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Synthesis of Microcin SF608 through Nucleophilic Opening of an Oxabicyclo[2.2.1]heptane

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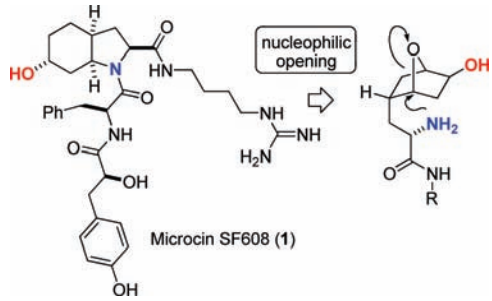
ABSTRACT



The total synthesis of Microcin SF608 is reported. Access to the octahydroindole core structure of Microcin SF608 relies on the TMSOTf/NEt_3-mediated opening of an oxabicyclic ring system. Additional highlights of the synthetic strategy that is reported include a highly regioselective epoxide reduction and photolytic excision of a 3° alcohol.

Microcin SF608 (**1**)[1,2] is a member of the Aeruginosin family of serine protease inhibitors. On the basis of their core structure, these biologically active natural products are differentiated into two distinct subclasses: the Aeruginosin and Dysinosin members, including Microcin SF608 (**1**) with a carboxy hydroxyoctahydroindole (Choi) core,[3] and those that share an azabicyclononane (Abn) core. Microcin SF608 was first isolated from the cyanobacterium *Microcystis* sp. in 1999 and was shown to selectively inhibit the serine protease trypsin over chymotrypsin (IC_{50} 0.5 and >20 μg mL^{-1}, respectively).[1]

Herein we report the total synthesis of Microcin SF608 relying on the TMSOTf-mediated nucleophilic opening of an oxabicyclo[2.2.1]heptane building block to rapidly assemble the Choi core common to the Aeruginosin members of this family of serine protease inhibitors.

As outlined in Scheme 1, the total synthesis of Microcin SF608 relies on a key TMSOTf-mediated nucleophilic opening of oxabicyclic diol **2**. Systems such as **2** were previously found to undergo rapid TMSOTf-mediated opening of the oxabicyclic framework by attack of an internal nucleophile and thereby give access to highly functionalized hydroindole structures.[4] Substrate **2** was to be obtained by regioselective hydroxylation and amination of the oxabicyclo[2.2.1]heptene building block **3**, the synthesis for which had been previously documented in the enantioselective synthesis of the azabicyclononane core of the Abn subclass of the Aeruginosin protease inhibitors.[5] The successful implementation of the versatile and easily accessible intermediate **3** in the synthesis of Microcin SF608 would allow the preparation

(1) Banker, R.; Carmeli, S. *Tetrahedron* **1999**, *55*, 10835.
(2) For a previous synthesis of **1**, see: Valls, N.; Vallribera, M.; Lopéz-Canet, M.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 4945.
(3) For a recent review covering Aeruginosin serine protease inhibitors, see: Del Valle, J. R.; Hanessian, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 1202.
(4) Schindler, C. S.; Diethelm, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6296.
(5) Schindler, C. S.; Stephenson, C. R. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8852.

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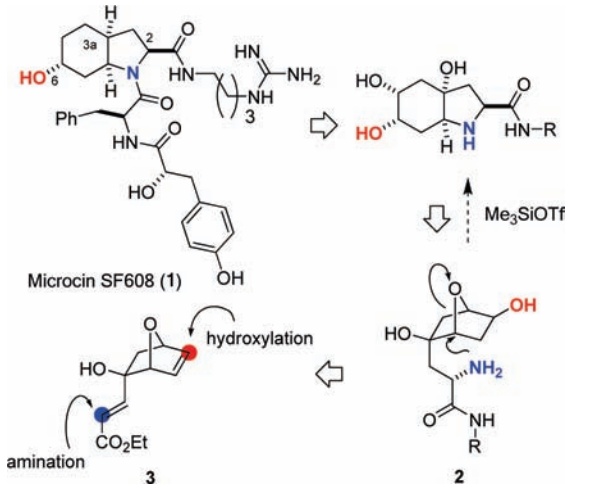
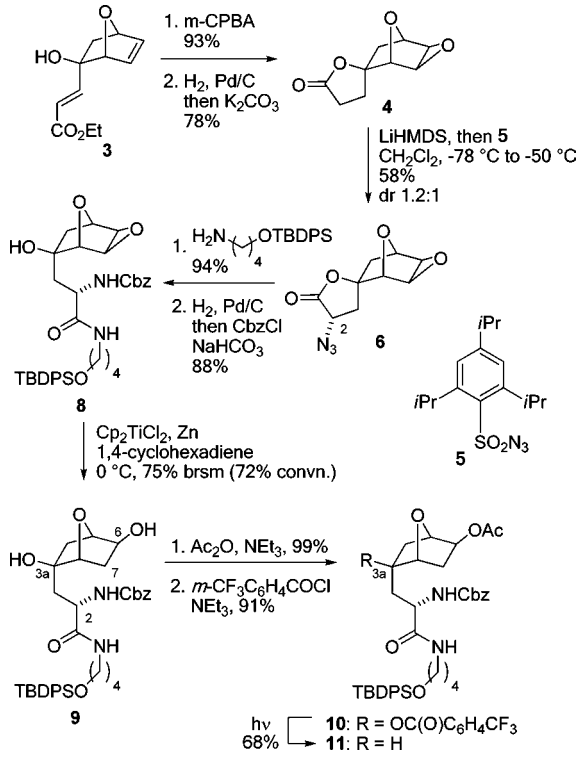
Scheme 1. Retrosynthetic Strategy



