Total Synthesis

International Edition: DOI: 10.1002/anie.201500066
German Edition: DOI: 10.1002/ange.201500066

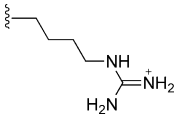
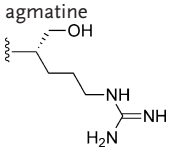
A General and Scalable Synthesis of Aeruginosin Marine Natural Products Based on Two Strategic C(sp^3)–H Activation Reactions**

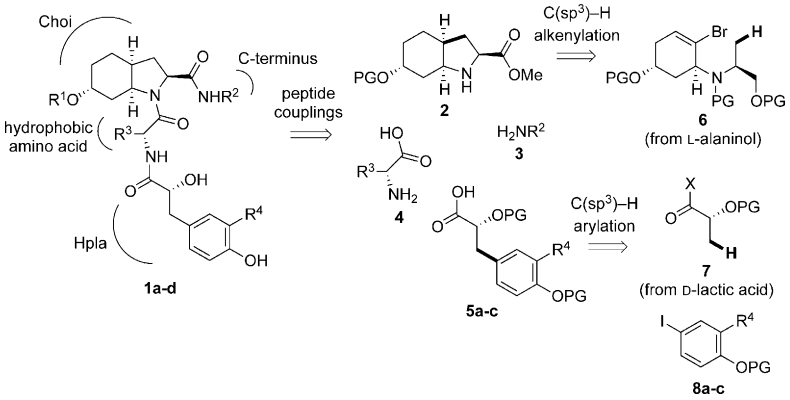
*David Dailler, Grégory Danoun, and Olivier Baudoin**

Abstract: *An efficient and scalable access to the aeruginosin family of marine natural products, which exhibit potent inhibitory activity against serine proteases, is reported. This synthesis was enabled by the strategic use of two different, recently implemented C(sp^3)–H activation reactions. The first method led to the common 2-carboxy-6-hydroxyoctahydroindole (Choi) core of the target molecules on a large scale, whereas the second one provided rapid and divergent access to the various hydroxyphenyllactic (Hpla) subunits. This strategy allowed the synthesis of the aeruginosins 98B and 298A, with the latter being obtained in unprecedentedly large quantities.*

Isolated from marine sponges and cyanobacterial water blooms, the aeruginosins include more than 20 congeners, including aeruginosin 98A (**1a**), 98B (**1b**), 98C (**1c**), and 298A (**1d**; Scheme 1, Table 1), which have shown potent in vitro inhibition of serine proteases.[1,2] These enzymes are involved in a number of important physiological processes, including the blood coagulation cascade. Aeruginosins have been isolated with yields in the range of 0.01–0.05% from dried algae, thereby stressing the need for the development of an efficient and modular total synthesis of these compounds. Structurally, the aeruginosins **1a–d** display four different elements linked by amide bonds, namely a 2-carboxy-6-hydroxyoctahydroindole (Choi) core, a C-terminus containing a terminal guanidine, a hydrophobic amino acid, and a D-hydroxyphenyllactic (Hpla) subunit. Retrosynthetic disconnections at the amide bonds thus provide four different fragments (**2–5**). Different approaches have been reported to construct the Choi core **2** in previous total syntheses of individual aeruginosins,[3] including a Michael-type addition reported by the groups of Bonjoch,[3a,c] Wipf,[3b] and Shibasaki,[3e] a ring-closing metathesis[3d] and an aza-Prins reaction[3f] reported by Hanessian and co-workers, a nucleophilic opening of an oxabicyclic system reported by Carreira and co-workers,[3h] and an intramolecular asymmetric allylic amination by the group of Trost.[3i] We envisioned that our recently developed intramolecular palladium(0)-catalyzed C(sp^3)–H alkenylation method[4,5] would allow access to **2** in a straightforward and scalable manner, thereby enabling the collective synthesis of the aeruginosins **1a–d**. Indeed, the required bromocyclohexene precursor **6** should be accessible from the abundant L-alaninol in a few steps only. To rapidly and efficiently access the Hpla fragments **5a–c** bearing different substituents on the benzene ring, a divergent approach from a common precursor would be the best option. We envisioned that the intermo-

Table 1: Structures of target aeruginosins.

