTCGACGCCGTCCGGAAGCAGAATGATCCGTTCCGGCTGGAGCGCCTCGA	
	25	p1839_50Single_strong_R	TCGAGGCGCTCCAGCCGGAACGGATCATTCTGCTTCCGGACGGCGTCGAG	

	26	p1839_50Single_weak	TCGATGTAGGACACACCTCTTGATGAGGAGATCTCACACAGATGGCGGAT	
	27	p1839_50Single_weak_R	ATCCGCCATCTGTGTGAGATCTCCTCATCAAGAGGTGTGTCCTACATCGA	
	28	p1839_50Quadruple	GATGGCGGATCACGGATCGGCCGAATGATCCATAACCAGTGGATCATCCA	
	29	p1839_50Quadruple_R	TGGATGATCCACTGGTTATGGATCATTCGGCCGATCCGTGATCCGCCATC	
	30	npio_B50	GCAATTCGTAGGACGGAAGTGCGCAGGGTGCCTCAAATGCGGCCCTATAG	Negative control
	31	npio_B50_R	CTATAGGGCCGCATTTGAGGCACCCTGCGCACTTCCGTCCTACGAATTGC	
Long EMSA fragments for possible methylation affection	32	p1839_ip_F	CCGCCGAACGAGTTTCTCC	*Eco*RI site inside PCR product, the fragment was digested using *Eco*RI and HindIII for inserting into pUC19
	33	p1839_ip_R_HindIII	GCATAAGCTTCCTCGGCCAACGTGCTG	
	34	noip_A_F_EcoRI	GCATGAATTCGCCGCCGTTCGGTGGTGTC	Negative control
	35	noip_A_R_HindIII	GCATAAGCTTGCCAGCGAGGCCCGCTTC	
Promoter probing	36	pSCO1839_F_BamHI	CGATGGATCCCTCATGGGAAGTGCGCTCTG	
	37	pSCO1839_R_SacI	ACGTGAGCTCTCCGTGATCCGCCATCTGTG	
qPCR	38	SCO1839_QF	GAGCATGCGGTGCACAAAG	
	39	SCO1839_QR	GCGGCAGACCTGAAGAAGAAG	
	40	SCO3873_qF	GCGTGGTGGACACGAAGAAG	Inner control
	41	SCO3873_qR	GCACCAAGACCGACGACTAC	
	42	SCO5359_qF	TACGTCGAGACGCAGGTCAG	Inner control
	43	SCO5359_qR	CTGCTTGCCCGTGTAGAAC	
atrA knock-out	44	AtrA_CrSP	CATGCCATGGTGCATGTTCAGGATTCTCATGTTTTAGAGCTAGAAATAGC	Spacer sequence in red
	45	atrA_UgR	TCGTCGAAGGCACTAGAAGGGACGCCTCGACGAGGATCCAC	
	46	atrA_UgF	CGTACTCATCGCACCGCCGGCCCGCCATCGAAAGCCGGAG	
	47	atrA_DgR	CCGGCGGTGCGATGAGTACG	
	48	atrA_DgF	GGTCGATCCCCGCATATAGGACGTCACCGGGACCGCTCTC	

Underlined characters indicating restriction sites or overhangs for assembly.
GGATCC, *Bam*HI; GAATTC, *Eco*RI; AGGCCT, *Stu*I; TCTAGA, *Xba*I; GAGCTC, *Sac*I; CATATG, *Nde*I; AAGCTT, *Hind*III

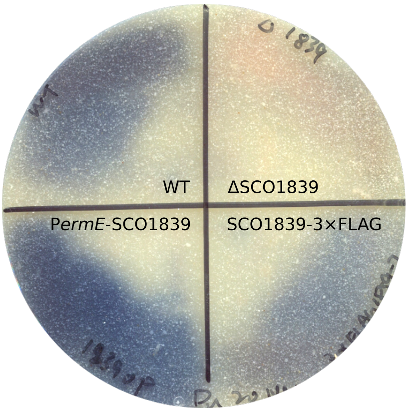

Figure S1. FLAG-tagged SCO1839 does not affect SCO1839 function. A strain expressing SCO1839-3×FLAG (lower right) produces a similar amount of blue-pigmented actinorhodin (Act) as the parental strain (upper left). Compare the SCO1839 deletion strain (upper right), which produces reduced amounts of Act, and a strain over-expressing SCO1839 (lower left) that shows enhanced Act production.

