Natural Products

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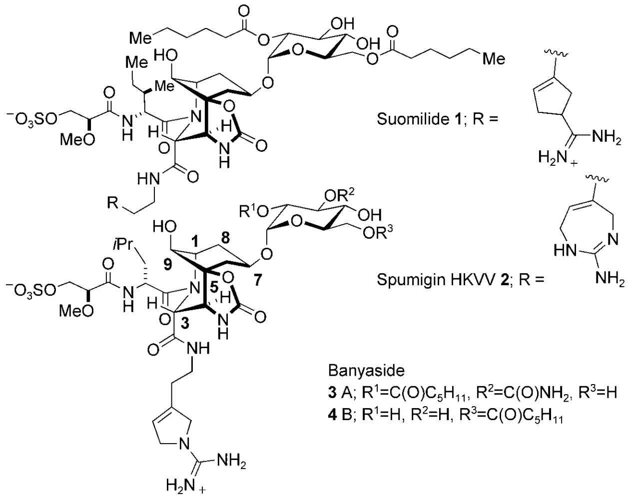
Enantioselective Synthesis of the Core of Banyaside, Suomilide, and Spumigin HKVV**

*Corinna S. Schindler, Corey R. J. Stephenson, and Erick M. Carreira**

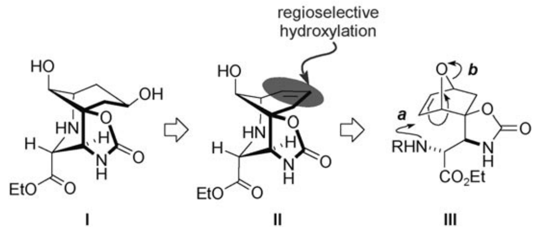
Dedicated to Professor Duilio Arigoni on the occasion of his 80th birthday

Banyaside A (**3**) and B (**4**), suomilide (**1**), and spumigin HKVV (**2**)[1] are novel natural products belonging to the aeruginosin family of serine protease inhibitors (Scheme 1).[2] The tricyclic azabicyclononane core common to these is densely functionalized with six stereogenic centers and incorporates glycosyl as well as peptide side-chains at its periphery. The biological activity along with the sheer complexity of the structure renders these notable as targets for synthesis studies. Herein we report a rapid enantioselective synthesis of the fully functionalized azabicyclononane (Abn) core common to the banyasides, suomilide, and spumigin HKVV. Key to the strategy is the implementation of a tandem catalytic sequence along with a series of novel, mechanistically intriguing transformations.



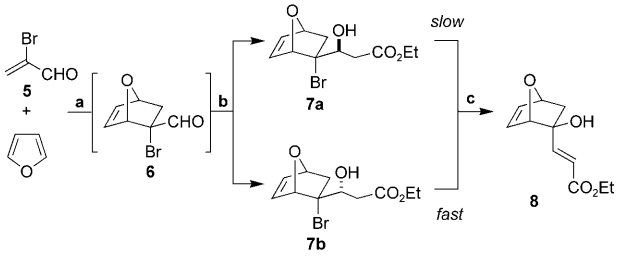
Scheme 1. Azabicyclononane members of the aeruginosin family.

As indicated in Scheme 2, the synthesis of the tricyclic core **I** relies on a strategy involving a late-stage regioselective olefin hydroxylation of **II**. Preparation of this key intermediate would necessitate the development of a series of reactions stemming from **III** formally involving C–N bond formation (*a* in Scheme 2) and cleavage of the C–O bond (*b* in Scheme 2). As described below, the preparation of the oxabicyclic norbornene presented an opportunity to establish a tandem catalytic sequence.



Scheme 2. Retrosynthetic analysis of the azabicyclononane core.

The synthesis commenced with the enantioselective Diels–Alder reaction[3] of furan and bromoacrolein[4] leading to aldehyde **6**, employing Corey's oxazaborolidine catalyst (Scheme 3). The sensitive *exo*-Diels–Alder adduct is allowed to react in situ with the lithium enolate derived from ethyl acetate to afford a mixture of aldol adducts **7a** and **7b** (63% yield, d.r. 1.6:1, e.r. 87:13). It is important to note that the enantioselective Diels–Alder reaction employing the oxazaborolidinone catalyst 3-methyl-substituted derivative of **9**, derived from *N*-tosyl (α*S*,β*R*)-β-methyltryptophan, is reported to proceed with greater than 98% yield (92% *ee*).[5] As a consequence of the subsequent step involv-



Scheme 3. a) 5 mol% **9** (see Scheme 4), CH_2Cl_2, furan, −78 °C; b) LDA, EtOAc, −78 °C, 63%, d.r. 1.6:1; c) KO*t*Bu, THF, −65 °C → −45 °C, 75% (brsm, 39% conv.). LDA = lithium diisopropylamide, brsm = based on recovered starting material.

