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Natural Products |*Hot Paper*|

Divergent Synthesis of Aeruginosins Based on a C(sp^3)–H Activation Strategy

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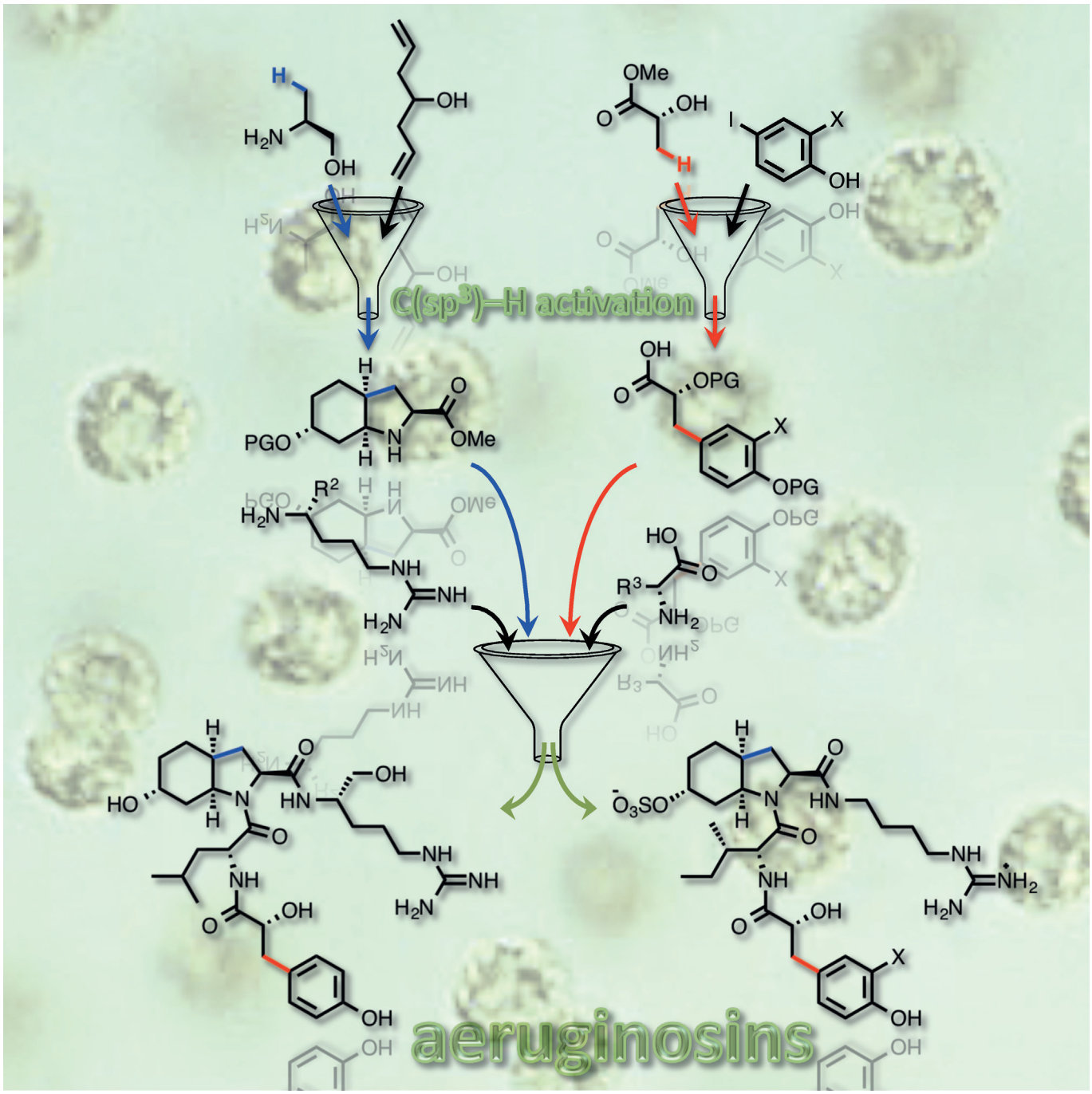
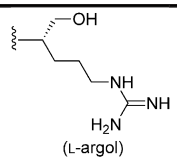
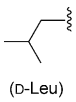
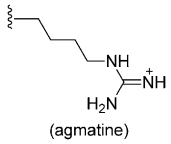


Abstract: A general and scalable access to the aeruginosin family of marine natural products, exhibiting potent inhibitory activity against serine proteases, is reported. This was enabled by the strategic use of two recently implemented Pd-catalyzed C(sp^3)–H activation reactions. The first method allowed us to obtain the common 2-carboxy-6-hydroxyoctahydroindole (Choi) core of the target molecules on a large scale, whereas the second method provided a rapid and divergent access to various hydroxyphenyllactic (Hpla) subunits, including halogenated ones. This unique strategy, together with an optimization of the fragment coupling sequence allowed the synthesis of four aeruginosins, that is, 98A–C and 298A from the chiral pool. Among them, aeruginosin 298A was synthesized on an unprecedentedly large scale. In addition, halogenated aeruginosins 98A and 98C were synthesized for the first time, thanks to a fine-tuning of the final hydrogenation step.

Introduction

Aeruginosins are marine natural products that have been isolated from sponges and cyanobacterial water blooms, and which include more than 20 congeners.[1] Among these, aeruginosin 298A (**1a**), 98A–C (**1b–d**), and 101 (**1e**) have shown potent in vitro inhibition of various serine proteases, including thrombin and trypsin (Scheme 1, Table 1). These enzymes are involved in a number of important physiological processes, in particular, the blood coagulation cascade. Aeruginosins **1a–e** have been isolated from dried algae with yields in the range of 0.01—0.05%.[2–3] This low availability, combined with their interesting biological properties, stresses the need for an efficient and modular total synthesis of these marine compounds.[4] Structurally, aeruginosins display four different units linked by three amide bonds: a 2-carboxy-6-hydroxyoctahydroindole (Choi) core containing a free (**1a**) or sulfated (**1b–e**) hydroxy group, a C-terminus (L-argol or agmatine) containing a terminal guanidine, a hydrophobic amino acid, and a D-hydroxyphenyllactic (Hpla) subunit which may include halogen (Cl, Br) atoms (**1b**, **1d**, **1e**). The structure of aeruginosin 298A (**1a**) was initially elucidated by Murakami and co-workers, who misassigned the configuration of the hydrophobic amino acid as L-leucine.[2] Later, the first total syntheses of this molecule were independently reported by the groups of Bonjoch[5] and Wipf,[6] and revealed a D-configuration for the leucine moiety.

Table 1. Structures of target aeruginosins.

