ChemPubSoc Europe

DOI: 10.1002/chem.201400046

CHEMISTRY
A European Journal
Full Paper

Natural Products

# Access to the Aeruginosin Serine Protease Inhibitors through the Nucleophilic Opening of an Oxabicyclo[2.2.1]heptane: Total Synthesis of Microcin SF608

Stefan Diethelm, Corinna S. Schindler, and Erick M. Carreira*[a]

**Abstract:** Serine proteases play key roles in many biological processes and are associated with several human diseases such as thrombosis or cancer. During the search for selective inhibitors of serine proteases, a family of linear peptides named the aeruginosins was discovered in marine cyanobacteria. We herein report an entry route into the synthetically challenging core fragment of these natural products. Starting from the common oxabicyclic building block **11**, we accessed the octahydroindole core of the aeruginosins, exemplified by the total synthesis of microcin SF608 (**2**). Key to the synthetic strategy is a highly efficient nucleophilic opening of an oxabicyclo[2.2.1]heptane producing the hydroindole motif of microcin SF608. Moreover, during the synthetic efforts we have observed an unusual regioselective epoxide reduction. Detailed experimental studies of this reaction led us to propose a mechanistic rationale involving intramolecular hydrogen atom delivery by a carbamate NH group to control the regioselectivity of the homolytic epoxide cleavage.

## Introduction

Proteolytic reactions are some of the most important enzyme-catalysed transformations in biological systems. Proteases are involved in a diverse set of physiological processes such as regulation of enzyme activity, signalling events or processing of biomolecules.[1] Moreover, these enzymes are associated with a number of human diseases such as cancer, thrombosis or neurological disorders.[2] In particular, the serine proteases have been the subject of extensive studies over the past decades.[3] The quest for selective and potent inhibitors of this class of peptidases is of key importance for the control of their associated biochemical processes and the study and treatment of human diseases. In a screening program for serine protease inhibitors initiated in the early 1990s, Murakami and co-workers isolated from the marine cyanobacterial strain *Microcystis aeuriginosa* the linear peptide aeurginosin 298A (**1**) (Figure 1).[4] Within a few years, an impressive array of closely related natural products, such as microcin SF608 (**2**) or dysinosin A (**3**), were isolated from marine sources.[5] Structure elucidation of the aeruginosins revealed a common core fragment comprising of a carboxy hydroxyl octahydroindole (Choi) ring **4**. Moreover, a terminal guanidine functionality represents a key feature of these oligopeptides.[6] Soon after the isolation of the first aeruginosins, a new subclass of this family of protease inhibitors was discovered, represented by banyaside B (**5**).[7] The key characteristic of these novel alkaloids is a densely packed glycosylated azabicyclononane (Abn) core **6** substituting for

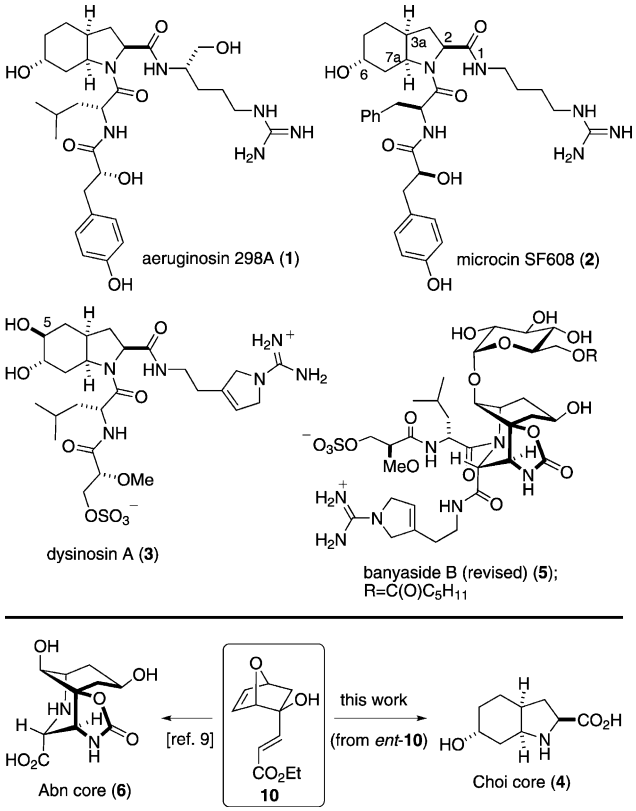


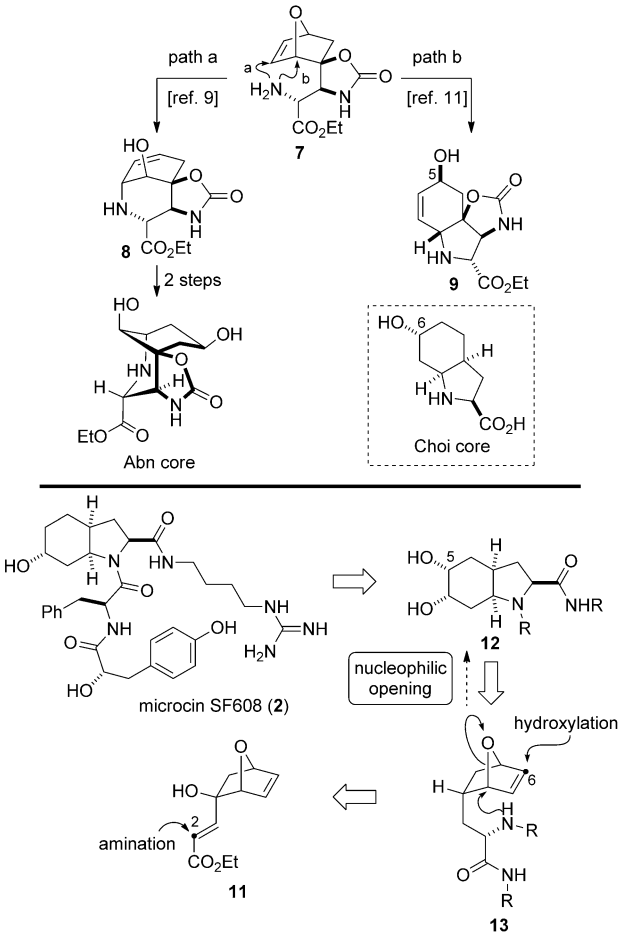

**Figure 1.** Aeruginosin family of serine protease inhibitors (top) and divergent access to the Abn and Choi core of the aeruginosins starting from allylic alcohol **10** (bottom).

[a] *S. Diethelm, C. S. Schindler, Prof. Dr. E. M. Carreira*
*Laboratorium für Organische Chemie*
*Eidgenössische Technische Hochschule Zürich*
*Vladimir-Prelog-Weg 3, 8093 Zürich (Switzerland)*
*E-mail: erickm.carreira@org.chem.ethz.ch*

*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201400046.*

the hydroindole moiety of the previously reported aeruginosins. Extensive biological investigation by in vitro assays of this natural product family revealed that the aeruginosins are selective inhibitors of important peptidase classes.[5a] For example, aeruginosin 298A (**1**) inhibits thrombin, a key enzyme in the human blood coagulation cascade, with an $IC_{50}$ value of 0.3 $\mu g\,mL^{-1}$,[4] whereas microcin SF608 (**2**) was reported to be a selective inhibitor of trypsin ($IC_{50}$ 0.5 $\mu g\,mL^{-1}$).[5b]

The promising biological activity, as well as the unprecedented core structure of the aeruginosin peptides, has attracted the interest of many synthetic chemists. A number of research groups have reported innovative strategies to access the carboxy hydroindole core found in most aeruginosins.[8,5a] Our group has recently reported the synthesis of the Abn core of the banyaside subclass[9] and the total synthesis of nominal banyaside B along with structural reassignment of this natural product.[10] Key to the synthetic strategy is the stepwise $S_N2'$ opening of oxabicyclo[2.2.1]heptane **7** to produce tricyclic scaffold **8** (Scheme 1, top, path a). In the course of these synthetic studies, we discovered an alternative reaction path that oxabicyclo[2.2.1]heptanes, such as **7**, can follow (Scheme 1, top, path b).[11] When **7** was treated with Lewis acids, such as TMSOTf, secondary alcohol **9** was produced resulting from a direct opening of the hydrofuran by attack of the nitrogen nucleophile. The product of this transformation shares its underlying carboxy hydroindole ring system with the Choi core of many of the aeruginosin peptides. This unexpected finding opened the possibility of accessing the core element of both aeruginosin subclasses from one common oxabicyclic precursor **10** (Figure 1, bottom). To implement such a divergent strategy to the synthesis of the whole family of the aeruginosin serine protease inhibitors, we opted for the total synthesis of microcin SF608 (**2**) employing the nucleophilic opening of an oxabicyclo[2.2.1]heptane.