of both polycyclic core structures, the Choi as well as the Abn core, found in the Aeruginosin family of natural products.

The synthesis of an appropriate precursor that would enable the installation of the C-6 hydroxyl group found in the Choi core commences with the diastereoselective epoxidation of **3** employing *m*-CPBA in CH_2Cl_2 to form the desired epoxide in 93% yield (Scheme 2). The intermediate epoxide was further converted into lactone **4** in 78% overall yield upon enoate reduction with H_2/Pd followed by K_2CO_3-promoted lactonization. The introduction of the amine at C-2 of the Choi core was effected by azidation of lactone **4**.[6] The corresponding enolate of **4** was generated by slow addition of the substrate to a dilute (0.02 M) solution of LiHMDS in CH_2Cl_2 at −78 °C, and it was allowed to react at −50 °C with a number of different sulfonyl azides (e.g., $PhSO_2N_3$, *p*-NO_2−$C_6H_4SO_2N_3$, $PhCH_2SO_2N_3$, camphor sulfonyl azide, and 2,4,6-triisopropylbenzenesulfonyl azide). Among these, trisyl azide **5** proved superior and led to the formation of desired azidolactone **6** in 58% yield as a mixture of diastereomers (1.2:1 **6**/C-2-*epi*-**6** as determined by ^{1}H NMR spectroscopic analysis), favoring the desired stereoisomer at C-2. These could be separated by chromatography on silica gel. The configuration of **6** was confirmed by X-ray crystallographic analysis of derivative **7**,[7] formed by treatment of lactone **6** with 1-phenethyl amine as shown in Figure 1.

Scheme 2



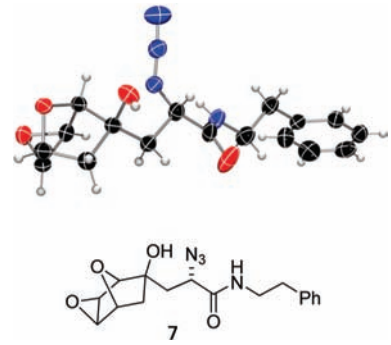


Figure 1. ORTEP representation of the X-ray crystal structure of derivative **7**.

The azidolactone in **6** was opened smoothly in 94% yield upon treatment with *O*-TBDPS-protected 4-aminobutanol, which serves as a synthetic precursor for the agmatine side chain of the natural product. The azide was reduced under hydrogenolytic conditions and the resulting amine protected in 88% yield as the corresponding Cbz-carbamate **8** upon treatment with CbzCl.

Key to the installation of the C-6 hydroxy group of the Choi core common to the Aeruginosin family of natural products is the regioselective reduction of the epoxide moiety in **8**. We decided to investigate the use of low-valent Ti reagents, relying on the hypothesis that regioselectivity might be observed because of the pendant side chain at C-3a in proximity to C-7, the desired site of attack. In this respect, titanocene(III)chloride (Cp_2TiCl) was investigated as reagent in the presence of 1,4-cyclohexadiene[8] in THF, according

(6) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(7) CCDC 785240 contains the supplementary crystallographic data for compound **7**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

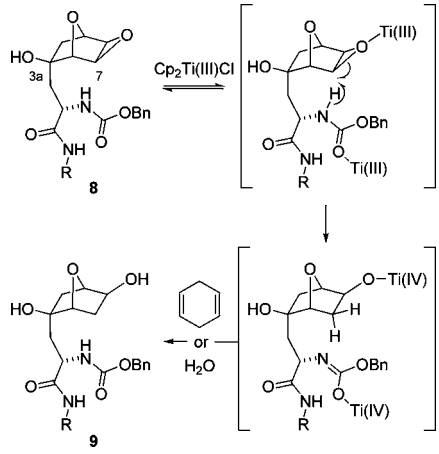
(8) Water can be used instead of 1,4-cyclohexadiene, affording the product in slightly lower yield.

