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Total Synthesis of Sulfobacin A (Flavocristamide B)

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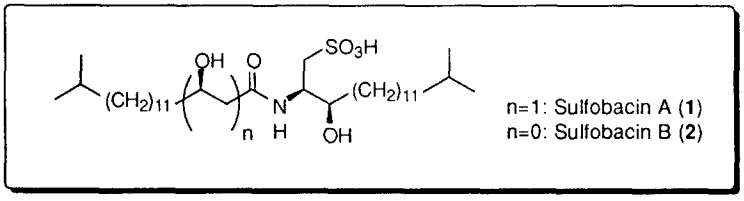
Abstract: Sulfobacin A (**1**), a novel von Willebrand factor receptor antagonist isolated from the culture broth of *Chryseobacterium* sp. NR 2993, was efficiently synthesized for the first time.

Sulfobacins A (**1**) and B (**2**), novel von Willebrand factor (vWF) receptor antagonists, have been isolated by Kamiyama *et al.*[1] from the culture broth of *Chryseobacterium* sp.(*Flavobacterium* sp.) NR 2993 in a soil sample collected in Iriomote Island, Okinawa Prefecture, Japan. Sulfobacin A (**1**) was also isolated by Kobayashi *et al.*[2] as flavocristamide B from *Flavobacterium* sp. in the marine bivalve *Cristria plicata* collected in Ishikari Bay, Hokkaido, Japan. Sulfobacins A (**1**) and B (**2**) inhibit the binding of vWF to the GPIb/IX receptors in a competitive manner with IC_{50}s of 0.47 and 2.2 μM, respectively.[1a] Furthermore, sulfobacin A (**1**) was found to have inhibitory activity against DNA polymerase α.[2] The structures are related to sulfonolipids having an aminosulfonic acid moiety and are analogous to sphingosine. The absolute configurations of the sulfobacins were determined using the modified Mosher method.[1b] We now wish to report the first total synthesis of sulfobacin A (flavocristamide B, **1**) in an effective and stereoselective manner.



Sulfobacin A (**1**) could be prepared from the corresponding thioacetate **3**, which could be constructed by coupling the left fragment **4** with the right fragment **5** using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[3] as a coupling reagent. The left fragment **4** would be obtained through the asymmetric reduction of the corresponding β-keto ester **6**. The right fragment would be constructed by the asymmetric aldol reaction using the Schiff base derived from (+)-2-hydroxy-3-pinanone ((+)-HyPN, **7**).[4]

The synthesis of the left fragment started from 1,10-decanediol (**8**). After protection of one of the hydroxy groups of **8** with benzyl bromide,[5] the Swern oxidation followed by the Wittig reaction with the ylide from the phosphonium bromide **9**[6] afforded the olefin **10**. Reduction of the double bond and hydrogenolytic deprotection over a 5% Pd/C catalyst afforded the alcohol **11**, which was converted to the carboxylic acid **12** with Jones reagent. The aldehyde **13** was also obtained from **11** by oxidation with PCC.