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[*] C. S. Schindler, Dr. C. R. J. Stephenson, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie, ETH Zürich, HCI H335
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)
Fax: (+41) 44-632-1328
E-mail: carreira@org.chem.ethz.ch

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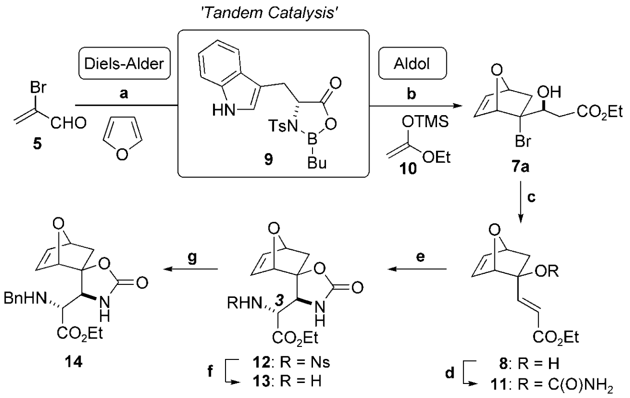
ing conversion to **8**, the generation of diastereomers in the aldol addition is inconsequential. Indeed, treatment of the diastereomeric mixture of bromohydrins **7a**/**7b** with KO*t*Bu (below −45 °C) afforded *E*-α,β-unsaturated ester **8** in 75 % yield. This transformation likely proceeds through an intermediate epoxy ester, which subsequently undergoes elimination to give **8**. It is worth noting that the rates of conversion of the β-hydroxy-γ-bromo esters to product **8** were markedly different for each of the diastereomers with **7b** as the faster-reacting component. Thus, when the reaction was stopped at 50 % conversion, the re-isolated material consisted exclusively of alcohol **7a**.[6]

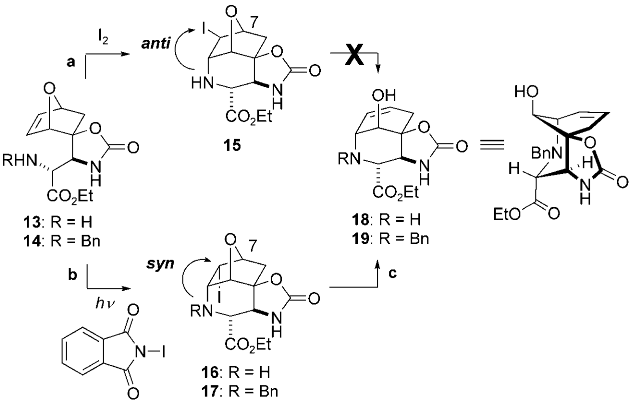
Oxazaborolidines have been shown to serve as catalysts in a variety of processes including cycloadditions as well as carbonyl addition reactions.[7] We were thus intrigued by the possibility of merging the Diels–Alder cycloaddition and a Mukaiyama aldol reaction to directly afford bromohydrin adducts. In this experiment, furan and bromoacrolein are allowed to react in the presence of 5 mol % oxazaborolidine **9** in CH_2Cl_2 at −78 °C; upon consumption of the educts, the silyl ketene acetal **10** was added as a solution in THF (Scheme 4). The application of such tandem-catalysis protocol led to the formation of **7a** in 67 % yield and improved diastereoselectivity (d.r. 5:1, e.r. 86:14).



Scheme 4. a) **9** (5 mol %), CH_2Cl_2, furan, −78 °C; b) **10**, THF, −78 °C, 67 %, d.r. 5:1; c) KO*t*Bu, THF, −65→−45 °C, 75 % (brsm, 39 % conv.); d) 1. $Cl_3CC(O)NCO$, CH_2Cl_2, 23 °C; 2. Al_2O_3, CH_2Cl_2, 23 °C, 95 %; e) 1. [Rh_2esp_2] (5 mol %), $PhI(OAc)_2$, MgO, CH_2Cl_2, reflux; 2. $NsNH_2$, NaH, DMF, 23 °C, 75 %; f) PhSH, K_2CO_3, CH_3CN, 23 °C, 91 %; g) PhCHO, $NaBH_3CN$, AcOH, MeOH, 0→23 °C, 92 %. Esp = Espino ligand,[10] Ns = *o*-nitrobenzenesulfonyl.