(9) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

to a procedure reported by RajanBabu and Nugent.[9] Under these conditions, **8** afforded the desired alcohol **9** selectively with only trace amounts (<5%) of the corresponding regioisomer being formed.[10]

Recently, a computational study based on density functional methods by Daasbjerg, Gansäuer, and Grimme describes the structure of $ClCp_2Ti$•oxirane complexes.[11] The investigators suggest that the reactions of the complexed epoxides proceed through early transition states with the spin density mostly located on the Ti center. Although N−H's are typically not hydrogen donors in free-radical reactions, the recent work by Wood, Renaud, and Newcomb[12] has underscored the ability of alcohols as well as water to serve as donors when complexed to Lewis acids. It has also been noted that proton donors, such as water, can serve as reductants in the presence of Ti(III).[13] Prior to the results we describe above, however, carbamates had not been shown to serve as hydrogen donors. We hypothesize that the surprising selectivity in the reductive opening of the epoxide arises from H-transfer at the C-7 carbon center by the N−H of the neighboring carbamate coordinated to titanium as shown in Scheme 3.

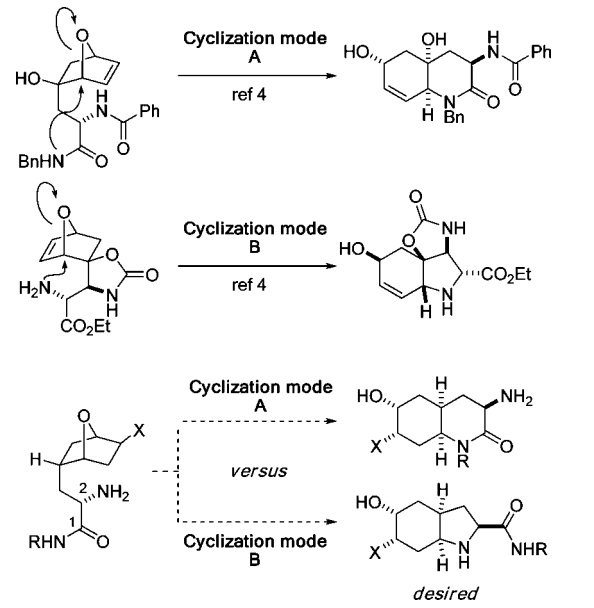
Scheme 3. Proposed Mechanism of Epoxide Reduction



With a route to the selective formation of diol **9** secured, attention was focused on protocols to effectively deoxygenate the C-3a OH in **9**. The secondary alcohol in **9** was selectively converted into the corresponding acetate in 99% yield (Scheme 2), and several procedures were evaluated to achieve removal of the 3° alcohol at C-3a (natural product numbering system). The standard, known methods that have been documented to effect deoxygenation of tertiary alcohols (Et_3SiH/TFA or BF_3•Et_2O, Barton-McCombie, SmI_2, $NaBH_3CN/ZnI_2$) proved unsuccessful on this substrate. However, the hydroxyl group could be easily excised employing a mild photocleavage protocol reported by Saito and co-workers.[14] Functionalization of the tertiary alcohol as a *m*-CF_3-substituted benzoate proceeded in 91% yield to afford **10**, which was immediately subjected to UV irradiation in the presence of *N*-methylcarbazole and 1,4-cyclohexadiene to yield the desired product **11** in 68% yield. It is especially noteworthy that 3° alcohols had been previously found to be poor substrates under these sets of conditions, as a consequence of the formation of products arising from disproportionation.[14]

With a route to oxabicycle **11** secured, attention was focused on the key step, involving TMSOTf-mediated nucleophilic opening, to assemble the highly functionalized carboxy octahydroindole core of Microcin SF608 (Schemes 4 and 5). Preceeding studies had revealed that oxabicyclic systems can undergo TMSOTf-mediated nucleophilic opening in either of two modes (A versus B in Scheme 4) to give rise to perhydroquinoline (mode A) or perhydroindole (mode B) products, respectively. Depending on the position of the amine or amide functional group in the side chain of the oxabicyclic substrate, the reaction can be tuned to form either product selectively. In the case of two competing amide substituents for 5- vs 6-ring formation, an intrinsic preference of these systems to form the corresponding

Scheme 4. Cyclization Modes of the $TMSOTf/NEt_3$-Mediated Nucleophilic Opening of Oxabicyclo[2.2.1]heptenes



(10) **9** was obtained as a 3:1 mixture of diastereomers at C-2.