Compound	R^1	R^2	R^3	R^4
aeruginosin 98A (**1a**)	SO_3^-			Cl
		(agmatine)	(D-*allo*-Ile)	
aeruginosin 98B (**1b**)	SO_3^-	agmatine	D-*allo*-Ile	H
aeruginosin 98C (**1c**)	SO_3^-	agmatine	D-*allo*-Ile	Br
aeruginosin 298A (**1d**)	H			H
		(L-argol)	(D-Leu)	



Scheme 1. Retrosynthetic analysis. PG = protecting group.

[*] D. Dailler,[+] Dr. G. Danoun,[+] Prof. Dr. O. Baudoin
Université Claude Bernard Lyon 1, CNRS UMR 5246, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CPE Lyon
43 Boulevard du 11 Novembre 1918 (France)
E-mail: olivier.baudoin@univ-lyon1.fr
Homepage: http://cosmo.univ-lyon1.fr/Index.html

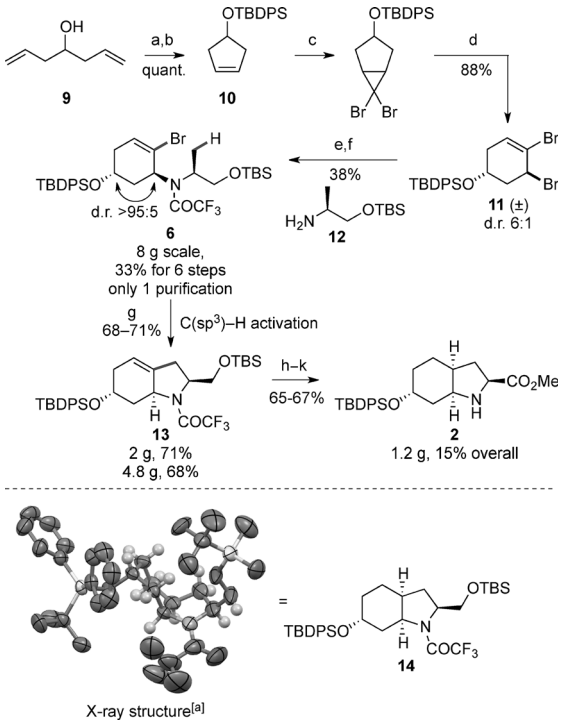
[+] These authors contributed equally to this work.

[**] Financial support was provided by Région Rhône-Alpes (ARC Santé), Fondation Pierre Potier pour le Développement de la Chimie des Substances Naturelles et ses Applications, and Institut Universitaire de France. We thank Dr. G. Pilet, UCBL, for X-ray diffraction analysis, the group of Prof. M. Lemaire, (in particular Dr. E. Métay and Dr. C. Guyon), UCBL, for helpful suggestions, Dr. J.-Y. Ortholand and Dr. H. Lemoine, Edelris, for assistance with preparative HPLC.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500066.

lecular palladium(II)-catalyzed directed C–H arylation[6] of a suitable derivative of D-lactic acid would fulfill such an objective. Altogether, the above C(sp^3)–H activation based retrosynthetic strategy[7] should allow us to prepare **1a–d** in a straightforward and modular manner from the chiral pool.