Compound	R^1	R^2	R^3	R^4	R^5
aeruginosin 298A (**1a**)	H	 (L-argol)	 (D-Leu)	H	H
aeruginosin 98A (**1b**)	SO_3^-	 (agmatine)	 (D-*allo*-Ile)	Cl	H
aeruginosin 98B (**1c**)	SO_3^-	agmatine	D-*allo*-Ile	H	H
aeruginosin 98C (**1d**)	SO_3^-	agmatine	D-*allo*-Ile	Br	H
aeruginosin 101 (**1e**)	SO_3^-	agmatine	D-*allo*-Ile	Cl	Cl

To access aeruginosins **1a–e**, we first considered classical retrosynthetic disconnections at the amide bonds, leading to the four fragments **2–5** (Scheme 1). Different approaches have been reported to construct the bicyclic Choi core **2** in previous total syntheses of aeruginosins 298A (**1a**). The groups of Bonjoch,[5] Wipf,[6] and Shibasaki[7] employed intramolecular Michael-type additions to build the C–N bond of the pyrrolidine ring from precursors that were either obtained from L-tyrosine by a reductive[5] or an oxidative[6] process, or by catalytic asymmetric phase-transfer alkylation of a glycine derivative.[7] These Michael addition based strategies all furnished a mixture of diastereoisomers, which required an additional equilibration step to obtain the desired stereoisomer. In their synthesis of aeruginosin 98B (**1c**), Trost and co-workers, employed a different strategy, based on an intramolecular asymmetric Tsuji–Trost reaction, which directly led to a hexahydroindole intermediate possessing the required configuration.[8] In light of these precedents,[9] we envisioned that our recently developed intramolecular palladium(0)-catalyzed C(sp^3)–H alkenylation[10,11] would allow access to compound **2** in a straightforward and scalable manner, thereby enabling the collective synthesis of aeruginosins. The required bromocyclohexene precursor **6** should be accessible from abundant L-alaninol **10** in a few steps only. In order to access Hpla fragments **5**, which may include potentially labile halogen atoms, in a straightforward manner, a divergent approach from a common precursor would be ideal. We envisioned that the intermolecular palladium(II)-catalyzed directed C–H arylation of a suitable derivative of D-lactic acid would fulfill such an objective. Indeed, Daugulis and co-workers initially introduced the use of the bidentate 8-aminoquinoline directing group to perform the direct C(sp^3)–H arylation of alkyl carboxylic acids at the β position.[12] Since this discovery, important developments were achieved in this field, including the introduction of new directing groups, thereby establishing it as one of the most powerful and practical strategies to construct valuable arylated alkyl

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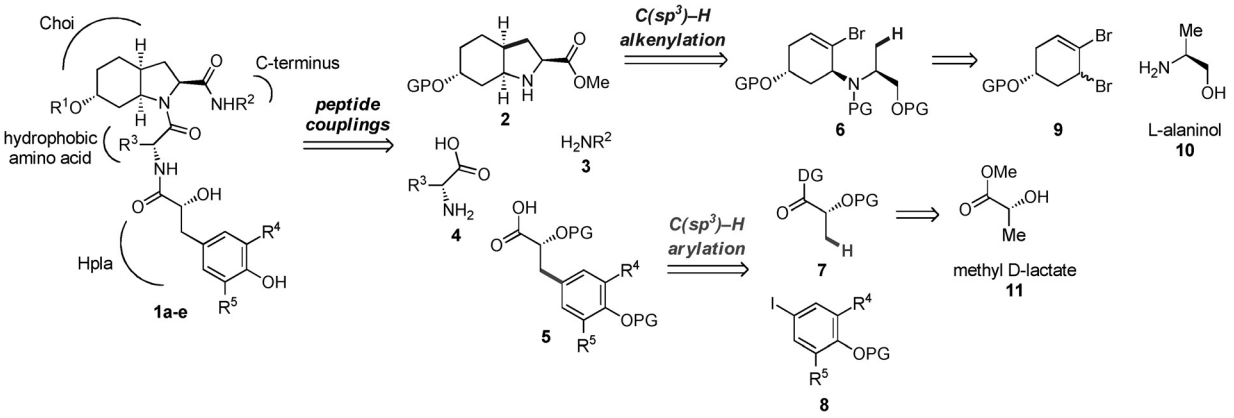


Scheme 1. Retrosynthetic analysis. PG = protecting group; DG = directing group.

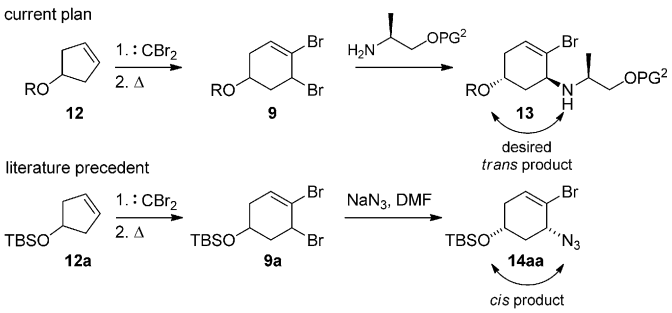
scaffolds.[13] This methodology has been already applied in several total syntheses.[14,15]

In this article, we report in detail our investigations that led to the general and scalable total synthesis of the four aeruginosin congeners **1a–d** from simple chiral pool precursors.[16] Halogenated aeruginosins at the Hpla fragment (including **1b** and **1d**) had never been synthesized before. This achievement was enabled by a combination of two key C(sp^3)–H activation reactions with the optimization of the fragment coupling sequence and protecting-group strategy.

Results and Discussion

Synthesis of the choi core

The construction of the Choi core through C(sp^3)–H activation required the synthesis of the enantiomerically pure precursor **6** possessing a *trans* relationship between the hydroxy and amino groups on the cyclohexene ring. We hypothesized that the dibromocyclopropanation of a protected cyclopent-3-enol **12** followed by thermal electrocyclic ring-opening[17] would provide a short and easy access to this precursor despite a potential diastereoselectivity issue (Scheme 2). Indeed, Banwell and co-workers used a similar sequence to obtain TBS-protected dibromocyclohexenol **9a**, which was submitted to nucleophilic substitution with sodium azide.[18] The *cis*-configured product (**14aa**) was obtained with a diastereoselectivity of 9:1 starting from a 6:1 diastereoisomeric mixture of **9a**, thereby

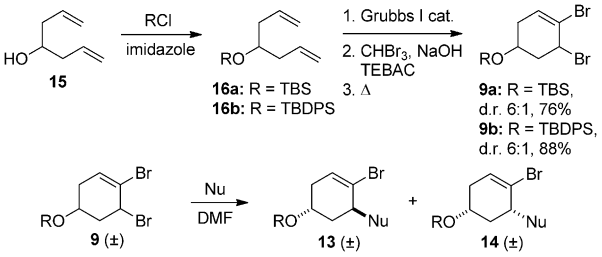


Scheme 2. Synthetic plan for precursor **13**. TBS = *tert*-butyldimethylsilyl.

supporting an S_N1-type mechanism. In the case of amine **13**, we surmised that the use of the much bulkier alaninol-derived nucleophile might allow an inversion of the diastereoselectivity in favor of the *trans*-product by virtue of steric effects.