**Scheme 1.** Differential opening of oxabicycle **7** (top) and retrosynthetic strategy for microcin SF608 (**2**) (bottom).

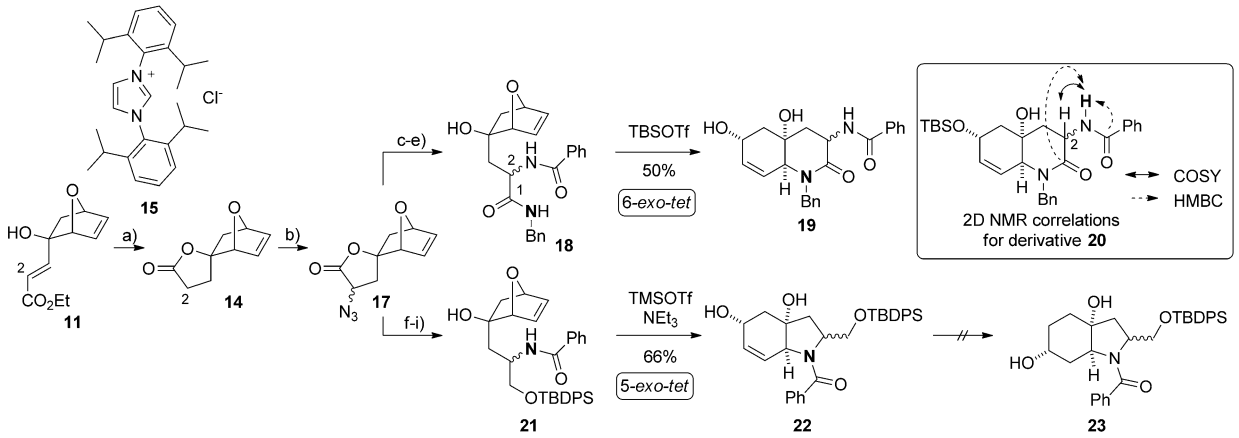
As depicted in Scheme 1, bottom, the synthetic strategy we pursued towards microcin SF608 leads back to allylic alcohol **11**, the enantiomer (**10**) of which has been previously employed for the synthesis of the banyaside Abn core and thus serves as common precursor to both of the aeruginosin central amino acids.[9] Diol **12** was envisioned as a late-stage intermediate, whereas the C(5) alcohol stemming from the hydrofuran opening has to be removed to arrive at an intermediate incorporating the substitution pattern of the natural product. Hydroindole **12** could be accessed by the nucleophilic opening of oxabicyclo[2.2.1]heptene **13**. Moreover, selective introduction of the C(6) hydroxyl group would be required either before or after the key cyclization step. Finally, **13** might be synthesized from oxabicyclic building block **11** by amination in the $\alpha$-position to the ester and removal of the C(3a) hydroxyl.

Herein we present a full account of the implementation of this strategy towards the total synthesis of microcin SF608.[12,13] In the course of the synthetic studies conducted toward this end, we have gained detailed insight into the nucleophilic opening of oxabicycles employed as a key step in the synthesis. In addition, we have discovered a highly regioselective epoxide reduction. Based on experimental studies we propose a detailed mechanistic rationale for this transformation involving intramolecular hydrogen atom donation by a neighbouring NH group. Accordingly, we have established oxabicyclic building block **11** as a common precursor to the entire family of the aeruginosin serine protease inhibitors.

## Results and Discussion

### Prospecting studies

According to the proposed synthetic plan, we initially opted for the construction of a suitable cyclization precursor to evaluate the feasibility of the strategy in a model system as outlined in Scheme 2. To this end, introduction of an amine at C(2) of building block **11** was required. To facilitate the diastereoselective installation of the amine, we envisioned lactone **14** as a suitable substrate. The rigidity of the tricyclic scaffold **14** could help to differentiate the two diastereotopic faces of the corresponding ester enolate. Accordingly, lactone **14** was synthesized by conjugate reduction of $\alpha,\beta$-unsaturated ester **11** mediated by an N-heterocyclic carbene (NHC) copper catalyst derived from **15**[14] as recently described by Buchwald.[15] Proper adjustment of reaction conditions allowed for concomitant cyclization of the intermediate tertiary alcohol to the cor-

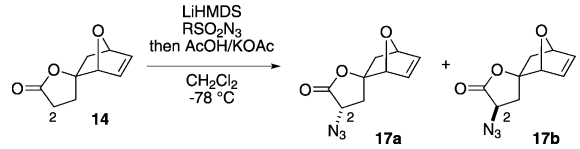


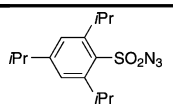
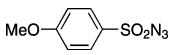
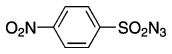
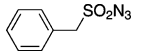
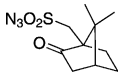
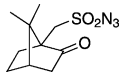

**Scheme 2.** Prospecting studies: a) **15** (3 mol%), $CuCl_2{\cdot}2H_2O$ (3 mol%), KO*t*Bu (0.3 equiv), PMHS (3.0 equiv), *t*BuOH (0.5 equiv), THF, 0 °C, 10 min, 62%; b) LiHMDS (1.5 equiv), −78 °C, 30 min; then $TrisN_3$ (1.3 equiv), −45 °C, 2 min; then AcOH/KOAc (4.6 equiv), $CH_2Cl_2$, 73% (81% brsm); c) $BnNH_2$ (3.0 equiv), HCl (0.2 equiv), $CH_2Cl_2$, 25 °C, 2 h, 79%; d) $PMe_3$ (2.0 equiv), MeCN/THF (5:1), 25 °C, 30 min; then $H_2O$, 73%; e) $Bz_2O$ (1.1 equiv), $CH_2Cl_2$, 25 °C, 1 h, 76%; f) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 30 min, 67%; g) TBDPSCl (1.5 equiv), $NEt_3$ (1.5 equiv), DMAP (cat.), $CH_2Cl_2$, 25 °C, 1 h, 94%; h) $PMe_3$ (2.0 equiv), MeCN/THF (5:1), 25 °C, 30 min; then $H_2O$, 71%; i) $Bz_2O$ (1.1 equiv), DMAP (cat.), $CH_2Cl_2$, 25 °C, 1 h, 98%. PHMS = Polymethylhydrosiloxane; LiHMDS = lithium hexamethyldisilazane; $TrisN_3$ = 2,4,6-triisopropylbenzenesulfonyl azide; Bz = benzoyl; TBDPS = *tert*-butyldiphenylsilyl; DMAP = *N*,*N*-dimethyl-4-aminopyridine.

responding lactone **14**, isolated in 62% yield. Interestingly, the endocyclic double bond in **14** also proved reactive under the conditions originally reported by Buchwald. Only upon careful optimization of the reaction parameters (base, additive, temperature, reaction time), complete selectivity for 1,4-reduction could be achieved (see the Supporting Information for further details). We speculate that the high reactivity of the endocyclic double bond likely follows from strain induced by the oxabicyclic scaffold.

With **14** in hand, we explored its functionalization in the α-position by enolate formation and reaction with various electrophilic amination reagents. However, the poor solubility of **14** in ethereal solvents, such as $Et_2O$ or THF, precluded efficient enolate formation with a variety of bases tested (lithium diisopropylamide (LDA), KHMDS, NaHMDS, LiHMDS, $LiNH_2$, KH). Gratifyingly, slow addition of a dilute solution of **14** in $CH_2Cl_2$ to a solution of LiHMDS at −78 °C effectively produced the lithium enolate. Introduction of an azido group in lactone **14** was examined based on a protocol reported by Evans.[16] The lithium enolate derived from **14** was therefore treated with triisopropylbenzenesulfonyl azide ($TrisN_3$) **16** at −78 °C followed by quenching of the reaction with AcOH. No product formation was observed under these conditions, but instead starting material was recovered unchanged. However, when after enolate formation at −78 °C the reaction temperature was increased to −45 °C, the desired azidolactone **17** was isolated in good yield (73%), albeit with low diastereoselectivity (1.2:1) slightly favouring the desired isomer.[17] To avoid undesired side reactions, such as formation of the diazolactone, it proved essential to carefully control the reaction time by quenching the reaction after 2 min, following addition of the sulfonyl azide. We reasoned that improved diastereoselectivity might be achieved by fine-tuning the properties of the azidation reagent. Accordingly, a number of sulfonyl azides were screened as outlined in Table 1.[18] Neither electron-rich nor -deficient arylsulfonyl azides gave improved diastereoselectivity (Table 1, entries 2 and 3). Alkyl-substituted reagents, such as benzylsulfonyl azide, also did not change the reaction outcome (entry 4). However, when (+)-camphorsulfonyl azide was employed, the product was obtained with a diastereomeric ratio (d.r.) of 2:1 favouring the undesired isomer (entry 5). Interestingly, the enantiomeric reagent derived from (−)-camphor resulted in a 1:1 selectivity, which indicated a mismatch pairing of reagent and substrate (entry 6). To the best of our knowledge, the former is the first example of a diastereoselective enolate azidation based on reagent control.