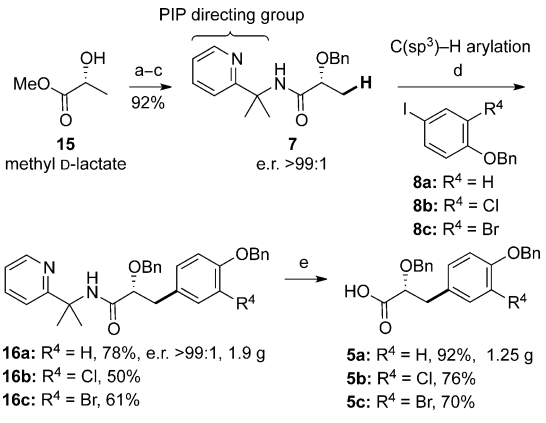
The synthesis of **2** is depicted in Scheme 2. The C–H activation precursor **6** was prepared through a robust, and



Scheme 2. Synthesis of the Choi core **2**. Reagents and conditions: a) TBDPSCl, imidazole, CH_2Cl_2, 0°C; b) $(PCy_3)_2Cl_2Ru$=CHPh (3 mol%), CH_2Cl_2, 20°C; c) $CHBr_3$, NaOH, Et_3BnNCl, CH_2Cl_2, ultrasound, 20°C; d) 130°C (neat), 88% for 4 steps, d.r. 6:1; e) **12**, K_2CO_3, DMF, 20→90°C; f) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 20°C, 38% for 2 steps; g) [Pd(PCy_3)$_2$] (10 mol%), K_2CO_3, $tBuCO_2K$ (30 mol%), toluene, 120°C, 68–71%; h) 1. Rh/C (20 mol%), H_2 (1 atm), ethyl acetate, 20°C; 2. HCl (0.5%), CH_3OH, 20°C, 95%; i) Jones' reagent, acetone, 20°C, 86%; j) Me_3SiCHN_2, MeOH, 0°C, 97%; k) $NaBH_4$, MeOH, −10→20°C, 83%. [a] X-ray structure of **14** (shown with 50% probability ellipsoids, only selected H atoms are displayed for clarity). DMF = *N*,*N*-dimethylformamide, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

easily scalable route starting from the commercially available dihomoallylalcohol **9**.[8] The latter was protected with the bulky *tert*-butyldiphenylsilyl (TBDPS) group, and subsequent ring-closing metathesis employing the Grubbs' first-generation catalyst afforded the cyclopentenol **10** in quantitative yield over two steps. Dibromocyclopropanation and thermal electrocyclic ring opening[9] provided the racemic dibromocyclohexene **11** as an inconsequential 6:1 mixture of diastereoisomers. Nucleophilic substitution with the enantiopure TBS-protected L-alaninol **12** provided a 1:1 mixture of the two diastereoisomers possessing the *trans* relationship between the nitrogen and oxygen substituents of the cyclohexene ring. This outcome can be explained by the S_N1-type attack of **12** onto any of the equivalent terminal carbon atoms of the allyl cation arising from **11**, on the opposite face to the large OTBDPS group. The desired *trans,syn* diastereoisomer was separated, and **6** was isolated after introduction of a trifluoroacetyl group. Notably, **6** was obtained in 33% overall yield from **9**, and this six-step sequence could be conducted on multigram quantities with only one chromatographic purification. The intramolecular C(sp^3)–H alkenylation of **6** was then re-optimized, taking previously reported reaction conditions[4] as a starting point. An optimal yield was obtained with the well-defined complex [Pd(PCy_3)$_2$] as the catalyst, and K_2CO_3 and catalytic potassium pivalate as the basic system in toluene at 120°C. Importantly, this protocol allowed production of multigram quantities of the hexahydroindole **13** with yields in the range 68–71%. Hydrogenation of the alkene in **13** was best performed using Rh/C as the catalyst and occurred with high diastereoselectivity, presumably controlled by the angular hydrogen, to give the octahydroindole **14**, the structure and absolute configuration of which was confirmed by X-ray analysis (Scheme 2).[10] Then, removal of the TBS group, oxidation of the resulting primary alcohol to the carboxylic acid, and subsequent esterification and reductive cleavage of the trifluoroacetyl group furnished over 1 gram of **2** in 65–67% yield from **13** and 15% overall yield for the entire 11-step sequence from **9**.