In order to test this hypothesis, a study was conducted on the influence of both the nucleophile and the protecting-group (R) carried by the dibromocyclohexenol moiety (**9**). To this purpose, two dibromocyclohexenols protected with a TBS or TBDPS silyl group (**9a,b**) were prepared from 1,6-heptanedien-3-ol **15** (Table 2). Compounds **9a,b** were then submitted to nucleophilic substitution with various primary amines and with sodium azide (Table 2). First, an inversion of diastereoselectivity in favor of the *trans* product **13** was observed when a primary amine was used instead of the azide (Table 2, en-

Table 2. Study of the allylic nucleophilic substitution.[a]



Entry	R	Nucleophile (Nu)	d.r.[b]
1	TBS	N_3^-	1:8
2	TBS	*n*PrNH$_2$[c]	3:1
3	TBS	*i*BuNH$_2$[c]	3:1
4	TBS	*i*PrNH$_2$[c]	6:1
5	TBDPS	N_3^-	1:15
6	TBDPS	*n*PrNH$_2$[c]	7:1
7	TBDPS	*i*BuNH$_2$[c]	8:1
8	TBDPS	*i*PrNH$_2$[c]	11:1

[a] TBDPS = *tert*-butyldiphenylsilyl; TEBAC = Et_3BnNCl. [b] Ratio of **13**/**14** determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Relative configurations of the major diastereoisomers obtained with sodium azide and isopropylamine were determined by X-ray analysis of ferrocene derivatives **17** and **18** (Figure 1).[19] For other primary amines, the *trans* configuration was ascribed to major diastereoisomers by analogy of their chemical shifts in ^{1}H NMR spectra. [c] In combination with 1.1 equiv K_2CO_3.

tries 2–4 vs. 1; entries 6–8 vs. 5). Then, increasing the steric hindrance of the amine in the α-position to the N atom increased the diastereoselectivity in favor of the *trans* product (entries 2–4 and 6–8). In addition, the steric hindrance of the silyl protecting group also had a major influence on the diastereoselectivity (entries 5–8 vs. 1–4), with the bulkier TBPDS group consistently providing higher d.r. than the TBS group in favor of the major *cis* or *trans* diastereoisomer for each considered nucleophile. This study shows that both *cis* and *trans* diastereoisomers of 5-aminocyclohex-3-en-1-ols can be accessed with useful levels of diastereoselectivity by modifying the type of nucleophile (i.e. azide vs. amine) and by introducing a sufficiently bulky protecting group on the alcohol. These findings might be useful in other syntheses of alkaloids and related compounds (Figure 1).[20]

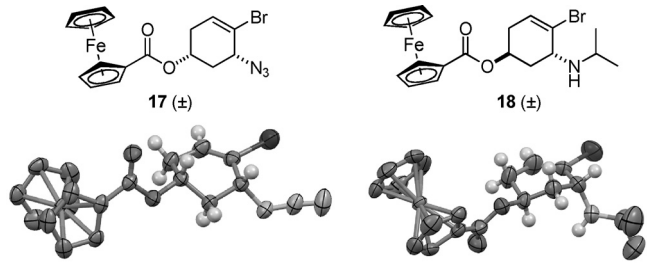
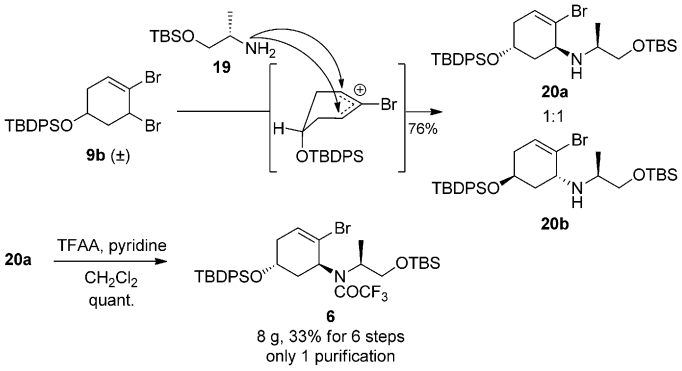


Figure 1. X-ray structures of major diastereoisomers **17** and **18** (thermal ellipsoids at the 50% probability level, some H atoms are omitted for clarity).[19]

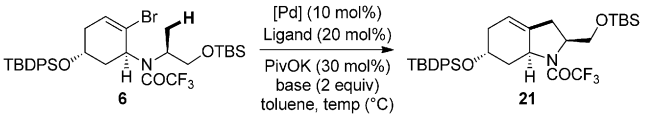
The application of the above *trans*-selective nucleophilic substitution to TBS-protected L-alanilol **19** and TBDPS-protected dibromocyclohexenol **9b** provided a 1:1 mixture of two diastereoisomers **20a**,**b** possessing the desired *trans* configuration at the cyclohexene ring (Scheme 3). Indeed, the symmetrical allyl cation, which is expected from the S_N1-type mechanism, should be attacked by the enantiopure nucleophile indiscriminately on both electrophilic positions, opposite to the OTBDPS group. Gratifyingly, diastereoisomers **20a**,**b** could be easily separated by column chromatography on silica gel.[21] The amine group of the desired diastereoisomer (**20a**) was then protected as a trifluoroacetamide, thus leading to the C(sp^3)–H activation precursor **6**. Despite the production of two diastereoisomers in the nucleophilic substitution step (out of the four possible), this synthetic pathway proved to be efficient and robust, since it allowed the preparation of 8 g of bromocyclohexene **6** with only one purification and 33% overall yield for 6 steps (83% average yield per step).



Scheme 3. Synthesis of the C–H activation precursor **6**. TFAA = trifluoroacetic anhydride.

The key Pd-catalyzed intramolecular C(sp^3)–H alkenylation of compound **6** was then examined, using previously reported conditions as a starting point (Table 3, entry 1).[10] These conditions afforded 45% of the desired cyclic compound **21**. A rapid screening of palladium sources and ligands (entries 2–4) allowed the yield to be increased to 75% when engaging the well-defined complex $Pd(PCy_3)_2$ (entry 4). A decrease of the temperature induced a drop of the reaction efficiency (entries 5–6). The nature of the base was then investigated (entries 7 and 8), and K_2CO_3 furnished the highest yield (85%) of cyclic product **21** (entry 8). Finally, an attempt at decreasing the catalyst loading to 5 mol% Pd was met with little success (entry 9).

Table 3. Optimization of the C(sp^3)–H alkenylation.

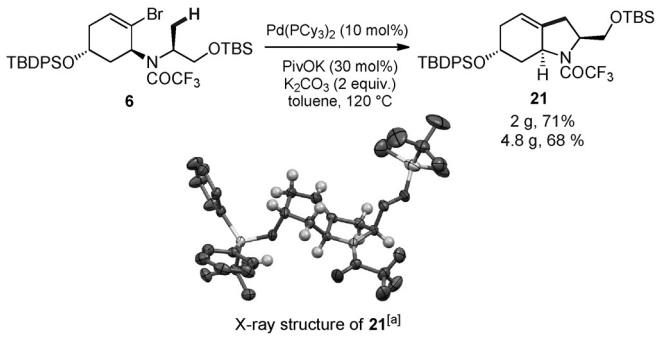


Entry	[Pd]	Ligand	Base	*T* [°C]	Yield [%][a]
1	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	Rb_2CO_3	120	45
2	$[Pd_2(dba)_3]$	$PCy_3{\cdot}HBF_4$	Rb_2CO_3	120	45
3	$[Pd(PPh_3)_4]$	–	Rb_2CO_3	120	32
4	$Pd(PCy_3)_2$	–	Rb_2CO_3	120	75
5	$Pd(PCy_3)_2$	–	Rb_2CO_3	110	70
6	$Pd(PCy_3)_2$	–	Rb_2CO_3	100	18
7	$Pd(PCy_3)_2$	–	Cs_2CO_3	120	40
8	$Pd(PCy_3)_2$	–	K_2CO_3	120	85
9[b]	$Pd(PCy_3)_2$	–	K_2CO_3	120	50

[a] NMR yield, determined by ^1H NMR spectroscopy using trichloroethylene as an internal standard. [b] Using 5 mol% of $Pd(PCy_3)_2$.