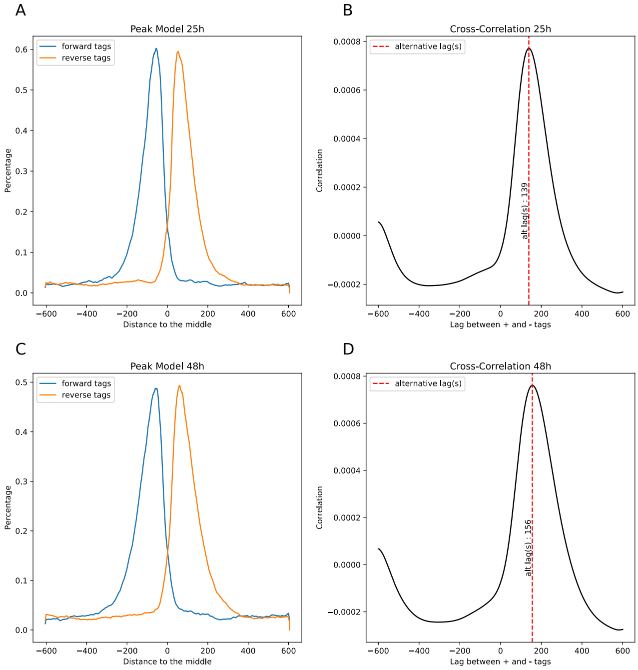

Figure S2. MACS model of 25 h and 48 h ChIP-Seq data. A and B, 25 h ChIP model, C and D, 48 h ChIP model. A and C, 5' ends of strand-separated tags (reads) from a random sample of 1,000 model peaks, aligned by the centre of their Watson (forward) and Crick (reverse) peaks. B and D, combined correlation peak from both strands, showing the distance (lag) of enriched tags to the centre of predicted binding region.

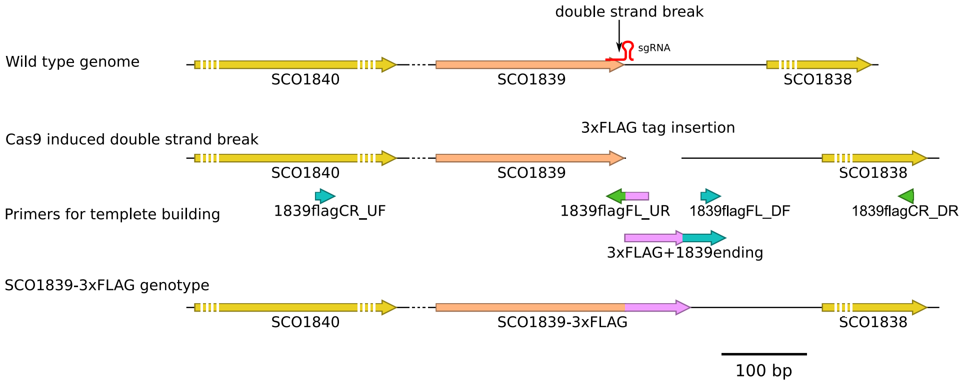

Figure S3. Schematic of construct to allow 3×FLAG tag integration at the C-terminal end of SCO1839. Spacer sequence locates at the end of SCO1839, the sgRNA with this spacer guides the Cas9 protein to make a double-strand break after the stop codon. Templates for homology-directed repair (HDR) were made by cloning SCO1839 and its upstream region from genome with additional connecting sequence, thus replacing the stop codon for connecting with 3×FLAG sequence. The downstream region was PCR-amplified from the genome proceeded by the sequence for a full 3×FLAG sequence. Then these two fragments were connected by overlap extension PCR.