**Table 1.** Azidation of lactone **14**.



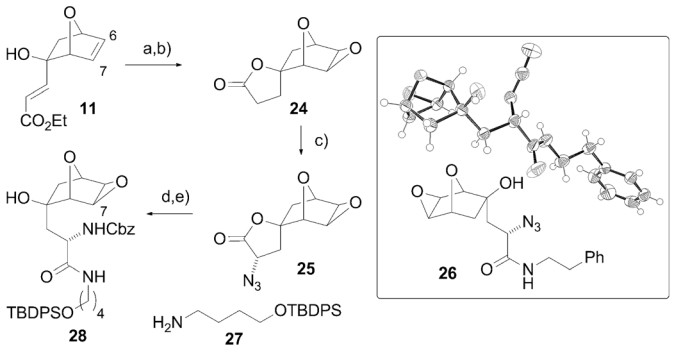

| Entry[a] | Azidation reagent | d.r. (**17a**/**17b**)[b] | Yield [%] |
|---|---|---|---|
| 1[c] |  | 1.2:1 | **81** |
| 2 |  | 1.2:1 | 55 |
| 3 |  | 1.2:1 | 75 |
| 4 |  | 1:1 | 68 |
| 5 |  | **1:2** | 58 |
| 6 |  | 1.1:1 | 60 |

[a] General conditions: LiHMDS (1.5 equiv), $CH_2Cl_2$, −78 °C; then reagent (1.3 equiv), −15 °C; then AcOH/KOAc. [b] Determined by crude NMR spectroscopic analysis. [c] Reagent added at −45 °C.

Synthesis of the projected cyclization precursor then involved introduction of the peptide appendage found in the natural product. However, for these model studies, we decided to introduce simplified side chains incorporating fewer functionalities to facilitate spectroscopic analysis of the products.[19] Accordingly, the lactone ring in **17** was first opened with benzylamine (79% yield) as a mimic for the agmatidine side chain of the natural product. Subsequent reduction of the azide under Staudinger conditions delivered the corresponding primary amine (73%). Treatment of this intermediate with $Bz_2O$ afforded bisamide **18** in 76% yield. Both amide nitrogen atoms in **18** could now serve as potential nucleophiles in the cyclization event, thus opening the possibility of forming two cylization products, namely, hydroindole versus hydroquinoline. We surmised, however, that formation of a five-membered ring by cyclization of the C(2) nitrogen atom might be kinetically preferred over six-ring formation. When bisamide **18** was treated with TBSOTf as an activator, indeed, only one product was obtained. Analysis by 2D NMR spectroscopic experiments of the TBS-protected derivative **20** (Scheme 2, box, only diagnostic NMR correlations shown) revealed the presence of a free C(2) amide NH confirmed by HMBC and COSY signals. This clearly suggested the exclusive formation of a hydroquinoline system **19** instead of the desired hydroindole derivative. A possible explanation for the complete selectivity for 6-*exo* attack of the benzylamide on the hydrofuran ring is the reduced steric hindrance of the *N*-benzylamide compared to the more congested C(2) counterpart. To circumvent the intrinsic preference for 6-*exo* cyclization of the bisamide substrate, we decided to synthesize a cyclization precursor lacking the C(1) amide. To this end, azidolactone **17** was reduced with $NaBH_4$ to provide an unstable diol product in 67% yield.[20,21] Immediate protection with TBDPSCl followed by conversion of the azide into the corresponding benzoate proceeded smoothly under the previously employed conditions to give **21**. When substrate **21** was subjected to optimized cyclization conditions by using TMSOTf/$NEt_3$, only the desired hydroindoline product **22** was obtained in 66% yield. The successful generation of this hydroindole moiety validated the synthetic strategy towards the aeruginosin Choi core. We next envisioned introduction of a secondary alcohol at C(6) to complement the substitution pattern of the natural product. However, a number of attempts including hydroboration, metal-mediated hydration,[22] reductive epoxide opening or reductive double bond transposition[23] followed by olefin oxidation failed to give the desired products, such as **23**. For this reason we decided to investigate introduction of the C(6) hydroxyl prior to the cyclization step.

### C(6) oxidation by epoxidation

Initial experiments for selective hydroboration/oxidation of the double bond in oxabicyclic substrates, such as **14** or **18**, under a variety of conditions ($BH_3$·$SMe_2$, 9-borabicyclo[3.3.1]nonane (9-BBN), (+)- or (−)-diisopinocampheylborane (-$Ipc_2BH$)) were unsuccessful. An alternative approach to hydration of the endocyclic double bond in **11** would proceed by initial olefin epoxidation followed by selective reductive opening of the epoxide at C(7). Accordingly, diene **11** was subjected to epoxidation by using *m*CPBA (93% yield) followed by palladium-catalysed hydrogenation of the α,β-unsaturated ester and concomitant base promoted cyclization to produce epoxylactone **24** in 78% yield (Scheme 3). Introduction of the C(2) amine was again

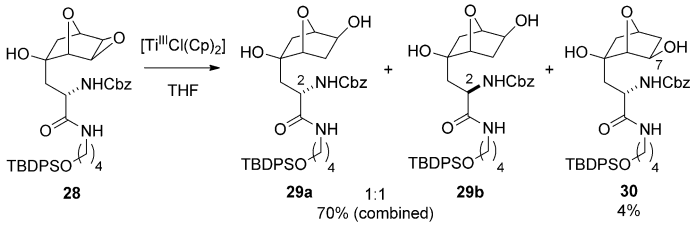



**Scheme 3.** Synthesis of epoxide **28**: a) *m*CPBA (2.0 equiv), $CH_2Cl_2$, 25 °C, 6 h, 93%; b) $H_2$ (1 atm.), Pd/C (10 wt%), 1 h; then $K_2CO_3$ (5 mol%), MeOH, 25 °C, 78%; c) LiHMDS (1.5 equiv), −78 °C, 30 min; then $TrisN_3$ (1.3 equiv), −45 °C, 2 min; then AcOH/KOAc (4.6 equiv), $CH_2Cl_2$, 58% (92% brsm), d.r. 1.2:1; d) *O*-TBDPS-4-amino-1-butanol (**27**) (1.1 equiv), $CH_2Cl_2$, 25 °C, 12 h, 94%; e) $H_2$ (1 atm.), Pd/C, MeOH, 25 °C, 1 h; then CbzCl (1.2 equiv), $NaHCO_3$ (5.0 equiv), EtOAc/$H_2O$ (1:1), 25 °C, 12 h, 88%; *m*CPBA = *m*-chloroperbenzoic acid; Cbz = benzyl carbonoyl.

achieved as described previously[16] to give **25** in 79% yield with a d.r. of 1.2:1. The two diastereomers could be separated by chromatography on silica gel, and the configuration of the major isomer was confirmed by X-ray crystallographic analysis of derivative **26** obtained by lactone opening with 2-phenylethylamine (Scheme 3, box).[24] Interestingly, when (+)-camphorsulfonyl azide was used as an azidation reagent for this substrate, the product was formed in a diastereomeric ratio of 1:5, again favouring the undesired isomer as observed before (data not shown, for further details see the Supporting Information). Next, introduction of the agmatidine side chain of microcin SF608 was envisioned by opening of the lactone ring by an amine nucleophile. Model studies had indicated before that a protected guanidine derivative[25] would not be tolerated under the reaction conditions required for the nucleophilic opening of the oxabicycle (TMSOTf/$NEt_3$). We therefore envisioned the introduction of a surrogate of the agmatidine side chain. To this end, azidolactone **25** was opened smoothly with *O*-TBDPS-protected 4-amino-1-butanol **27** in 94% yield. The protected alcohol could later serve as a handle for the introduction of the guanidine. The azide was subsequently hydrogenated and the resulting free amine was protected as a Cbz carbamate under biphasic conditions to deliver **28** (88%). With epoxide **28** in hand, we now focused on the installation of the C(6) hydroxyl group by reduction of the C(7)–O bond.