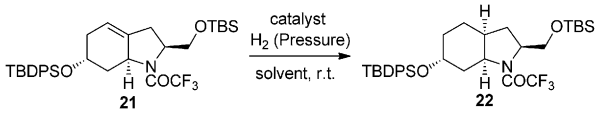
With these new conditions in hand, the reaction was gradually and successfully scaled up, thereby allowing the bicyclic product **21** to be obtained in approximately 70% isolated yield in a reproducible manner on a multigram scale (Scheme 4). The absolute stereochemistry of this compound was confirmed by X-ray analysis.[19]

Then, we studied the diastereoselective reduction of the trisubstituted alkene by catalytic hydrogenation. Surprisingly, among the homogeneous (Table 4, entries 1–2) and heterogeneous (entries 3–10) catalysts tested, only Rh/C led to complete conversion (entries 7–10). Of note, Pearlman's catalyst, which we previously employed on a similar hexahydroindole scaffold lacking the OTBDPS group,[10] proved completely inefficient in the present case (entry 3). Moreover, the pressure of hydrogen affected the diastereoselectivity of the reaction. Indeed, a decrease of the d.r. in favor of the desired product was observed when the pressure was increased (entries 7–10).



Scheme 4. Scale-up of the C(sp^3)–H alkenylation. [a] Thermal ellipsoids at the 50% probability level, some H atoms are omitted for clarity.[19]

Table 4. Optimization of the hydrogenation of **21**.



Entry	Catalyst	Solvent	P_{H_2} [bar]	Conv. [%][a]	d.r.[a]
1	$[RhCl(PPh_3)_3]$	AcOEt	1	–	–
2	$[Ir(cod)(C_5H_5N)(PCy_3)]PF_6$	AcOEt	1	–	–
3	$Pd(OH)_2/C$	THF	1	–	–
4	PtO_2	MeOH	1	< 10	–
5	Ru/Al_2O_3	AcOEt	1	< 10	–
6	Ru/C	AcOEt	1	< 10	–
7	Rh/C	AcOEt	1	100	> 20:1
8	Rh/C	AcOEt	3	100	10:1
9	Rh/C	AcOEt	10	100	8:1
10	Rh/C	AcOEt	20	100	6:1

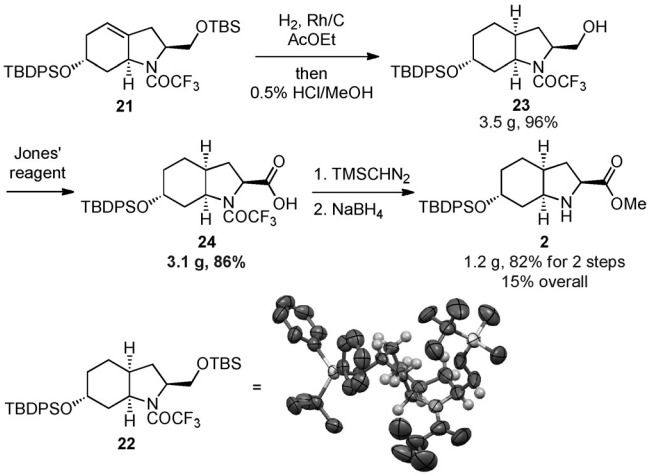
[a] Determined by ^1H NMR spectroscopy.

Gratifyingly, a complete diastereocontrol of the hydrogenation on the convex face of the hexahydroindole system was achieved under one atmosphere of hydrogen (entry 7), and the *cis* configuration of the corresponding product **22** was confirmed by X-ray analysis (Scheme 5).[19]

The isolation of product **22** showed a partial but inconsequential deprotection of the TBS group, probably due to the residual acidity of the rhodium catalyst. Consequently, the hydrogenation and the acid-mediated deprotection of the TBS group were performed in a one-pot manner, yielding 3.5 g of alcohol **23** in 96% yield (Scheme 5). The primary alcohol was then oxidized under Jones' conditions. Finally, the resulting carboxylic acid **24** was esterified and the trifluoroacetyl group was removed under reductive conditions to give over 1 g of amino ester **2** in good overall yield (15% for 11 steps) from alcohol **15**.

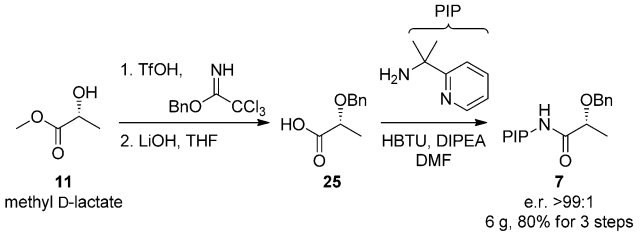
Synthesis of the Hpla fragments

We then investigated the second key C(sp^3)–H activation step, relevant to the synthesis of the various Hpla fragments. First of all, a benzyl group was chosen as protecting group of the lactate moiety in light of a precedent on the directed arylation of this motif.[12b] We initially chose to install a triisopropylsilyl ether (TIPS) protecting group on the phenol by analogy to previous syntheses of aeruginosin 298A.[6,7] With these coupling partners, a rapid screening of various directing groups such as the quinolinyl and methylthiophenyl groups introduced by Daugulis and co-workers[12] and the 2-pyridinylisopropyl (PIP) group introduced by Shi and co-workers[22] was performed. The latter turned out to be the best choice, especially because it allowed the preservation of the integrity of the sensitive lactate stereogenic center. The corresponding C–H arylation precursor **7** was synthesized in three steps from commercially available methyl D-lactate **11** (Scheme 6).[23] Of note, directed C(sp^3)–H arylation is known to give rise to various byproducts such as polyarylated compounds, thereby complicating purification and up-scaling.[12–13] We thus performed the reaction optimization with the main objective to devise a practical, scalable process (Table 5).



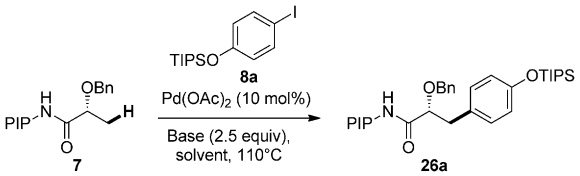
Scheme 5. Synthesis of the Choi core **2**.

Standard conditions were first tested using $Pd(OAc)_2$ as the catalyst, K_2CO_3 as the base in *t*-amyl alcohol at 110 °C, which provided the desired arylated product **26a** in 50% yield, together with 10% of unreacted starting material **7** (Table 5, entry 1). The investigation of various solvents (entries 1–5) revealed acetonitrile as the most effective to maintain the mass balance of the reaction (entry 5). The amount of aryl iodide **8a**



Scheme 6. Synthesis of C–H arylation substrate **7**. HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; DIPEA = diisopropylethylamine.

Table 5. Optimization of the intermolecular C(sp^3)–H arylation.