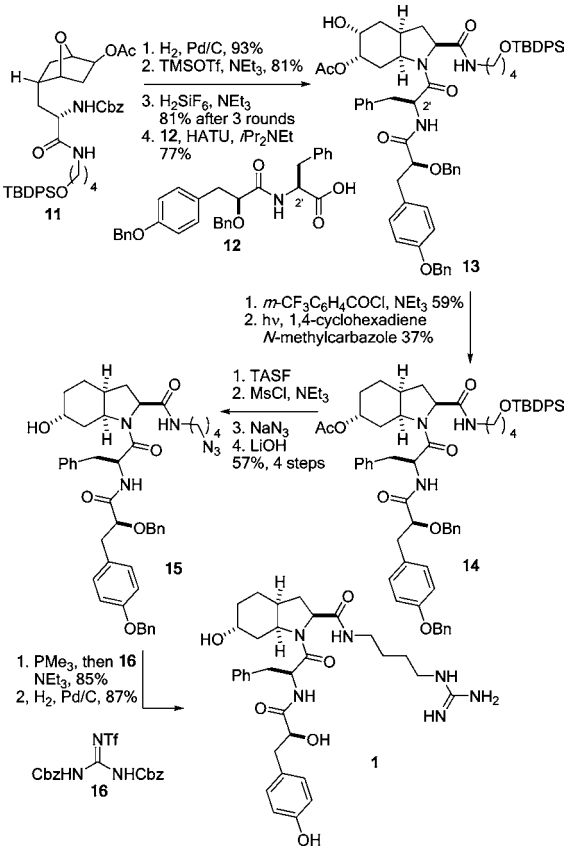
(11) (a) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556. (b) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041. (c) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359.

(12) (a) Spiegel, D. A.; Wiber, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513. (b) Pozzi, D.; Scanlan, E. M.; Renaud, P. *J. Am. Chem. Soc.* **2005**, *127*, 14204. (c) Jin, J.; Newcomb, M. *J. Org. Chem.* **2007**, *72*, 5098.

(13) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522.

(14) Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M.; Matsuura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3115.

Scheme 5



hydroquinolines was observed (cyclization mode A in Scheme 4). However, the case of a competing amine- vs amide-substituent had not yet been examined in our earlier work. Nevertheless, a free 1° amine at C-2 was expected to override the system's inherent preference to form perhydroquinoline derivatives as a consequence of the enhanced nucleophilicity of the 1° amine compared to the corresponding C-1 amide.

Generation of the amine from **11** by hydrogenolytic cleavage of the *N*-Cbz group and subsequent exposure to the reaction conditions established for the nucleophilic opening of oxabicyclic systems (TMSOTf/NEt_3) resulted in formation of the desired octahydroindole core, obtained as the corresponding bis(trimethylsilyl)ether in 81% yield (Scheme 5). Removal of the TMS groups proceeded smoothly using H_2SiF_6/NEt_3 to afford the desired product in 81% yield.[15] The resulting hindered 2° amine was then coupled to acid **12** using standard peptide coupling protocols (HATU and Hünig's base) to afford peptide **13** in 77% yield.[16] Deoxygenation of the 2° alcohol at C-5 was achieved relying on the previously described photochemical conditions to give rise to **14**.

To complete the total synthesis of Microcin SF608, protected 1° alcohol **14** was transformed into the desired guanidine. Removal of the silyl group using TASF afforded the corresponding free 1° alcohol. Subsequent conversion of the alcohol into the corresponding mesylate proceeded smoothly and was immediately followed by standard nucleophilic substitution with NaN_3 and acetate deprotection to yield the desired azide **15** in 57% yield over 4 steps. The final installation of the guanidine subunit relied on reduction of the azide using Staudinger conditions followed by reaction with di-Cbz-trifluoromethanesulfonyl guanidine **16** to yield the desired di-*N*-Cbz protected guanidine in 85%.[17] Final overall hydrogenolytic deprotection afforded the natural product Microcin SF608 **1** in 87% yield. The spectroscopic data of the synthetic material (^1H and ^{13}C NMR, MS, optical rotation) matched that which has been previously documented.[1,2]

In conclusion, we have demonstrated the utility of a TMSOTf-mediated nucleophilic opening of oxabicyclic ring systems for the total synthesis of Microcin SF608. Thus, treatment of **11** with TMSOTf/NEt_3 produces the core structure of the natural product and establishes that an amine can effectively compete with an amide in the ring-opening event. Additional salient features of the route include: a highly regioselective Ti(III)-mediated epoxide reduction to install the C-6 hydroxyl group and smooth photocleavage of a 3° alcohol. Starting with allylic alcohol **3** as a common, versatile, and easily accessible oxabicyclic building block, it is now possible to synthetically access both polycyclic Choi and Abn core structures of the Aeruginosin family of natural products.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Newton, R. F.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *41*, 3981.

(16) **13** was obtained as a 2:1 mixture of diastereomers at C-2′.

(17) (a) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804. (b) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432.