With a route to the key bicyclic ester secured, we envisioned the introduction of both the oxazolidinone moiety and C(3)-nitrogen atom using a one-pot sequence consisting of an intramolecular enoate aziridination and ring-opening. Despite literature precedence[8] which indicated a preference for the aziridine opening at the internal position to afford the 1,3-oxazinan-2-one, we anticipated that the activation by the ester group would bias the system to yield the desired oxazolidin-2-one.

The allylic alcohol **8** was readily converted to carbamate **11** upon reaction with trichloroacetyl isocyanate followed by treatment with activated basic alumina.[9] A number of Rh^{II} catalysts were screened to effect the aziridination reaction, and best results were observed using the protocol developed by Du Bois and Espino.[10] We were able to cleanly effect opening of the aziridine with *o*-nitrobenzenesulfonamide to afford the desired product **12** in 75 % yield. Deprotection of **12** with K_2CO_3/PhSH gave amine **13** (91 %). Although **13** could be taken forward through the sequence to the desired target, it was readily protected upon treatment with benzaldehyde and $NaBH_3CN$ to afford **14**.

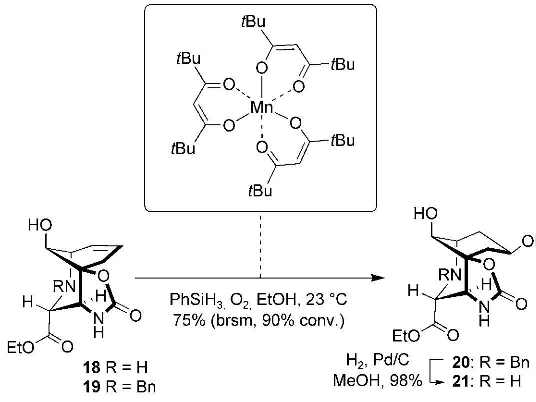


Scheme 5. a) I_2, $NaHCO_3$, THF, H_2O, 23 °C, 73 % (**13**→**15**); b) *N*-iodophthalimide, *hν*, CH_2Cl_2, 89 % (**14**→**17**), 63 % (**13**→**16**); c) 4.0 equiv SmI_2, THF, 0→23 °C, 82 % (**17**→**19**), 62 % (**16**→**18**).

The critical point had been reached in the synthesis that demanded the identification of a process that would effect the conversion of **14** into the tricyclic azabicyclononane **19** (Scheme 5). Attention was focused on a two-step sequence involving a haloamination of the oxabicyclonorbornene and a fragmentation to realize the desired Abn framework. Treatment of amine **14** with I_2/$NaHCO_3$ in THF[11] led to exclusive formation of *exo*-iodide **15**, as expected from the addition proceeding in an *anti* fashion. Surprisingly, however, the reaction of **14** with either NIS or *N*-iodophthalimide[12] resulted in exclusive formation of the *endo*-iodide **17** within 10 min in 89 % yield, consistent with a formal *syn*-addition across the olefin. Although the mechanism of this unusual transformation is unclear at present, we have made some observations that would need to be reconciled with any mechanistic proposal. Firstly, the *syn*-iodoamination reaction proceeds slower and affords considerable quantities of the *exo*-adduct when conducted in the dark under otherwise identical conditions. Secondly, in a series of ^1H NMR spectroscopic experiments, we observed that at short reaction times (60 s) a mixture of starting material **14** and NIS in CD_2Cl_2 leads to the transient formation of an intermediate in which the olefin is intact. As the reaction proceeded to completion this intermediate disappears, giving the *syn*-iodoamination product **16** and merely traces of *N*-Bn-**15**. Analysis of the spectroscopic data is consistent with a tentative assignment of the intermediate as the *N*-iodo derivative of **14**. Importantly, we were able to show that the unprotected primary amine **13** could be subjected to the same set of conditions to give **16** with a small decrease in overall yield.

Attempts to achieve cleavage of the C7–O bond by treatment of the compounds **15**, *N*-Bn-**15**, **16**, or **17** with *t*BuLi or Li-naphthalide led to intractable mixtures of products. Interestingly, undesired C–N bond cleavage was favored in the reaction of **15** and **16** with Zn in AcOH. However, treatment of *endo*-iodide **17** with 4 equivalents SmI_2[13] in THF at 0 °C and subsequent warming to ambient temperature resulted in isolation of the desired alkene **19** in 82 % yield. By contrast, the corresponding *exo*-iodide **15** was found to be unreactive under these reaction conditions. Thus, the combination of the fortuitous *syn*-iodoamination and the subsequent cleavage provides access to the core tricyclic ring system.