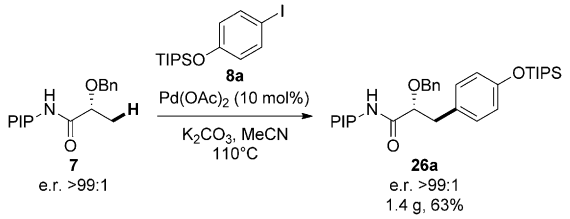


Entry	ArI [equiv]	Base	Solvent	Yield [%] **26a**/**7**[a]
1	2	K_2CO_3	*tert*-amylOH	50:10
2	2	K_2CO_3	DMF	0:67
3	2	K_2CO_3	toluene	12:66
4	2	K_2CO_3	dioxane	20:60
5	2	K_2CO_3	MeCN	42:45
6	4	K_2CO_3	MeCN	65:7
7	4	Li_2CO_3	MeCN	0:85
8	4	Na_2CO_3	MeCN	3:75
9	4	Rb_2CO_3	MeCN	35:41
10	4	Cs_2CO_3	MeCN	0:90
11	4	K_3PO_4	MeCN	58:20

[a] NMR yields determined by ^{1}H NMR spectroscopy using trichloroethylene as an internal standard.

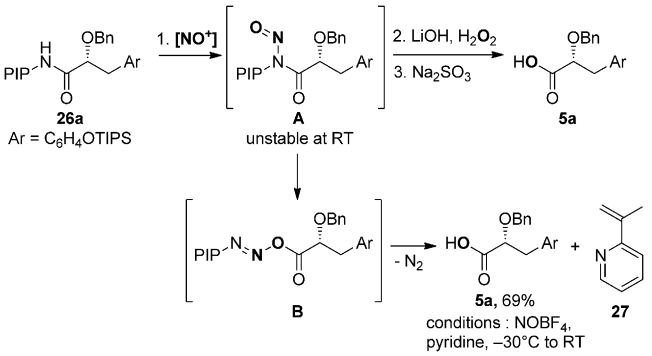
was then increased to four equivalents, which allowed **26a** to be obtained in 65% yield (entry 6). The countercation of the carbonate base was then varied (entries 7–10), but K_2CO_3 remained the most efficient base. Potassium phosphate was also less effective (entry 11).

With these optimized conditions (Table 5, entry 6), a scale-up was performed, and 1.4 g of the desired C–H arylated product **26a** obtained in 63% yield after a single chromatographic purification (Scheme 7).[24] Moreover, the HPLC analysis of **26a** on a chiral stationary phase revealed no epimerization of the stereocenter during the reaction.



Scheme 7. Scale-up of the C(sp^3)–H arylation.

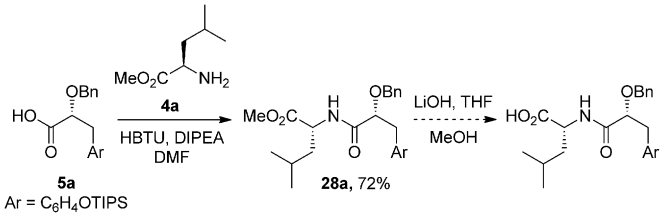
For the cleavage of the PIP directing group, Shi and coworkers employed a three-step sequence (Scheme 8, top), involving an initial nitrosation with a mixture of $NaNO_2$/AcOH/Ac_2O.[22] Unfortunately, applying these conditions to compound **26a** only led to the recovery of the starting material. Various precursors of NO^+, such as *t*BuONO (with or without acid) and $NOBF_4$, were tested, and only the latter allowed the conversion of the starting material, albeit into an intractable mixture of products. Consequently, we decided to modify the hydrolysis process while keeping $NOBF_4$ as the source of NO^+. According to literature elements, the putative *N*-nitrosamide intermediate



Scheme 8. Cleavage of the PIP directing group.

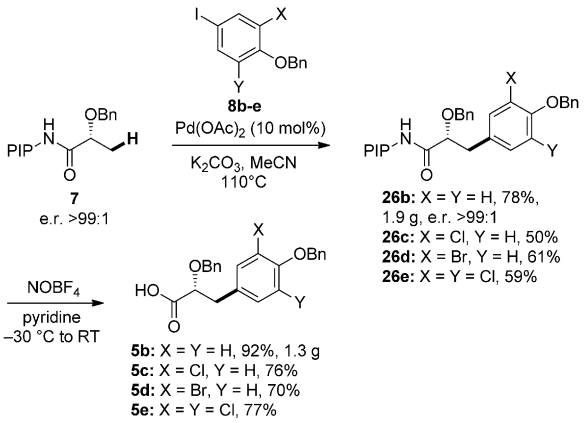
A, arising from the nitrosation of **26a**, should be unstable at room temperature and should rearrange to diazoester **B**, which should spontaneously loose N_2 to lead to the formation of carboxylic acid **5a** and propenyl pyridine **27**.[25] Several tests were performed using $NOBF_4$ and pyridine as reagents. Two parameters were found to be important: the temperature and the amount of employed pyridine. Indeed, an optimal yield of 69% was obtained when the reaction was performed in pyridine as the solvent at −30 °C and warming to room temperature (Scheme 8).

The corresponding carboxylic acid **5a** was then submitted to peptidic coupling with D-leucine methyl ester (**4a**) to provide the southern part of aeruginosin 298A (**28a**) in 72% yield (Scheme 9). However, the hydrolysis of methyl ester **28a** under mild conditions led to a partial cleavage of the TIPS group. As a result, we decided to change the phenol protecting group for a benzyl group, which is insensitive to saponification conditions.

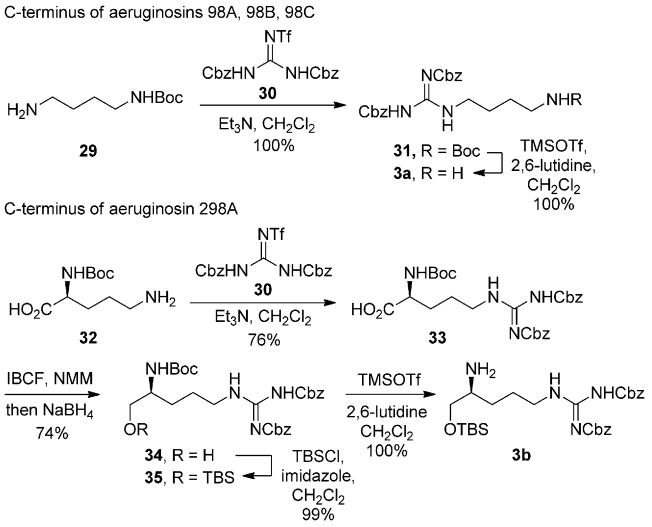


Scheme 9. Attempt at synthesizing the southern part of aeruginosin 298A from TIPS-protected lactate **5a**.