At the outset of our studies on the synthesis of the Hpla fragments **5a–c** through a directed C(sp^3)–H arylation strategy, we tested various known directing groups such as the quinolinyl and methylthiophenyl groups introduced by Daugulis and co-workers[11] and the 2-pyridinylisopropyl (PIP) group introduced by Shi and co-workers (Scheme 3).[12] The latter turned out to be the best choice, both because it furnished the highest arylation yields and because it allowed preservation of the integrity of the sensitive lactate stereogenic center. The PIP group was



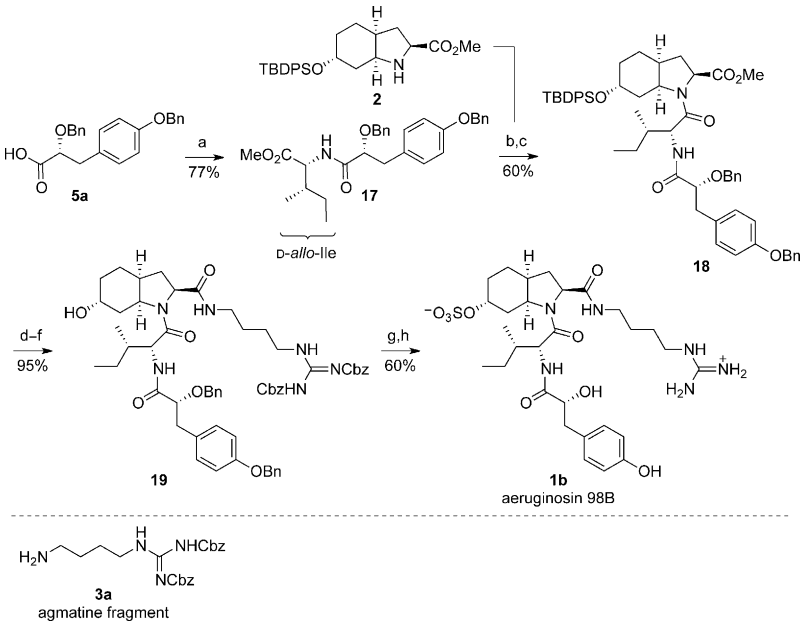
Scheme 3. Synthesis of the Hpla fragments **5a–c**. Reagents and conditions: a) BnOC(=NH)CCl_3, TfOH, hexane/CH_2Cl_2 (6:1), 20°C; b) LiOH, THF, 20°C; c) 2-(pyridin-2-yl)propan-2-amine, HBTU, iPr_2NEt, DMF, 0→20°C, 92% for 3 steps; d) **8a** or **8b** or **8c**, $Pd(OAc)_2$ (10 mol%), K_2CO_3, CH_3CN, 110°C, yields: 78% for **16a**, 50% for **16b**, 61% for **16c**; e) $NOBF_4$, pyridine, CH_2Cl_2, −30→20°C, yields: 92% for **5a**, 76% for **5b**, 70% for **5c**. HBTU = O-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, Tf = trifluoromethanesulfonyl.

introduced by peptide coupling between 2-(pyridin-2-yl)propan-2-amine and Bn-protected D-lactic acid, the latter being accessible in two steps and quantitative yield from commercially available methyl D-lactate (**15**). After screening various reported reaction conditions for the C–H arylation of **7** with the benzyl-protected iodoarene **8a** under palladium(II) acetate catalysis, we found that K_2CO_3 as the base and acetonitrile as the solvent allowed isolation of the aryllactate **16a** in an optimal 78% yield. Notably, this procedure could be conducted on gram scale without any racemization despite the use of basic conditions, as verified by HPLC analysis on a chiral stationary phase employing independently prepared racemic samples of **7** and **16a** as references. To remove the PIP directing group in **16a** without racemization of the base-sensitive stereocenter, we designed a new, very mild protocol employing $NOBF_4$ as a nitrosation agent[13] and pyridine at low temperature. In this manner, the enantiopure carboxylic acid **5a** was obtained in excellent yield. The same C–H arylation/PIP cleavage sequence was then applied to the halogenated iodoarenes **8b**,**c**, which are relevant to the synthesis of halogenated aeruginosins 98A and 98C, thereby furnishing the halogenated Hpla fragments **5b**,**c** chemoselectively and in good overall yields.