### Reduction of epoxide 28

The reductive opening of epoxides is a widely used transformation for the synthesis of alcohols. Generally, the reductions involve harsh reaction conditions or highly reactive reagents, such as $LiAlH_4$, Birch conditions ($Li/NH_3$) or $LiBEt_3H$ (super hydride).[26] We reasoned that the dense substitution pattern of epoxide **28** including the TBDPS ether, Cbz carbamate, tertiary alcohol as well as the strained ether bridge would not allow for the use of these commonly employed reagents. However, RajanBabu and Nugent reported in 1990 the use of $[Ti^{III}Cl(Cp)_2]$[27] in the presence of hydrogen donors to effect reductive cleavage of highly functionalized oxiranes.[28] The high functional-group tolerance of the conditions described prompted us to study this approach for substrate **28** as outlined in Scheme 4.

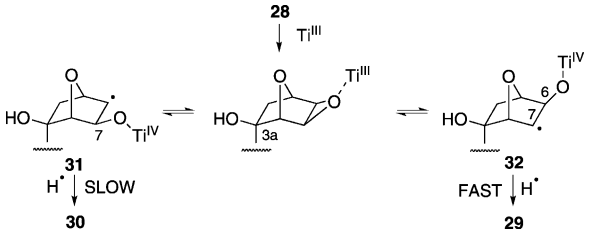



**Scheme 4.** Reductive epoxide opening of **28**. Conditions: $[TiCl(Cp)_2]$ (2.0 equiv), THF, 25 °C, 6 h, 70% (combined yield of **29a** and **29b**). Cp = cyclopentadienyl.

To our surprise, when **28** was treated with freshly prepared $[TiCl(Cp)_2]$ in the absence of a hydrogen atom donor, formation of a single product was observed by TLC analysis and LCMS monitoring. Spectroscopic analysis revealed that only the desired C(6) alcohol was formed. However, the stereocenter at C(2) had epimerized completely to produce a chromatographically inseparable 1:1 mixture of diastereomers **29a** and **29b** in a combined yield of 70%. The regioisomeric product **30** was only isolated in a trace amount (4% yield) but without any epimerization at C(2).[29] This unexpected and puzzling result caught our interest and a more detailed analysis of this reaction was initiated.

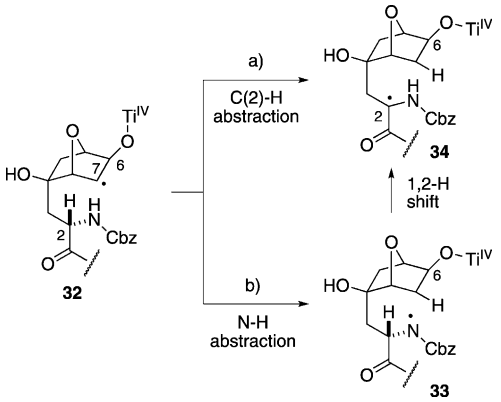
### Mechanistic studies on the epoxide opening

Based on the generally accepted mechanism for this transformation,[30] it can be assumed that after initial association of $[TiCl(Cp)_2]$ to the oxirane oxygen reductive cleavage of one C–O bond in **28** occurs to produce either radical **31** or **32** as indicated in Scheme 5. An equilibrium between these two species likely exists, as has been postulated for 1,2-disubstituted epoxide substrates by Gansäuer et al. based on computational and experimental studies.[30b] It is, however, not obvious that formation of one of the two radical intermediates is preferred over the other. To account for the exclusive formation of product **29**, we therefore hypothesize that a Curtin–Hammett scenario is operating, whereby only one of the two rapidly equilibrating radical intermediates, namely **32**, undergoes further reductive tranformation, while regioisomer **31** has no comparable low-energy pathway available.




**Scheme 5.** Proposed equilibrium between radical intermediates **31** and **32**.

Selective reductive quenching of only one radical intermediate is difficult to explain on the basis of steric or electronic factors, as the only differentiating stereocenter at C(3a) seems too remote from the reactive site to impact the reaction. We therefore reasoned that a directing effect, possibly exerted by the C(3a) alkyl substituent, might determine the choice for one reaction path over the other (Scheme 6). In particular, this side chain could act as an internal quencher of radical **32** by intramolecular hydrogen atom delivery. Two R–H bonds can thereby be considered as potential hydrogen atom sources: 1) the C(2)–H or, alternatively, 2) the NH of the proximal Cbz carbamate. Although OH and NH groups are known to be very poor hydrogen atom donors due to the heteroatom–H bond strength (85–110 kcal mol$^{-1}$ for N–H), a number of recent reports have demonstrated that this bond strength can be considerably attenuated upon coordination of a Lewis acid, such as $BEt_3$[31] or $[TiClCp_2]$,[32] to the heteroatom. Thereby, these groups can be turned into potent hydrogen atom donors. Initial molecular modelling of radical intermediate **32** indicated that C(2)–H is not within good reach for the C(7) radical as a consequence of the constraints induced by the bicyclic system. However, the carbamate NH can be brought into alignment with the SOMO of a carbon centered radical at C(7) in **32**. To test this hypothesis, a number of simple deuteration experiments were carried out (data not shown, see Supporting Information for more de-

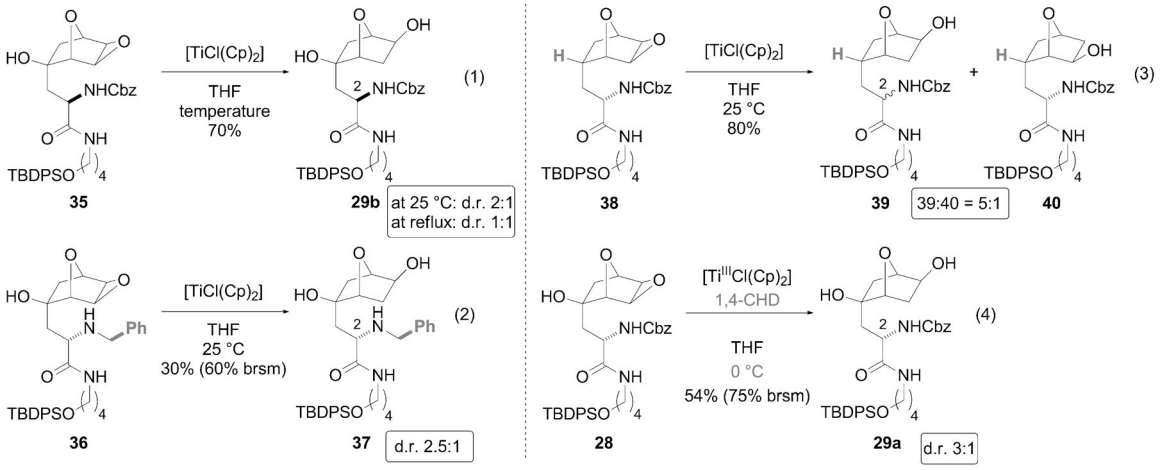



**Scheme 6.** Trapping of radical **32** by intramolecular hydrogen atom delivery.

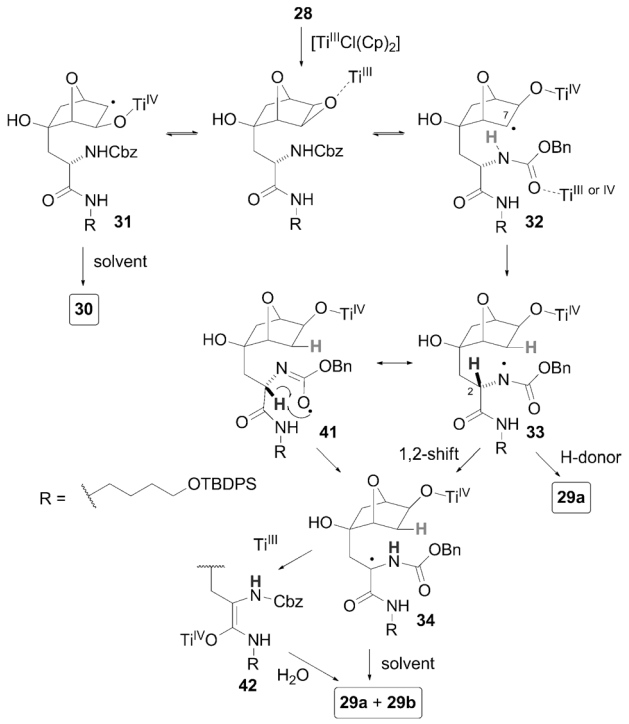
tails). Deuterium incorporation into the C(7) methylene group of the product could indeed be observed when the carbamate NH proton of the substrate had been exchanged by deuterium. A mechanistic rationale based on hydrogen abstraction at the nitrogen does not yet explain epimerization at C(2) of the product. However, a number of theoretical and experimental studies on nitrogen-centered radicals suggests that these species readily undergo a [1,2]-hydrogen migration to produce a more stable carbon centered radical.[33] If such a reaction path is operating in our system, the observed epimerization at C(2) could be readily explained by formation of an intermediate radical at C(2) through such an [1,2]-hydrogen shift in intermediate **33** to the adjacent nitrogen-centered radical producing **34** (Scheme 6).