Thus, benzyl-protected iodophenol **8b** was prepared and submitted to the optimized C–H activation conditions (Scheme 10). Remarkably, the corresponding arylated product **26b** was isolated in 78% yield on a 1.9 g scale without detectable racemization. The cleavage of the directing PIP group was also performed on 1.3 g scale with an excellent yield of 92% for compound **5b**. The overall yield of this sequence was thus better than the previous one featuring the TIPS protecting group, which can be imputed to the higher sensitivity of the latter to the employed reaction conditions. The same sequence was then applied to PIP-amide **7** and halogenated iodoarenes



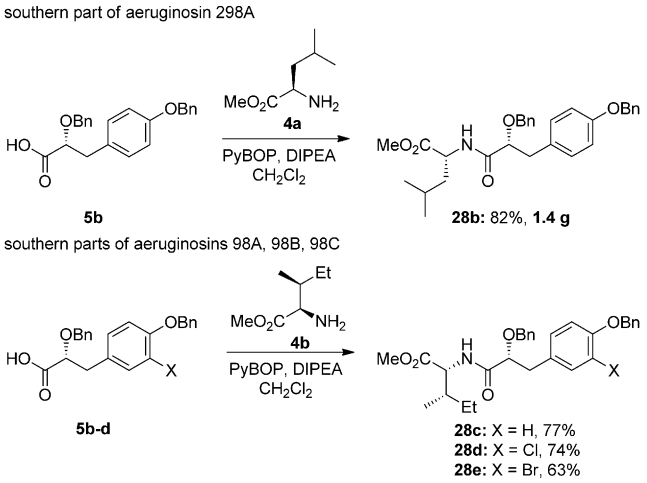
Scheme 10. Final route to Hpla fragments.



Scheme 12. Synthesis of the C-termini. Cbz = carboxybenzyl; Tf = trifluoromethanesulfonyl; IBCF = isobutyl chloroformate; NMM = *N*-methylmorpholine; TMS = trimethylsilyl.

8c–e, relevant to the synthesis of aeruginosins 98A, 98C, and 101, thus furnishing halogenated Hpla fragments **5c–e** in good overall yields.

Hpla fragments **5b–d** were then submitted to peptidic coupling with the requisite amino esters **4a** and **4b**,[26] thus giving rise to the various southern parts of aerugniosins 298A (**28b**) and 98A–C (**28c–e**) (Scheme 11).[27]



Scheme 11. Synthesis of the southern parts of aeruginosins. PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

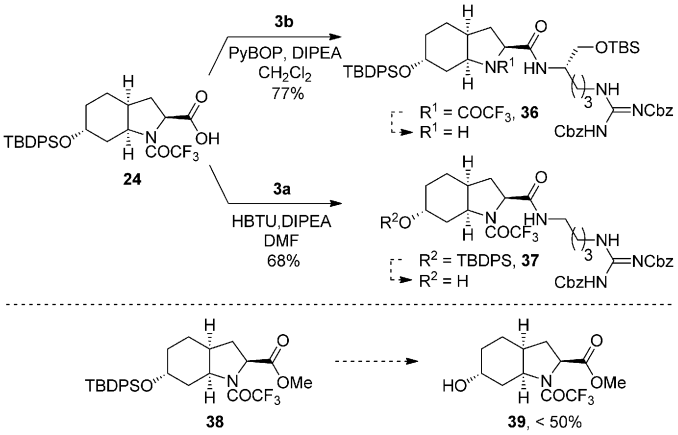
Synthesis of the C-termini

In parallel, we synthesized the two C-termini required for aeruginosins **1a–d** (Scheme 12). For the C-terminus of aeruginosins 98A–C (**1b–d**), an optimized two-step sequence was applied, as described by Trost and co-workers[8] and afforded Cbz-protected agmatine **3a** in quantitative overall yield.[28]

The L-argol fragment **3b**, relevant to the synthesis of aeruginosin 298A (**1a**), was prepared by a sequence starting with the guanidinylation of *tert*-butoxycarbonyl (Boc)-protected L-ornithine **32**. The carboxylic acid of the resulting protected L-arginine fragment **33** was then reduced, and alcohol **34** was protected as a TBS silyl ether (compound **35**). Finally, the Boc group was removed in the presence of TMSOTf, to afford 1.25 g of L-argol fragment **3b** in 4 steps, 56% overall yield.

Fragment coupling and completion of total syntheses

With the required fragments in hand, we investigated our first coupling strategy, which consisted of coupling the C-termini with *N*-trifluoroacetyl carboxylic acid **24** (Scheme 13). The latter was thus reacted with C-termini **3a,b** under standard peptidic coupling conditions. The resulting fragments **36** and **37** were then submitted to deprotection reactions for both trifluoroacetyl and TBDPS groups. With regard to fragment **36**, various mild conditions to cleave the trifluoroacetyl group, such as K_2CO_3/MeOH and NH_3/MeOH, were employed, but no conversion was observed, which might be imputable to excessive steric hindrance. Reductive conditions were also evaluated ($NaBH_4$ in MeOH), but only led to degradation. With regard to fragment **37**, several attempts at cleaving the TBDPS group using fluorides or acidic conditions led to degradation or re-



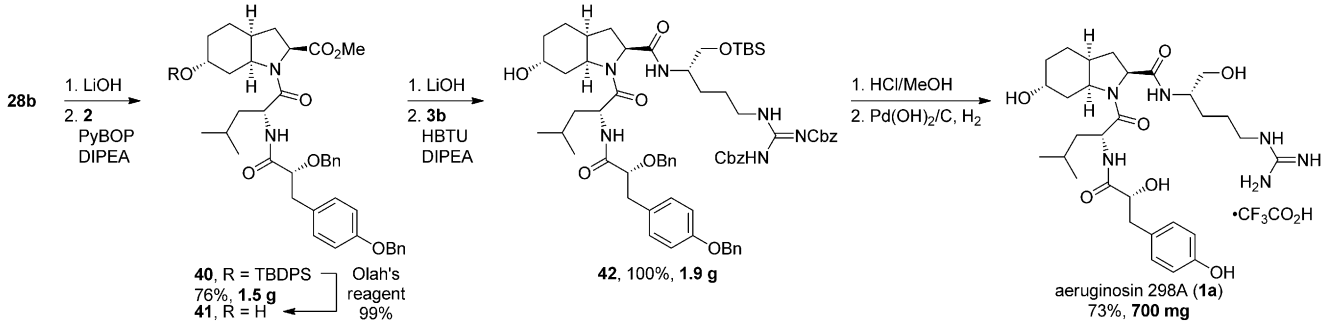
Scheme 13. First coupling strategy.

covery of the starting material. The same deprotection was also attempted on the trifluoroacetyl-protected methyl ester **38**, but only poor or moderate yields were obtained for the corresponding product **39**.