The completion of the synthesis required the regioselective hydration of the newly generated alkene in **19**. Initially hydroboration and epoxidation conditions were investigated. However, the olefin proved to be unreactive with the standard reagents (i.e. mCPBA, $BH_3{\cdot}SMe_2$, 9-BBN). Application of the Mn-catalyzed hydration initially developed by Mukaiyama and Isayama[14] and studied by us[15] resulted in the formation of the desired diol **20** as a single regio- and diastereoisomer in 75 % yield (Scheme 6). It is important to note that the presence of the axial hydroxy group in **19** was crucial for the success of this reaction, as the acylated congener failed to react.



Scheme 6. Formation of diol **20**.

The complete structural assignment of **20** was initially based on detailed NMR spectroscopic analysis and was subsequently confirmed by X-ray crystallography (Figure 1).[16] Hydrogenolysis of the *N*-benzyl amine was accomplished with Pd/C under standard conditions, completing the synthesis of the core of banyaside, suomilide, and spumigin HKVV **21** in 98 % yield. It is interesting to note that the unprotected secondary amine **18** was also a substrate for the olefin hydration reaction (59 %), thus providing a route to the core **21** without protecting groups.

In conclusion the first synthesis of the unique azabicyclononane core found in the aeruginosin class of serine protease inhibitors is described. The salient features of the route include: 1) a tandem catalysis sequence to provide access to a substituted oxanorbornene; 2) a Rh-catalyzed aziridination reaction; 3) an unusual *syn*-iodoamination which proved critical for 4) a subsequent oxanorbornene C–O cleavage; and 5) a Mn-catalyzed olefin hydration, which permits installation of the hydroxy group. The route we have described is characterized by its efficiency (eight steps via **13** or ten steps via **14** starting from bromoacrolein **5**) and sets the stage for subsequent introduction of the glycosyl and peptidyl side-chains that differentiate the members of the aeruginosin family of natural products.

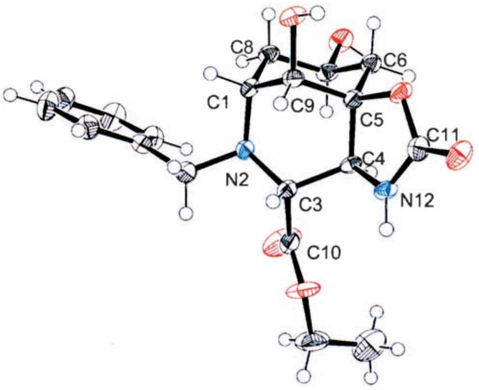


Figure 1. Ortep representation of **20** (probability ellipsoids at 50 %).

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[6] The relative configuration of **7a** was determined by analysis of the corresponding Mosher's ester and finally confirmed by X-ray crystallographic analysis of **7a**. Crystallographic data for **7a**: $C_{11}H_{15}BrO_4$, $M = 291.15$, monoclinic, space group $P2_1/c$, $a = 6.7577(2)$, $b = 21.6919(6)$, $c = 8.4629(3)$ Å, $V = 1237.93(7)$ Å^3, $\rho_{calcd} = 1.562\ \mathrm{Mg\,m^{-3}}$, $T = 298$ K, reflections collected: 4803, independent reflections 2812 ($R(\mathrm{int}) = 0.0660$), $R(\mathrm{all}) = 0.0940$, $wR(\mathrm{gt}) = 0.1975$.

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[16] Crystallographic data for **18**: $C_{19}H_{24}N_2O_6$, $M = 376.41$, orthorhombic, space group $P2_12_12_1$, $a = 6.5399(2)$, $b = 8.0975(3)$, $c = 34.228(2)$ Å, $V = 1812.59(12)$ Å^3, $\rho_{calcd} = 1.379\ \mathrm{Mg\,m^{-3}}$, $T = 203$ K, reflections collected: 2553, independent reflections 2535 ($R(\mathrm{int}) = 0.0556$), $R(\mathrm{all}) = 0.0689$, $wR(\mathrm{gt}) = 0.1499$. CCDC 695727 (**7a**) and 695726 695727 (**18**) 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.