To gain further insight into the mechanistic possibilities so far discussed, a number of experiments were carried out as depicted in Scheme 7. Initially, we tested epoxide substrate **35** with *R* configuration at C(2) under the reaction conditions previously employed for the reductive opening of epimer **28** (Scheme 7, Eq. (1)). Interestingly, although the regioselectivity remained high, only partial epimerization at C(2) had occurred in the product **29b** (d.r. 2:1). Thus, only the epimerization event seems to depend on the C(2) configuration, whereas the regioselectivity determining step does not. This finding renders a direct abstraction of the C(2)–H by an intermediate C(7) radical unlikely. Assuming that the postulated [1,2]-hydrogen shift is indeed operating, substitution of the Cbz carbonyl group on nitrogen by an alkyl substituent would open the possibility of an alternative [1,2]-migration path involving this alkyl substituent. This should result in reduced epimerization at C(2). Indeed, when benzyl amine **36** was treated with $[TiCl(Cp)_2]$, the expected product **37** was obtained with excellent regioselectivity with a d.r. of 2.5:1 (Scheme 7, Eq. (2)). This result is consistent with partial quenching of the nitrogen-centered radical through [1,2]-hydrogen migration from the benzyl substituent. We next envisioned to probe a possible influence of the C(3a) hydroxyl group on the reaction outcome. Accordingly, deoxygenated substrate **38** was synthesized[34] and subjected to $[TiCl(Cp)_2]$ (Scheme 7, Eq. (3)). A mixture of regioisomeric alcohol products **39** and **40** was obtained in a ratio of 5:1. The reduced selectivity observed for this substrate indicates some minor influence of the C(3a) hydroxyl group. This can either be explained by direct electronic control of the reaction or by influence of the substitution at C(3a) on the conformational flexibility of the alkyl side chain harbouring the NH group. Finally, extensive optimization of the reaction conditions revealed that addition of a large excess of the hydrogen atom donor 1,4-cyclohexadiene (1,4-CHD) along with a lowering of the reaction temperature to 0 °C led to reduced epimerization to produce the desired product with a d.r. of 3:1 (Scheme 7, Eq. (4)). Alternatively, water can be used as a hydrogen atom source,[32] although the product is obtained in lower yield (37%, 71% brsm). Once again, under these conditions we observed high regioselectivity. This result indicates that initial regioselective quenching of the C(7) radical is fast and thus is not intercepted by an external hydrogen atom donor. In contrast, the epimerization event can be inhibited by an external reductant. In addition, we have observed that performing the reductive opening of diastereomer **35** at reflux temperature produces a fully epimerized product ((Scheme 7, Eq. (1)). It is noteworthy, that this strategy allows for partial recovery of the undesired C(2) diastereomer initially produced during the azidation reaction of lactone **24**.

In summary, Scheme 8 depicts a detailed mechanistic explanation of this unusual regioselective epoxide reduction based on the aforementioned experimental data. We hypothesize that treatment of epoxide **28** with $[TiCl(Cp)_2]$ initially generates two rapidly equilibrating radical intermediates **31** and **32** by homolytic cleavage of one C–O bond of the oxirane. In accordance with the Curtin–Hammett principle, only the C(7) radical isomer **32** can undergo rapid follow-up reaction while isomer **31** only slowly undergoes intermolecular reductive quenching by the solvent THF. Radical **32** is trapped through intramolecular hydrogen-atom donation by the carbamate NH, enabled by coordination of titanium to the Cbz carbonyl group. It is useful to consider the resulting nitrogen-centered




**Scheme 7.** Investigation of factors influencing the epoxide reduction.

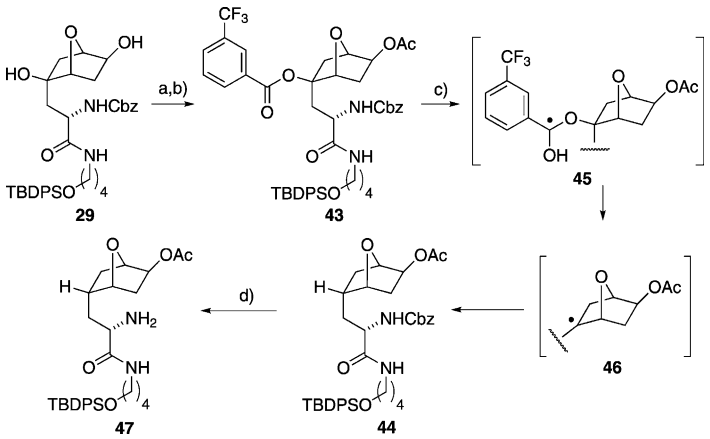



**Scheme 8.** Mechanistic rationale based on the experimental data.

radical **33** in its mesomeric form **41**. In the case of a Cbz-protected amine, this allows for two alternative pathways for abstraction of the C(2)–H. Thus, either of two pathways may be envisioned, involving a [1,2]-H-shift from intermediate **33** or a 1,4-hydrogen abstraction from C to O from radical **41** as depicted. Both pathways lead to intermediate **34** with concomitant loss of the C(2) stereocenter. Finally, generation of the observed product can either occur through radical quenching by solvent or by titanium enolate **42** and subsequent protonation during workup. In the presence of an excess of a reactive H-atom donor, the nitrogen-centered radical **33** may be intercepted before hydrogen migration can occur, thus leading to product **29a** that has not suffered epimerization. The efficiency of the [1,2]-shift likely depends on the conformation of the C(2)–N bond. Only when an optimal orbital overlap between the SOMO of the nitrogen and the C–H bond is achieved can the migration occur. The conformational preference and flexibility of the C(2)–N bond is influenced by a number of factors including the configuration at C(2), the reaction temperature as well as the substituents on the nitrogen atom.

### Excision of the C(3a) hydroxyl group

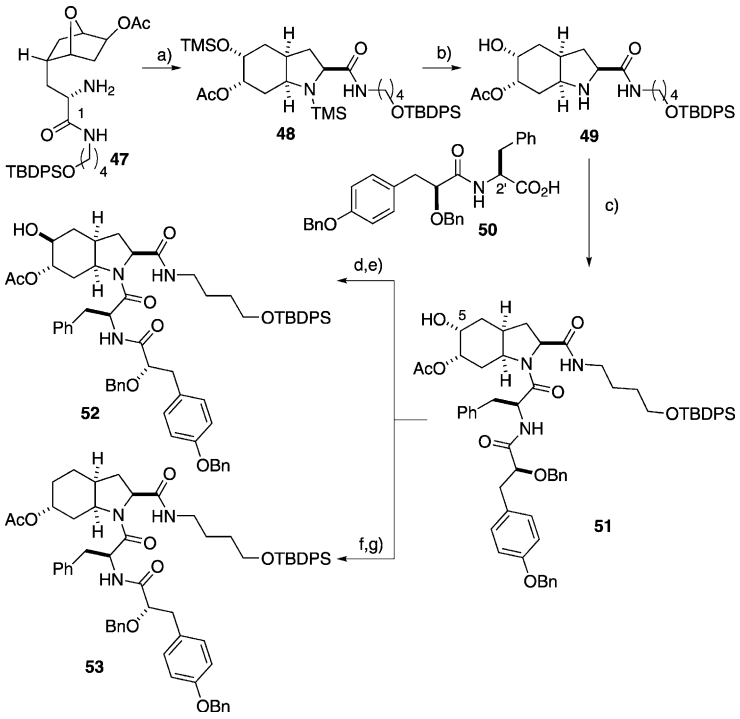
After successful installation of the C(6) hydroxyl group, we now focused on accessing a cyclization precursor. To address the functionalization pattern of the Choi core of the aeruginosins, deoxygenation of the C(3a) alcohol is needed. To this end, a number of deoxygenation procedures were evaluated. Initially, protocols based on acid-mediated activation of the tertiary alcohol (TFA, $BF_3{\cdot}OEt_2$, $ZnI_2$[35]) to generate a carbocation intermediate followed by reductive quenching were investigated. Under a variety of conditions tested, complex product mixtures resulted. This can likely be attributed to rearrangement events of the intermediate oxabicyclic carbocation. To circumvent problems associated with carbocation formation, we turned our attention to radical-based deoxygenation strategies.[36] Interestingly though, functionalization of the C(3a) hydroxyl group proved challenging. In particular, conversion into conventional precursors prescribed for deoxygenation, such as xanthates or thioester derivatives, failed, leading to either recovery of starting material or complete decomposition when strong bases were employed (e.g. KH). We then turned our attention to a scarcely used photochemical deoxygenation protocol originally reported by Saito.[37] This procedure relies on conversion of the alcohol into an activated *m*-$CF_3$ benzoate derivative. Irradiation of this species with UV light in the presence of *N*-methylcarbazole initiates an electron transfer from the electron-rich carbazole to the π-system of the benzoate. The resulting aryl radical anion then undergoes protonation followed by fragmentation, ultimately leading to cleavage of the C–O bond. To test this approach, benzoate **43** was synthesized by selective acetylation of the secondary alcohol in **29** with $Ac_2O$ (99%) followed by treatment of the tertiary alcohol with 3-trifluoromethylbenzoyl chloride, affording ester **43** in 91% yield (Scheme 9). Irradiation of **43** with UV light in the presence of *N*-methylcarbazole and 1,4-cyclohexadiene as a hydrogen-atom donor produced the desired deoxygenated product **44** in an excellent yield of 68% (96% brsm) via intermediates **45** and **46**. It is noteworthy that tertiary radical **46** is trapped exclusively from the *exo*-face producing only the observed product **44**. Moreover, the clean outcome of this reaction is in stark contrast with previous observations reporting that tertiary alcohol substrates are prone to disproportionation, generating significant amounts of an alkene side product.[37a] We did not observe such side reactions.