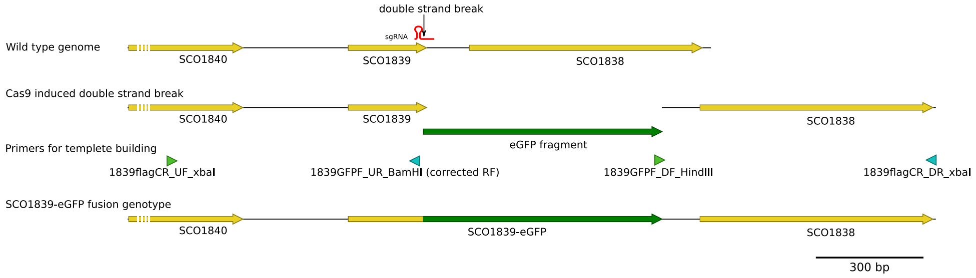

Figure S4. Schematic of construct to allow eGFP integration at the C-terminal end SCO1839. The spacer sequence is fused behind SCO1839, allowing the sgRNA with this spacer to guide Cas9 protein to make a double-strand break after the stop codon. Templates for homology-directed repair (HDR) were made by connecting the SCO1839 region, the eGFP fragment, and the downstream region of SCO1839. The sequence for eGFP was cloned from pGWS526 expressing FtsZ-eGFP as described in Zhang *et al.* (2016).

Curriculum vitae

Chao Du was born on the 15th of August 1987 in Dalian, Liaoning province, China. In the year 2006, he was admitted by Southwest University in Chongqing municipality, China, and obtained Bachelor of Science on the 21th of June 2010. He then performed his research as a master student under the supervision of Prof. dr. Junrong Liang at Diatom Laboratory, Xiamen University, Xiamen, Fujian province, China. On 30th of September 2013, he finished his research on diatom growth and development and obtained his master's degree. Then, he participated in phytoplankton investigation cruises in the coastal area of Fujian province, China. On the 15th of September 2014, he joined Leiden University as a PhD student under the supervision of Prof. dr. Gilles P. van Wezel. Here in Leiden, he performed studies on the development and antibiotics production in *Streptomyces*, the results are presented in this thesis. Currently, he is preforming his post-doctoral research in the laboratory of Prof. dr. Gilles P. van Wezel.

List of publications

Du, C., and van Wezel, G.P. (2018) Mining for microbial gems: Integrating proteomics in the postgenomic natural product discovery pipeline. *Proteomics* 18: 1700332.

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Sulheim, S., Kumelj, T., van Dissel, D., Salehzadeh-Yazdi, A., **Du, C.**, van Wezel, G.P., Nieselt, K., Almaas, E., Wentzel, A., and Kerkhoven, E.J. (2020) Enzyme-constrained models and omics analysis of Streptomyces coelicolor reveal metabolic changes that enhance heterologous production. iScience: 101525.

Xiao, X., Elsayed, S.S., Wu, C., van der Heul, H.U., Metsä-Ketelä, M., **Du, C.**, Prota, A.E., Chen, C., Liu, W., Guo, R., Abrahams, J.P., and van Wezel, G.P. (2020) Functional and structural insights into a novel promiscuous ketoreductase of the lugdunomycin biosynthetic pathway. ACS Chem. Biol.

Du, C., Liang, J., Chen, D., Xu, B., Zhuo, W., Gao, Y., Chen, C., Bowler, C., and Zhang, W. (2014) iTRAQ-based proteomic analysis of the metabolism mechanism associated with silicon response in the marine diatom *Thalassiosira pseudonana*. J. Proteome Res. 13: 720-734.