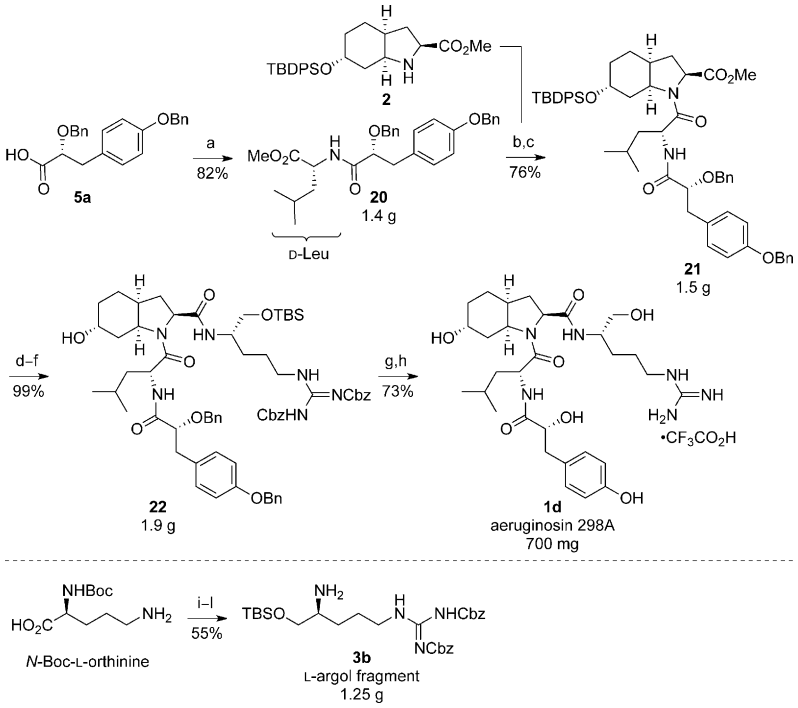
With the various requisite fragments in hand, we turned to the synthesis of our first target, aeruginosin 98B (**1b**; Scheme 4). First, **5a** was reacted with D-*allo*-isoleucine methyl ester[3i,14] under classical peptide coupling conditions to give the intermediate **17**, which upon hydrolysis and peptide coupling with **2** gave the methyl ester **18**. Then, the TBDPS group of **2** was removed using Olah's reagent, and the methyl ester was subsequently hydrolyzed. The coupling of the resulting carboxylic acid with the Cbz-protected agmatine **3a** furnished the intermediate **19** in high yield. The latter underwent sulfation under previously reported reaction conditions,[3i] followed by hydrogenolysis of all four benzyl-containing protecting groups to give aeruginosin 98B (37 mg). The synthetic product, which showed identical spectroscopic data to previously reported compounds,[2b,3i] was obtained in 5.1% overall yield (84% average yield per step) for the longest linear sequence of 17 steps starting from **9**. In principle, the same synthetic sequence employing **5b**,**c** instead of **5a** would lead to aeruginosins 98A and 98C (Table 1). In these cases, the final hydrogenation step is challenging because of the presence of sensitive carbon–halogen bonds. Studies towards these targets are currently on-going in our laboratory and will be reported in due course.