**Scheme 9.** Synthesis of cyclization precursor **47**: a) $Ac_2O$ (1.5 equiv), $NEt_3$ (4.0 equiv), DMAP (cat.), $CH_2Cl_2$, 25 °C, 30 min, 99%; b) *m*-$CF_3$-$C_6H_4COCl$ (1.5 equiv), $NEt_3$ (3.0 equiv), DMAP (cat.), $CH_2Cl_2$, 25 °C, 2 h, 91%; c) *hν* (UV), *N*-methylcarbazole (1.5 equiv), 1,4-cyclohexadiene (100 equiv), $THF/H_2O$ (1:1), 25 °C, 12 h, 68% (96% brsm); d) $H_2$ (1 atm.), Pd/C (10 wt.%), MeOH, 25 °C, 1 h, 93%.

### Nucleophilic opening of oxabicycle 47

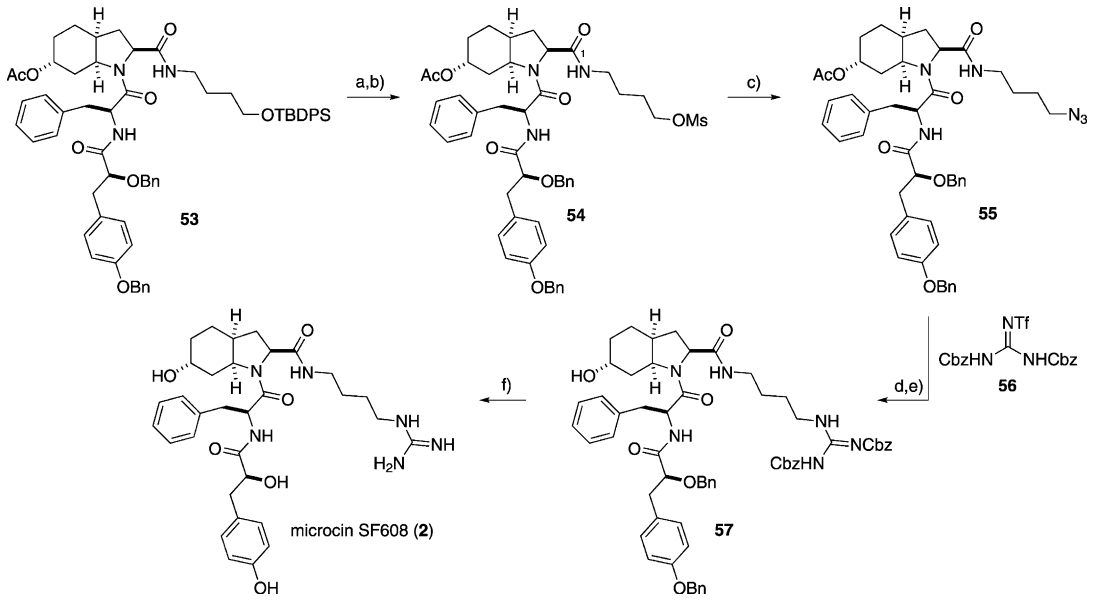
We now turned our attention to the key hydroindole ring closure. As observed before, the presence of two amide substituents in a cyclization precursor led to the exclusive formation of a hydroquinoline product (vide supra, Scheme 2). However, we reasoned that the presence of an unprotected amine at C(2) might override this inherent preference for 6-*exo* cyclization based on the higher nucleophilicity of a primary amine compared to an amide nitrogen. Accordingly, the Cbz protecting group in **44** was removed under hydrogenolytic conditions to provide amine **47** in excellent yield. Upon exposure of **47** to TMSOTf/$NEt_3$ formation of a single product **48** was observed as monitored by TLC and LCMS (Scheme 10). Isolation and characterization of the product revealed that the desired hydroindole system is formed exclusively, and no product resulting from attack of the C(1) amide nitrogen atom could be detected. The product was obtained as a bistrimethylsilyl derivative. Removal of the silyl groups proved unexpectedly difficult. Using mild deprotection protocols no reaction was observed and starting material was reisolated unchanged. In contrast, when employing harsher conditions, undesired side reactions including loss of the TBDPS group and migration of the C(6) acetate to the C(5) alcohol were observed. After extensive screening of conditions (see the Supporting Information for details), we found that hexafluorosilic acid in the presence of triethylamine cleanly afforded a mixture of fully deprotected hydroindole **49** along with some partially deprotected product.[38] Subjecting this compound again to the same conditions gave aminoalcohol **49** in a total of 81% yield after three rounds of deprotection.




**Scheme 10.** Synthesis of Choi derivatives **52** and **53**: a) TMSOTf (6.0 equiv), $NEt_3$ (8.0 equiv), $CH_2Cl_2$, 25 °C, 1 h, 81%; f) $H_2SiF_6$ (1.0 equiv), $NEt_3$ (1.5 equiv), MeCN, 65 °C, 12 h, 81% (after three rounds of deprotection); c) **50** (1.1 equiv), HATU (1.2 equiv), $iPr_2NEt$ (1.2 equiv), $CH_2Cl_2$, 25 °C, 12 h, 77%; d) TPAP (0.1 equiv), NMO (3.0 equiv), $CH_2Cl_2$, 25 °C, 30 min, 91%; e) $NaBH_4$ (2.0 equiv), THF, 0 °C, 30 min, 63%; f) *m*-$CF_3$-$C_6H_4COCl$ (1.5 equiv), $NEt_3$ (3.0 equiv), DMAP (cat.), $CH_2Cl_2$, 25 °C, 2 h, 59%; g) *hν* (UV), *N*-methylcarbazole (1.0 equiv), 1,4-cyclohexadiene (200 equiv), THF/$H_2O$ (1:1), 25 °C, 12 h, 37% (75% brsm). TMS = trimethylsilyl; Tf = trifluoromethanesulfonyl; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; DMF = dimethylformamide.

With the aeruginosin core fragment **49** in hand, only a few steps were required to access the natural product microcin SF608. Introduction of the dipeptide side chain **50** was studied first. Initial experiments revealed that the C(2′) stereocenter is prone to epimerization during the peptide coupling event. A number of coupling reagents (*N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC), (benzotriazol-1-yloxy)tripyrrolidinophosphonium (PyBOP),[39] 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT),[40] (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU)) and conditions were evaluated to avoid epimerization (see the Supporting Information for more details).[41] Finally, we found HATU to be the most effective coupling agent. Under these conditions amide coupling of hindered secondary amine **49** with acid **50** proceeded in 77% yield producing peptide **51** without any observable epimerization.