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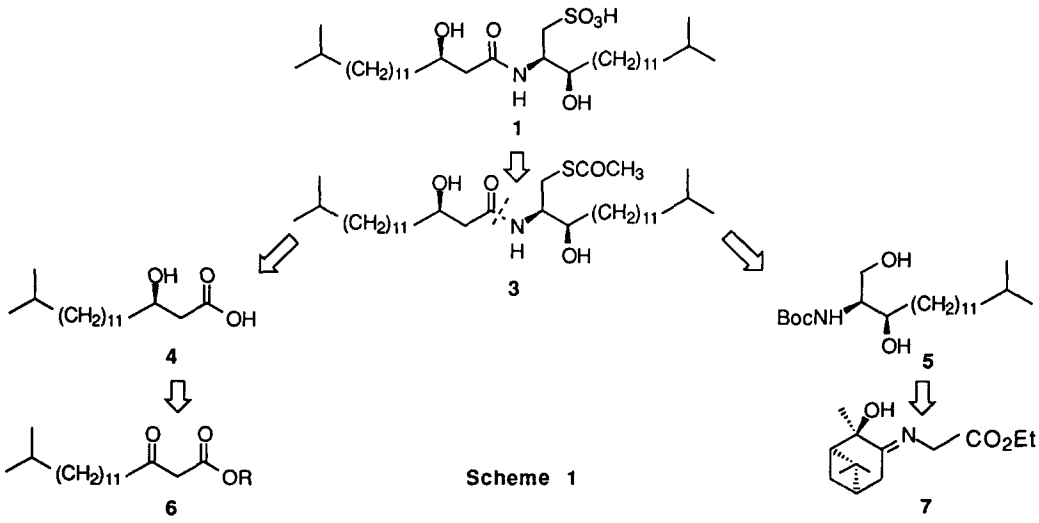
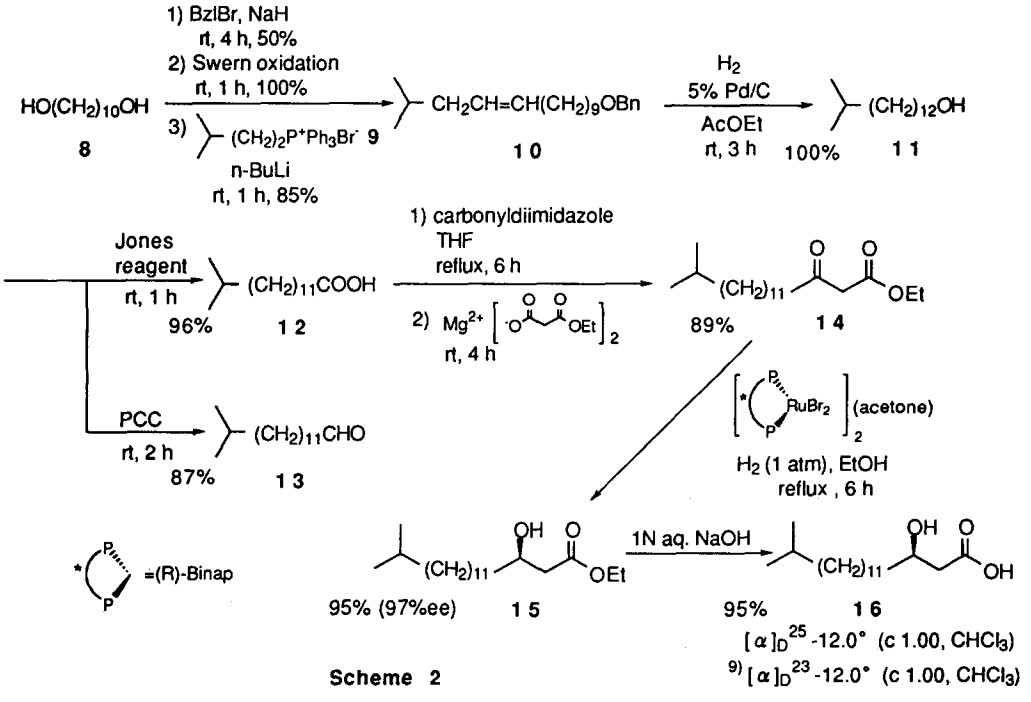