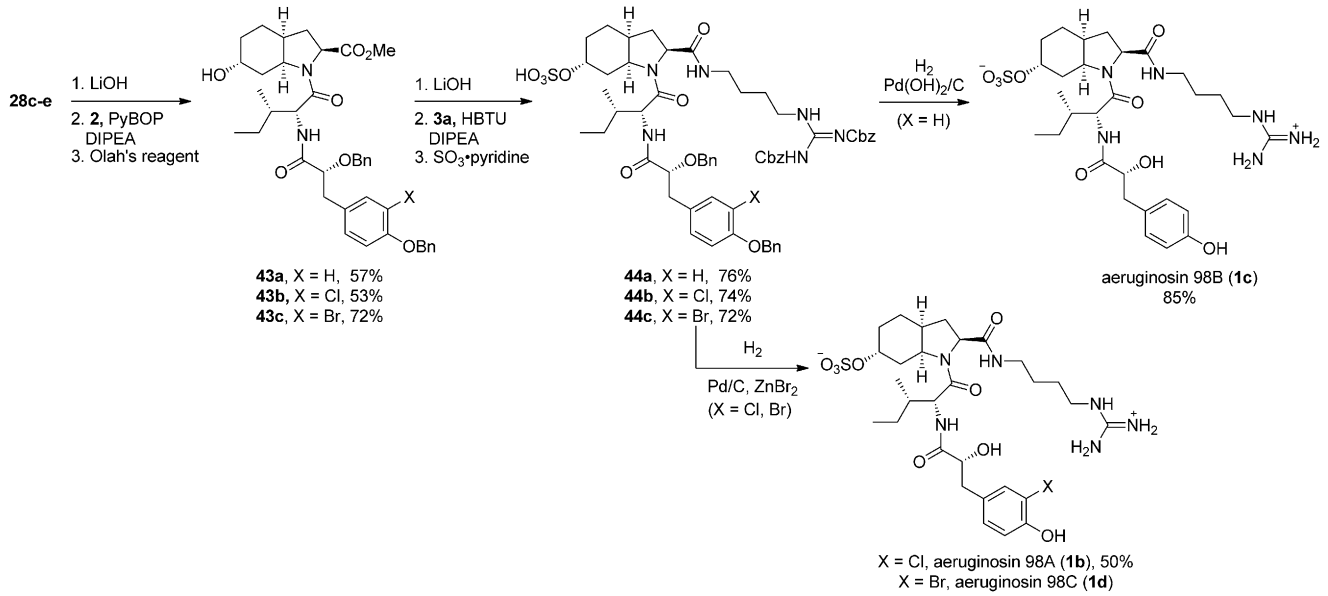
These experiments provided us with guidelines on the best coupling strategy to adopt. The southern part of aeruginosins (**28**) should be first coupled to the Choi core (**2**), in order to avoid the problematic cleavage of the trifluoroacetyl group. In addition, the cleavage of the TBDPS group should occur before the installation of the sensitive C-terminus (**3**).

Accordingly, the ester part of fragment **28b** was hydrolyzed, and the corresponding carboxylic acid was subjected without intermediate purification to peptidic coupling with the Choi core **2** (Scheme 14). The resulting product **40** was obtained on a 1.5 g scale in 76% yield as an 85:15 mixture of two rotamers, as shown by 2D NMR spectroscopic experiments, and in accordance with previous data.[5] In contrast to the above-mentioned deprotection issues (Scheme 13), the TBDPS group of **40** was cleaved in high yield using Olah's reagent (HF•pyridine). The resulting methyl ester **41** was then hydrolyzed and coupled with L-argol fragment **3b**. This synthetic strategy allowed the production of 1.9 g of advanced intermediate **42** in quantitative manner from **40**. Finally, acid-mediated cleavage of the TBS group on the argol fragment and hydrogenolysis of Bn and Cbz groups afforded 700 mg of aeruginosin 298A (**1a**), which was isolated as the salt formed with trifluoroacetic acid, as described previously.[2,5c,6,7a] 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 alcohol **15**. Both the overall yield and scale of this total synthesis are unprecedented.

Following this achievement, we turned to the syntheses of aeruginosin 98A–C (**1b**–**d**) (Scheme 15). The same sequence of ester hydrolysis, peptidic coupling with the core Choi **2**, and cleavage of the TBDPS group was applied to the three different southern parts **28c**–**e**, thereby furnishing intermediates **43a**–**c** in good overall yields. After hydrolysis of the methyl ester of the Choi core, the agmatine fragment **3a** was coupled to the resulting carboxylic acids. The free hydroxy group was then sulfated using the SO_3•pyridine complex as previously described (compounds **44a**–**c**).[8] In the case of compound **44a**, the final hydrogenolysis was performed using H_2 (1 bar) and $Pd(OH)_2/C$ as above for **1a**, thereby furnishing aeruginosin 98B (**1c**) with 85% yield. This final deprotection step was much



Scheme 14. Synthesis of aeruginosin 298A.



Scheme 15. Syntheses of aeruginosin 98A, 98B, and 98C.

more challenging for halogenated intermediates **44b,c**, due to a total concomitant dehalogenation under the same conditions. This is a recurrent issue in total synthesis, especially when hydrogenolysis is employed in the final steps. This problem was sometimes avoided by internal poisoning of the catalyst by heteroatoms present on the targets.[29] Studies have been conducted to avoid this overreduction,[30] but they often lack generality. We were particularly interested in reports by Wu and co-workers, prescribing the use of a combination of Pd/C and $ZnBr_2$.[31] We first performed model experiments with Bn-protected 2-chlorophenol and 2-bromophenol. Various parameters were studied such as the ratio between $ZnBr_2$ and Pd/C, the pressure of H_2, and the solvent. The best results were obtained using a 1:1 ratio of $ZnBr_2$ and Pd/C, especially in the case of the most sensitive brominated compound, in acetonitrile under 1 bar of hydrogen. This system was then applied to advanced intermediates **44b,c** (Scheme 15). Chlorinated compound **44b** was successfully converted into aeruginosin 98A (**1b**) without observable dechlorination (50% yield). In contrast, brominated substrate **44c** afforded a 1:1 ratio of aeruginosin 98B (**1c**) and 98C (**1d**), as observed in the crude mixture, and these products were separated by preparative HPLC. Synthetic aeruginosins 98A–C showed identical spectroscopic data to previously reported compounds.[3,8]

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. To this purpose, two recently discovered Pd-catalyzed C(sp^3)–H activation methods were employed in a strategic manner. Indeed, an intramolecular C–H alkenylation reaction enabled the large-scale synthesis of the common (Choi) heterocyclic core of the target molecules, and an intermolecular directed C–H arylation furnished a rapid and divergent access to diversely decorated Hpla fragments. The power of this strategy was demonstrated in the synthesis of four aeruginosins, that is, aeruginosin 298A (**1a**), 98B (**1c**), which had been synthesized before, and for the first time aeruginosins 98A (**1b**) and 98C (**1d**), which include a halogenated Hpla fragment. Importantly, these syntheses can be scaled up, as demonstrated with aeruginosin 298A which was obtained in unprecedentedly large quantities (700 mg). This study should facilitate the production of a library of analogues, and allow the conduction of more advanced pharmacological studies.

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Keywords: aeruginosin · C–H activation · marine natural products · palladium catalysis · total synthesis