The hydroindole core in **51** still incorporates a hydroxyl group at C(5), as a remnant of the nucleophilic opening of the oxabicyclic framework. To access microcin SF608, this alcohol needed to be removed as the natural product harbours a methylene at this position. However, it is important to note that a subgroup of aeruginosin protease inhibitors, namely the dysinosins, incorporate a *S*-configured hydroxyl group at C(5) of the Choi core (e.g. dysinosin A (**3**), Scheme 2).[5a,c] Thus, the C(5) alcohol in **51** can serve as a handle to access both Choi substructures from one common intermediate. To this end, inversion of the C(5) hydroxyl was tested. Under standard Mitsunobu conditions (diisopropyl azodicarboxylate (DIAD), $PPh_3$, 4-nitrobenzoic acid) no product was obtained. This is likely due to the inaccessibility of the concave face of the hydroindole ring, thus blocking $S_N2$ attack on C(5). However, a sequence including oxidation of the alcohol to the corresponding ketone (91%) followed by $NaBH_4$ reduction delivered the desired C(5)-*S*-configured alcohol **52** in 63% yield. Notably, ketone reduction occurred exclusively from the convex face of the hydroindole ring. The microcin Choi core in turn was accessed using the deoxygenation protocol used previously.[37] Thus alcohol **51** was converted into an intermediate *m*-$CF_3$ benzoate in 59% yield. Irradiation with UV light produced **53** in 37% yield (75% brsm). During the photochemical step some hydrolysis of the benzoate ester was observed. This side product could be easily recovered and was subjected again to the deoxygenation conditions.




**Scheme 11.** Completion of the total synthesis of microcin SF608: a) TAS-F (2.0 equiv), MeCN, 25 °C, 2 h, 88%; b) MsCl (1.2 equiv), $NEt_3$ (1.5 equiv), $CH_2Cl_2$, 25 °C, 1 h, 96%; c) $NaN_3$ (2.0 equiv), DMF, 50 °C, 12 h, 85%; d) LiOH (2.0 equiv), $THF/H_2O$ (5:1), 0 °C, 66% (70% brsm); e) $PMe_3$ (2.0 equiv), MeCN/THF (5:1), 25 °C, 30 min; then $H_2O$; then **56** (2.0 equiv), $NEt_3$ (2.0 equiv), $CH_2Cl_2$, 25 °C, 2 h, 85%; f) $H_2$ (1 atm.), Pd/C (10 wt.%), MeOH, 25 °C, 6 h, 87%; TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

**Completion of the total synthesis of microcin SF608**

To complete the total synthesis of **2**, the task of introducing the guanidine functionality on the agmatidine side chain remained. To this end, the TBDPS protecting group was removed using TAS-F and the primary alcohol was converted into mesylate **54** by using MsCl (Scheme 11). When mesylate **54** was treated with $NaN_3$ clean conversion to azide **55** was observed (85% yield). After cleavage of the acetate protecting group with LiOH (66%), the azide was reduced under Staudinger conditions followed by treatment with Goodman's reagent **56**[42] to afford Cbz-protected guanidine **57** (85%). Finally, all the remaining protecting groups could be globally removed by hydrogenation using Pd/C to afford microcin SF608 in 87% yield. It is noteworthy, that this protecting group strategy allows for easy purification of the natural product by simple filtration without the need of HPLC purification. The spectroscopic data obtained with synthetic **2** matched the reported data in all respects.[5b,12]

## Conclusion

We have developed a general entry route to the carboxy hydroxyl octahydroindole derivatives of the aeruginosin peptides relying on the nucleophilic opening of oxabicyclo-[2.2.1]heptanes. The strategy we document enables access to all the core structures of the aeruginosin serine proteases from a common oxabicyclic building block **11**. We have implemented this strategy in the total synthesis of microcin SF608, which was accessed in 21 synthetic steps from **11**. During these synthetic studies we have gained additional insight into the key nucleophilic opening of bicyclic hydrofuran derivatives. Moreover, a highly regioselective titanium mediated epoxide reduction was discovered in the course of the total synthesis. Detailed experimental studies prompted us to propose a mechanistic scheme for this transformation. Initial homolytic C–O bond cleavage promoted by titanium(III) is followed by intramolcular hydrogen atom delivery form a proximal NH group trapping the intermediate carbon centered radical. We further postulate that the generated nitrogen-centered radical can then undergo a [1,2]-hydrogen shift. This results in epimerization of the adjacent stereocenter in the epoxide substrate. These findings might open new possibilities for selective epoxide reduction in complex settings.

## *Acknowledgements*

We are grateful to Dr. B. Schweizer and M. Solar for X-ray crystallographic analysis of **26**, and to Dr. M.-O. Ebert, R. Arnold, R. Frankenstein and P. Zumbrunnen for NMR spectroscopic measurements. S.D. acknowledges the Stipendienfonds Schweizerische Chemische Industrie (SSCI) and Novartis for a predoctoral fellowship. C.S.S. thanks the Roche Research Foundation for a predoctoral fellowship.

**Keywords:** aeruginosins · epoxide reduction · hydroindoles · natural products · serine protease inhibitors

[1] M. A. Phillips, R. J. Fletterick, *Curr. Biol. Curr. Opin. Sturct. Biol.* **1992**, *2*, 713–720.

[2] *Proteases in Health and Disease in Progress in Molecular Biology and Translational Science Vol. 99* (Ed: E. Di Cerca), Elsevier Academic Press, Burlington, **2011**, pp. 1–313.

[3] a) D. Voet, J. G. Voet in *Biochemistry* 4th edition, John Wiley & Sons, Hoboken, **2011**, 525–538; on the mechanism of serine proteases, see also: b) C. S. Craik, S. Roczniak, C. Largman, W. R. Rutter, *Science* **1987**, *237*, 909–913.

[4] M. Murakami, Y. Okita, H. Matsuda, T. Okino, K. Yamaguchi, *Tetrahedron Lett.* **1994**, *35*, 3129 – 3132.

[5] For a comprehensive review covering the chemistry and biology of the aeruginosin serine protease inhibitors, see: a) K. Ersmark, J. R. Del Valle, S. Hanessian, *Angew. Chem.* **2008**, *120*, 1220 – 1242; *Angew. Chem. Int. Ed.* **2008**, *47*, 1202 – 1223; b) for the isolation of microcin SF608, see: R. Banker, S. Carmeli, *Tetrahedron* **1999**, *55*, 10835 – 10844; c) for the isolation of dysinosin A, see: A. R. Carroll, G. K. Pierens, G. Fechner, P. deAlmeida Leone, A. Ngo, M. Simpson, E. Hyde, J. N. A. Hooper, S.-L. Boström, D. Musil, R. J. Quinn, *J. Am. Chem. Soc.* **2002**, *124*, 13340 – 13341.

[6] The guanidine group has been shown to play a key role in binding of the aeruginosin to the active site of serine proteases. For crystal structures of serine proteases in complex with aeruginosin peptides, see ref. [5a] and in particular: J. L. Rios Steiner, M. Murakami, A. Tulinsky, *J. Am. Chem. Soc.* **1998**, *120*, 597 – 598.

[7] For the isolation of banyaside B, see: a) A. Pluotno, S. Carmeli, *Tetrahedron* **2005**, *61*, 575 – 583; b) for the isolation of related natural products, see: K. Fujii, K. Sivonen, K. Adachi, K. Noguchi, Y. Shimizu, H. Sano, K. Hirayama, M. Suzuki, K. Harada, *Tetrahedron Lett.* **1997**, *38*, 5529 – 5532.

[8] For a few selected examples, see: a) N. Valls, M. López-Canet, M. Vallribera, J. Bonjoch, *J. Am. Chem. Soc.* **2000**, *122*, 11248 – 11249; b) P. Wipf, J.-L. Methot, *Org. Lett.* **2000**, *2*, 4213 – 4216; c) 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; d) S. Hanessian, R. Margarita, A. Hall, S. Johnstone, M. Tremblay, L. Parlanti, *J. Am. Chem. Soc.* **2002**, *124*, 13342 – 13343; e) S. Hanessian, M. Tremblay, J. F. W. Petersen, *J. Am. Chem. Soc.* **2004**, *126*, 6064 – 6071.

[9] C. S. Schindler, C. R. J. Stephenson, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 8984 – 8987; *Angew. Chem. Int. Ed.* **2008**, *47*, 8852 – 8855.

[10] C. S. Schindler, L. Bertschi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9229 – 9232.

[11] C. S. Schindler, S. Diethelm, E. M. Carreira, *Angew. Chem.* **2009**, *121*, 6414 – 6417; *Angew. Chem. Int. Ed.* **2009**, *48*, 6296 – 6299.