Following this first success, we decided to perform the synthesis of our second target, aeruginosin 298A (**1d**), on a larger scale. The compound **1d** possesses the same Choi core and Hpla fragment as aeruginosin 98B, but a different hydrophobic amino acid and C-terminus (Scheme 5). First, **5a** was reacted with D-leucine methyl ester on gram scale, and the resulting product **20** was hydrolyzed and coupled with **2**, thereby providing the intermediate **21**. Then, similarly as above with **1b**, cleavage of the TBDPS group, followed by ester hydrolysis and coupling with the protected L-argol fragment **3b**, which was synthesized through an improved protocol starting from Boc-protected L-ornithine in four steps (55% overall yield; Scheme 5, bottom), furnished 1.9 g of the intermediate **22** in excellent yield from **21**. Finally, acid-mediated cleavage of the TBS group on the argol fragment and hydrogenolysis provided 700 mg of **1d**, which was isolated as the salt formed with trifluoroacetic acid, as described previously.[2a,3b,e,g] Remarkably, the synthetic product was obtained in 8.2% overall yield (86% average yield per step) for the longest linear sequence of 17 steps starting from **9**. Both the overall yield and scale of this total synthesis are unprecedented.[15]

In conclusion, we have provided a general and scalable access to the aeruginosin family of marine natural products possessing interesting pharmacological properties, albeit low availability from natural sources. For this purpose, two recently discovered C(sp^3)–H activation reactions were employed in a strategic manner, with the first one enabling a large-scale synthesis of the common (Choi) heterocyclic core of the molecules and the second one a rapid and divergent access to diversely decorated Hpla fragments. This powerful strategy was successfully implemented in the synthesis of aeruginosins 98B and 298A, with the latter being performed on unprecedentedly large scale, and should streamline the access to other members of this family of marine products, including the halogenated congeners. Importantly, this



Scheme 4. Synthesis of aeruginosin 98B (**1b**). Reagents and conditions: a) D-*allo*-Ile-OMe, PyBOP, *i*Pr_2NEt, CH_2Cl_2, 20°C, 77%; b) LiOH, THF/MeOH 3:1, 0→20°C; c) **2** (1.2 equiv), PyBOP, *i*Pr_2NEt, CH_2Cl_2, 20°C, 60% for 2 steps; d) HF·pyridine, CH_3CN, 0°C, 95%; e) LiOH, THF/MeOH (2:1), 0→20°C; f) **3a** (1.2 equiv), HBTU, *i*Pr_2NEt, DMF, 0→20°C, 100% for 2 steps; g) SO_3·pyridine, pyridine, 50°C; h) H_2, $Pd(OH)_2$/C, MeOH/AcOEt (1:1), 20°C, 60% for 2 steps. PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, THF = tetrahydrofuran.



Scheme 5. Synthesis of aeruginosin 298A (**1d**). Reagents and conditions: a) D-Leu-OMe, PyBOP, iPr$_2$NEt, CH_2Cl_2, 20°C, 82%; b) LiOH, THF/MeOH (3:1), 0→20°C; c) **2** (1.2 equiv), PyBOP, iPr$_2$NEt, CH_2Cl_2, 20°C, 76% for 2 steps; d) HF·pyridine, CH_3CN, 0°C, 99%; e) LiOH, THF/MeOH (2:1), 0→20°C; f) **3b** (1.2 equiv), HBTU, iPr$_2$NEt, DMF, 0→20°C, quant. for 2 steps; g) HCl (0.5%), MeOH, 0°C, 78%; h) H_2, Pd(OH)$_2$/C, MeOH/AcOEt (1:1), 20°C, then CF_3CO_2H, 93%; i) TfN=C(NHCbz)$_2$, $CF_3C(=O)$-N(Me)SiMe$_3$, Et$_3$N, CH_2Cl_2, 20°C, 76%; j) isobutyl chloroformate, *N*-methylmorpholine, THF, −10°C, then $NaBH_4$, THF/H_2O (4:1), 0→20°C, 74%; k) TBSCl, imidazole, CH_2Cl_2, 0→20°C, 99%; l) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78→20°C, 100%. TMS = trimethylsilyl.

study allows access to significant quantities of pure compound, and therefore should enable more advanced pharmacological studies of these potent serine protease inhibitors.

Keywords: C–H activation · natural products · palladium · synthetic methods · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 4919–4922
Angew. Chem. **2015**, *127*, 5001–5004

[1] Review: K. Ersmark, J. R. Del Valle, S. Hanessian, *Angew. Chem. Int. Ed.* **2008**, *47*, 1202–1223; *Angew. Chem.* **2008**, *120*, 1220–1242.