[1] Leading review: K. Ersmark, J. R. Del Valle, S. Hanessian, *Angew. Chem. Int. Ed.* **2008**, *47*, 1202–1223; *Angew. Chem.* **2008**, *120*, 1220–1242.
[2] M. Murakami, Y. Okita, H. Matsuda, T. Okino, K. Yamaguchi, *Tetrahedron Lett.* **1994**, *35*, 3129–3132.
[3] a) M. Murakami, K. Ishida, T. Okino, Y. Okita, H. Matsuda, K. Yamaguchi, *Tetrahedron Lett.* **1995**, *36*, 2785–2788; b) K. Ishida, Y. Okita, H. Matsuda, T. Okino, M. Murakami, *Tetrahedron* **1999**, *55*, 10971–10988.
[4] Selected reviews on bioactive marine natural products: a) O. K. Radjasa, Y. M. Vaske, G. Navarro, H. Vervoort, K. Tenney, R. G. Linington, P. Crews, *Bioorg. Med. Chem.* **2011**, *19*, 6658–6674; b) W. H. Gerwick, B. S. Moore, *Chem. Biol.* **2012**, *19*, 85–98.
[5] a) N. Valls, M. López-Canet, M. Vallribera, J. Bonjoch, *J. Am. Chem. Soc.* **2000**, *122*, 11248–11249; b) N. Valls, M. López-Canet, M. Vallribera, J. Bonjoch, *Chem. Eur. J.* **2001**, *7*, 3446–3460; for a solid-phase synthesis of aeruginosin 298A employing a similar strategy: c) T. Doi, Y. Hoshina, H. Mogi, Y. Yamada, T. Takahashi, *J. Comb. Chem.* **2006**, *8*, 571–582.
[6] P. Wipf, J.-L. Methot, *Org. Lett.* **2000**, *2*, 4213–4216.
[7] a) T. Ohshima, V. Gnanadesikan, T. Shibuguchi, Y. Fukuta, T. Nemoto, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 11206–11207; b) Y. Fukuta, T. Ohshima, V. Gnanadesikan, T. Shibuguchi, T. Nemoto, T. Kisugi, T. Okino, M. Shibasaki, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5433–5438.
[8] B. M. Trost, T. Kaneko, N. G. Andersen, C. Tappertzhofen, B. Fahr, *J. Am. Chem. Soc.* **2012**, *134*, 18944–18947.
[9] For other strategies employed to build the Choi core in the total syntheses of other aeruginosin congeners: a) S. Hanessian, R. Margarita, A. Hall, S. Johnstone, M. Tremblay, L. Parlanti, *J. Am. Chem. Soc.* **2002**, *124*, 13342–13343 (dysinosin A, ring-closing metathesis); b) S. Hanessian, M. Tremblay, J. F. W. Petersen, *J. Am. Chem. Soc.* **2004**, *126*, 6064–6071 (oscillarin, aza-Prins reaction); c) S. Diethelm, C. S. Schindler, E. M. Carreira, *Org. Lett.* **2010**, *12*, 3950–3953 (microcin SF608, nucleophilic opening of an oxabicyclic system).
[10] 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.
[11] 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*, 4902–4911; c) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191–206; d) N. Dastbaravardeh, M. Christakakou, M. Haider, M. Schnürch, *Synthesis* **2014**, 1421–1439.
[12] 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; c) E. T. Nadres, G. I. F. Santos, D. Shabashov, O. Daugulis, *J. Org. Chem.* **2013**, *78*, 9689–9714; see also : d) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391–3394.
[13] For a review: G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; *Angew. Chem.* **2013**, *125*, 11942–11959.
[14] a) Y. Feng, G. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 958–961; *Angew. Chem.* **2010**, *122*, 970–973; b) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192–5196; *Angew. Chem.* **2011**, *123*, 5298–5302; c) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076–19079; d) W. R. Gutekunst, R. Gianatassio, P. S. Baran, *Angew. Chem. Int. Ed.* **2012**, *51*, 7507–7510; *Angew. Chem.* **2012**, *124*, 7625–7628; e) W. R. Gutekunst, P. S. Baran, *J. Org. Chem.* **2014**, *79*, 2430–2452; f) C. P. Ting, T. J. Maimone, *Angew. Chem. Int. Ed.* **2014**, *53*, 3115–3119; *Angew. Chem.* **2014**, *126*, 3179–3183; g) G. He, S.-Y. Zhang, W. A. Nack, R. Pearson, J. Rabb-Lynch, G. Chen, *Org. Lett.* **2014**, *16*, 6488–6491.
[15] 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.
[16] Total synthesis of nonhalogenated aeruginosins **1a** and **1c** was reported in a preliminary communication: D. Dailler, G. Danoun, O. Baudoin,

Angew. Chem. Int. Ed. **2015**, *54*, 4919 – 4922; *Angew. Chem.* **2015**, *127*, 5001 – 5004.
[17] B. Halton, J. Harvey, *Synlett* **2006**, 1975 – 2000.
[18] L. Petit, M. G. Banwell, A. C. Willis, *Org. Lett.* **2011**, *13*, 5800 – 5803.
[19] CCDC-1058439(**17**), 1058440(**18**), 1058441(**21**), and 1029844(**22**) contain 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.
[20] See for instance: a) H. Ishibashi, T. S. So, T. Sato, K. Kuroda, M. Ikeda, *J. Chem. Soc. Chem. Commun.* **1989**, 762 – 764; b) H. Ishibashi, H. Nakatani, S. Iwami, T. Sato, N. Nakamura, M. Ikeda, *J. Chem. Soc. Chem. Commun.* **1989**, 1767 – 1769; c) T. H. Jepsen, A. A. Jensen, M. H. Lund, E. Glibstrup, J. L. Kristensen, *ACS Med. Chem. Lett.* **2014**, *5*, 766 – 770; d) P. Wipf, S. R. Spencer, *J. Am. Chem. Soc.* **2005**, *127*, 225 – 235.
[21] Attempts at performing an asymmetric Tsuji – Trost reaction to control the site of nucleophilic attack were unsuccessful. For a review: B. M. Trost, T. Zhang, J. D. Sieber, *Chem. Sci.* **2010**, *1*, 427 – 440.
[22] a) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang, B.-F. Shi, *Chem. Sci.* **2013**, *4*, 4187 – 4192; b) 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.
[23] C. Dubost, B. Leroy, I. E. Markó, B. Tinant, J.-P. Declercq, J. Bryans, *Tetrahedron* **2004**, *60*, 7693 – 7704.
[24] After this work was completed, a scalable C(sp^3)–H arylation reaction using the aminoquinoline directing group was reported: K. Chen, S.-Q. Zhang, J.-W. Xu, F. Hu, B.-F. Shi, *Chem. Commun.* **2014**, *50*, 13924 – 13927.
[25] a) E. H. White, *J. Am. Chem. Soc.* **1955**, *77*, 6011 – 6014; b) P. Romea, F. Urpi, J. Vilarrasa, *J. Org. Chem.* **1989**, *54*, 3209 – 3211.
[26] D-*allo*-Isoleucine methyl ester was obtained from L-isoleucine through a described epimerization/resolution process: H. Noda, K. Sakai, H. Murakami, *Tetrahedron: Asymmetry* **2002**, *13*, 2649 – 2652.
[27] Synthesis of dichlorinated aeruginosin 101 employing Hpla fragment **5e** could not be completed within the time frame of this study.
[28] For a highly efficient guanidinylation reagent: K. Feichtinger, C. Zapf, H. L. Sings, M. Goodman, *J. Org. Chem.* **1998**, *63*, 3804 – 3805.
[29] See for instance: a) K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem. Int. Ed.* **1999**, *38*, 240 – 244; *Angew. Chem.* **1999**, *111*, 253 – 255; b) J. Li, X. Chen, A. W. G. Burgett, P. G. Harran, *Angew. Chem. Int. Ed.* **2001**, *40*, 2682 – 2685; *Angew. Chem.* **2001**, *113*, 2754 – 2757.
[30] See for instance: J. Li, S. Wang, G. A. Crispino, K. Tenhuisen, A. Singh, J. A. Grosso, *Tetrahedron Lett.* **2003**, *44*, 4041 – 4043.
[31] a) G. Wu, W. Tormos, *J. Org. Chem.* **1997**, *62*, 6412 – 6414; b) G. Wu, M. Huang, M. Richards, M. Poirier, X. Wen, R. W. Draper, *Synthesis* **2003**, 1657 – 1660.

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