[12] For a previous total synthesis of microcin SF608, see: N. Valls, M. Vallribera, M. López-Canet, J. Bonjoch, *J. Org. Chem.* **2002**, *67*, 4945 – 4950.

[13] S. Diethelm, C. S. Schindler, E. M. Carreira, *Org. Lett.* **2010**, *12*, 3950 – 3953.

[14] NHC ligand **15** was synthesized according to: A. J. Arduengo III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523 – 14534.

[15] V. Jurkauskas, J. P. Sadighi, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 2417 – 2420.

[16] D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011 – 4030.

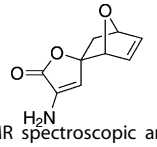
[17] The two diastereomers of **17** were not separable by column chromatography. The relative configuration was assigned in analogy to the reaction of epoxide **25** (vide infra), which could be characterized by X-ray crystallographic analysis of derivative **26**.

[18] For a more detailed screening of reagents and their preparation, see the Supporting Information, Table S2, page S6.

[19] We observed that many of these Choi containing peptides appear as rotamers, thus making spectroscopic analysis more difficult.

[20] We have previously observed that oxabicyclic system harboring an endocyclic double bond and an azide functionality in its proximity are prone to decomposition. This could be explained by reaction of the azide with the strained olefin followed by further decomposition.

[21] When the reduction of **17** was performed in MeOH instead of THF, exclusive formation of an enamine product was observed: The structure



was confirmed by 2D NMR spectroscopic analysis (see the Supporting Information).

[22] P. Magnus, A. H. Payne, M. J. Waring, D. A. Scott, V. Lynch, *Tetrahedron Lett.* **2000**, *41*, 9725 – 9730.

[23] A. G. Myers, B. Zheng, *Tetrahedron Lett.* **1996**, *37*, 4841 – 4844.

[24] CCDC-785240 (**26**) 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.

[25] *tert*-Butoxycarbonyl (Boc)- or Cbz-protected amine and guanidine derivatives proved incompatible with the cyclization conditions (TMSOTf/$NEt_3$). In the case of Boc-protected nitrogen functionalities, loss of the Boc group was observed.

[26] S. Murai, T. Murai, S. Kato in *Comprehensive Organic Synthesis Vol. 8* (Eds. B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 871 – 893.

[27] For all reactions described [$Ti^{III}Cl(Cp)_2$] was freshly prepared from [$Ti^{IV}Cl_2(Cp)_2$] and Zn powder (see the Supporting Information).

[28] a) T. V. RajanBabu, W. A. Nugent, M. S. Beattie, *J. Am. Chem. Soc.* **1990**, *112*, 6408 – 6409; b) T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986 – 997; c) for a review on titanium mediated epoxide reduction, see: A. Gansäuer, T. Lauterbach, S. Narayan, *Angew. Chem.* **2003**, *115*, 5714 – 5731; *Angew. Chem. Int. Ed.* **2003**, *42*, 5556 – 5573.

[29] In all reactions performed, re-isolated starting material and all side products including regioisomeric alcohol and alkene retained the configuration at C(2) (see the Supporting Information). This strongly suggests that epimerization is directly coupled to the formation of the desired regioisomer **29**.

[30] For early mechanistic investigations, see ref. [28b]; for further experimental and computational studies, see also: a) K. Daasbjerg, H. Svith, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, A. Gansäuer, A. Barchuk, F. Keller, *Angew. Chem.* **2006**, *118*, 2095 – 2098; *Angew. Chem. Int. Ed.* **2006**, *45*, 2041 – 2044; b) A. Gansäuer, A. Barchuk, F. Keller, M. Schmitt, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, K. Daasbjerg, H. Svith, *J. Am. Chem. Soc.* **2007**, *129*, 1359 – 1371.

[31] a) D. A. Spiegel, K. B. Wiberg, L. N. Schacherer, M. R. Medeiros, J. L. Wood, *J. Am. Chem. Soc.* **2005**, *127*, 12513 – 12515; b) J. Jin, M. Newcomb, *J. Org. Chem.* **2007**, *72*, 5098 – 5103; for a related example, see: c) D. Pozzi, E. M. Scanlan, P. Renaud, *J. Am. Chem. Soc.* **2005**, *127*, 14204 – 14205; for computational studies, see: d) W. Tantaway, H. Zipse, *Eur. J. Org. Chem.* **2007**, 5817 – 5820.

[32] a) J. M. Cuerva, A. G. Campaña, J. Justicia, A. Rosales, J. L. Oller-López, R. Robles, D. J. Cárdenas, E. Buñuel, J. E. Oltra, *Angew. Chem.* **2006**, *118*, 5648 – 5652; *Angew. Chem. Int. Ed.* **2006**, *45*, 5522 – 5526; b) J. Jin, M. Newcomb, *J. Org. Chem.* **2008**, *73*, 7901 – 7905; c) M. Paradas, A. G. Campaña, T. Jiménez, R. Robles, J. E. Oltra, E. Buñuel, J. Justicia, D. J. Cárdenas, J. M. Cuerva, *J. Am. Chem. Soc.* **2010**, *132*, 12748 – 12756.

[33] a) B. F. Yates, L. Radom, *J. Am. Chem. Soc.* **1987**, *109*, 2910 – 2915; b) V. Vrček, H. Zipse, *J. Org. Chem.* **2009**, *74*, 2947 – 2957.

[34] Compound **38** was synthesized by using the same deoxygenation protocol as used for alcohol **29** later in the synthesis.

[35] C. K. Lau, C. Dufresne, P. C. Bélanger, S. Piétré, J. Scheigetz, *J. Org. Chem.* **1986**, *51*, 3038 – 3043.

[36] For a review covering radical deoxygenation of alcohols, see: W. Hartwig, *Tetrahedron* **1983**, *39*, 2609 – 2645.

[37] a) I. Saito, H. Ikehira, R. Kasatani, M. Watanabe, T. Matsuura, *J. Am. Chem. Soc.* **1986**, *108*, 3115 – 3117; for an application of this methodology in the context of natural product synthesis, see also: b) A. G. Myers, K. R. Condroski, *J. Am. Chem. Soc.* **1995**, *117*, 3057 – 3083.

[38] a) R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, S. M. Roberts, *Tetrahedron Lett.* **1979**, *20*, 3981 – 3982; b) A. S. Pilcher, D. K. Hill, S. J. Shimshock, R. E. Waltermire, P. DeShong, *J. Org. Chem.* **1992**, *57*, 2492 – 2495.

[39] J. Coste, D. Le-Nguyen, B. Castro, *Tetrahedron Lett.* **1990**, *31*, 205 – 208.

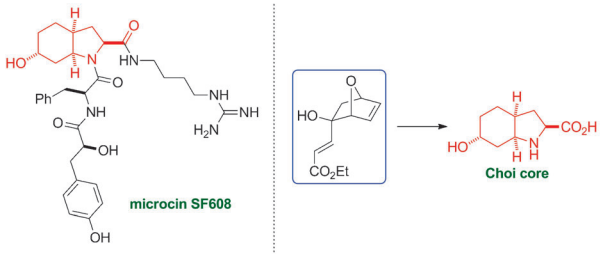
[40] H. Li, X. Jiang, Y.-h. Ye, C. Fan, T. Romoff, M. Goodman, *Org. Lett.* **1999**, *1*, 91 – 93.

[41] For a review covering peptide coupling reagents, see: E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606 – 631.

[42] a) K. Feichtinger, C. Zapf, H. L. Sings, M. Goodman, *J. Org. Chem.* **1998**, *63*, 3804 – 3805; b) K. Feichtinger, H. L. Sings, T. Baker, K. Matthews, M. Goodman, *J. Org. Chem.* **1998**, *63*, 8432 – 8439.

Received: January 6, 2014
Published online on ■■ ▮▮, 0000

# FULL PAPER




**Expect the unexpected!** An entry route to the aeruginosin protease inhibitors is reported and showcased on the total synthesis of microcin SF608 (see scheme). Detailed experimental studies of an unusual regioselective epoxide reduction observed during this synthesis led us to propose a mechanistic rationale for this transformation involving intramolecular hydrogen atom delivery by a carbamate NH to direct the regioselectivity of the homolytic epoxide cleavage.

**Natural Products**

*S. Diethelm, C. S. Schindler, E. M. Carreira**

■■ – ■■

**Access to the Aeruginosin Serine Protease Inhibitors through the Nucleophilic Opening of an Oxabicyclo[2.2.1]heptane: Total Synthesis of Microcin SF608**