[2] Isolation: a) M. Murakami, Y. Okita, H. Matsuda, T. Okino, K. Yamaguchi, *Tetrahedron Lett.* **1994**, *35*, 3129–3132; b) M. Murakami, K. Ishida, T. Okino, Y. Okita, H. Matsuda, K. Yamaguchi, *Tetrahedron Lett.* **1995**, *36*, 2785–2788; c) K. Ishida, Y. Okita, H. Matsuda, T. Okino, M. Murakami, *Tetrahedron* **1999**, *55*, 10971–10988.

[3] a) N. Valls, M. López-Canet, M. Vallribera, J. Bonjoch, *J. Am. Chem. Soc.* **2000**, *122*, 11248–11249 (aeruginosin 298A); b) P. Wipf, J.-L. Methot, *Org. Lett.* **2000**, *2*, 4213–4216 (aeruginosin 298A); c) N. Valls, M. López-Canet, M. Vallribera, J. Bonjoch, *Chem. Eur. J.* **2001**, *7*, 3446–3460 (aeruginosins 298A,B); d) S. Hanessian, R. Margarita, A. Hall, S. Johnstone, M. Tremblay, L. Parlanti, *J. Am. Chem. Soc.* **2002**, *124*, 13342 (dysinosin A); e) T. Ohshima, V. Gnanadesikan, T. Shibuguchi, Y. Fukuta, T. Nemoto, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 11206–11207 (aeruginosin 298A); f) S. Hanessian, M. Tremblay, J. F. W. Petersen, *J. Am. Chem. Soc.* **2004**, *126*, 6064–6071 (oscillarin); g) T. Doi, Y. Hoshina, H. Mogi, Y. Yamada, T. Takahashi, *J. Comb. Chem.* **2006**, *8*, 571–582 (aeruginosin 298A); h) S. Diethelm, C. S. Schindler, E. M. Carreira, *Org. Lett.* **2010**, *12*, 3950–3953 (microcin SF608); i) B. M. Trost, T. Kaneko, N. G. Andersen, C. Tappertzhofen, B. Fahr, *J. Am. Chem. Soc.* **2012**, *134*, 18944–18947 (aeruginosin 98B).

[4] J. Sofack-Kreutzer, N. Martin, A. Renaudat, R. Jazzar, O. Baudoin, *Angew. Chem. Int. Ed.* **2012**, *51*, 10399–10402; *Angew. Chem.* **2012**, *124*, 10545–10548.

[5] For reviews: a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; b) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; c) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191; d) N. Dastbaravardeh, M. Christakakou, M. Haider, M. Schnürch, *Synthesis* **2014**, 1421.

[6] For a recent review: G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; *Angew. Chem.* **2013**, *125*, 11942–11959.

[7] For reviews on C–H functionalization strategies in total synthesis: a) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; b) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; *Angew. Chem.* **2012**, *124*, 9092–9142.

[8] L. Petit, M. G. Banwell, A. C. Willis, *Org. Lett.* **2011**, *13*, 5800–5803.

[9] For a review: B. Halton, J. Harvey, *Synlett* **2006**, 1975.

[10] CCDC 1029844 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155; b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.

[12] Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 13588–13592; *Angew. Chem.* **2013**, *125*, 13833–13837.

[13] P. Romea, F. Urpi, J. Vilarrasa, *J. Org. Chem.* **1989**, *54*, 3209–3211.

[14] H. Noda, K. Sakai, H. Murakami, *Tetrahedron: Asymmetry* **2002**, *13*, 2649–2652.

[15] The previous largest-scale synthesis allowed production of 59 mg of **1d** in 3.1% overall yield.[3a,c] The previous most efficient synthesis of **1d** displayed an overall yield of 5.3%.[3g]

Received: January 5, 2015
Published online: February 25, 2015