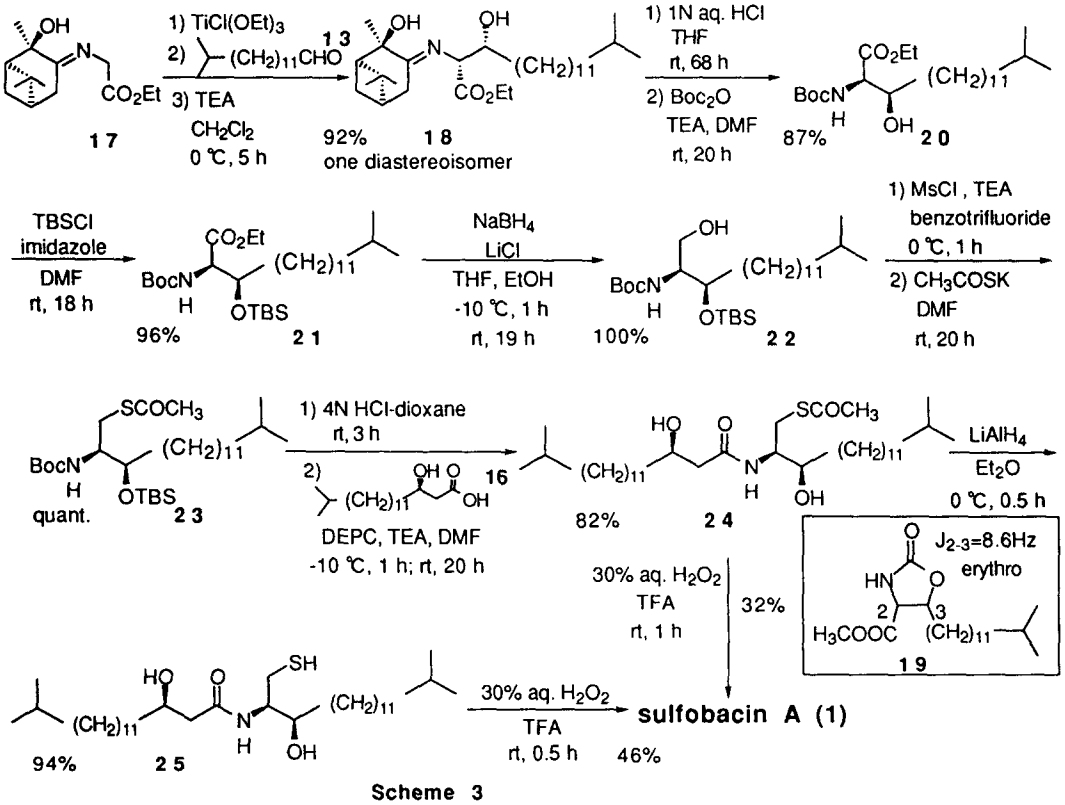
Scheme 1

Reaction of the carboxylic acid **12** with carbonyldiimidazole followed by the magnesium enolate of the malonic acid half-ester yielded the β-keto ester **14**. The asymmetric hydrogenation of the β-keto ester **14** with chiral Ru(II) catalysts at atmospheric pressure according to Genêt's method[7] smoothly proceeded to give the β-hydroxy ester **15** in 95% yield with 97% ee,[8] which was converted to the β-hydroxycarboxylic acid **16** by alkaline treatment. The stereogenic center of **16** was revealed to be (*R*) according to the comparison of the specific rotation of that already reported.[9]



Scheme 2

The right fragment was prepared from the aldehyde **13** and the chiral Schiff base of (+)-2-hydroxy-3-pinanone ((+)-HyPN, **17**) using the Solladié's methodology.[10] Thus, the asymmetric aldol reaction of the aldehyde **13** with the chiral titanium enolate generated from titanium chlorotriethoxide and the Schiff base **17** gave the erythro aldol adduct **18** in 92% yield as a single diastereoisomer. This adduct **18** was converted[11] to the oxazolidine **19** and the configuration was determined to be erythro by its ^{1}H NMR spectral analysis. The absolute configuration was determined using a modified Mosher method.[12] Removal of the chiral auxiliary with 1*N* aq. HCl, followed by treatment with Boc_2O, afforded the hydroxy ester **20**. After protection of the hydroxy group with *tert*-butyldimethylsilyl(TBS) chloride, the ester **21** was reduced to give the primary alcohol **22**, which was converted to the thioacetate **23** via the mesylate. After deprotection of the thioacetate **23** with hydrogen chloride in dioxane, the coupling of the deprotected right fragment with the left fragment **16** was smoothly achieved with DEPC. The thioacetate **24** was subjected to pertrifluoroacetic acid oxidation to give sulfobacin A (**1**). Alternatively, the thioacetate **24** was reduced with $LiAlH_4$ to give the corresponding thiol which underwent the pertrifluoroacetic acid oxidation to yield sulfobacin A (**1**). The synthetic sulfobacin A ($[\alpha]_D^{18}$ -31.6° (c 0.14, MeOH)) was identical with the natural one[1] ($[\alpha]_D^{24}$ -35° (c 0.14, MeOH)) in every respect (IR, ^{1}H NMR, ^{13}C NMR spectra, and TLC). Thus we have completed the first total synthesis of sulfobacin A (**1**).



Scheme 3

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References and Notes

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5. The dibenzyl derivative was also obtained in 7% yield.
6. The phosphonium bromide **9** was prepared from isoamyl bromide and triphenyl phosphine in acetonitrile at reflux temperature.
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8. Determined by ^{1}H NMR spectral analysis of the corresponding MTPA ester derivative.
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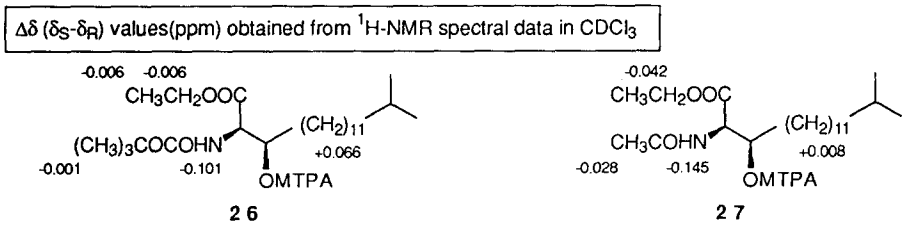
10. Solladié-Cavallo, A.; Koessler, J.L. *J. Org. Chem.* **1994**, *59*, 3240.
11. The adduct **18** was converted to the oxazolidinone **19** by the removal of the chiral auxiliary with hydrogen chloride in dioxane, amino protection with 4-methoxybenzyl S-(4.6-dimethylpyrimidin-2-yl)-thiocarbonate (Z(OMe)-SDP)(75%), cyclization with 1*N* NaOH, and methylation with iodomethane (80% in 2 steps).
12. The absolute configuration was determined by the $\Delta\delta(\delta_S-\delta_R)$ values (ppm) obtained from ^{1}H-NMR spectral data for the MTPA esters **26** and **27** in $CDCl_3$.



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