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Synthesis of Sulfobacin A and B, New Sulfonolipids Isolated from *Chryseobacterium* sp.

Hirosato Takikawa, Shin-etsu Muto, Dai Nozawa, Akihiro Kayo and Kenji Mori*

Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162-8601, Japan

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Abstract: Sulfobacin A (**1**) and B (**2**), new sulfonolipids isolated from *Chryseobacterium* sp. as von Willebrand factor antagonists, were synthesized stereoselectively by starting from L-cysteine.
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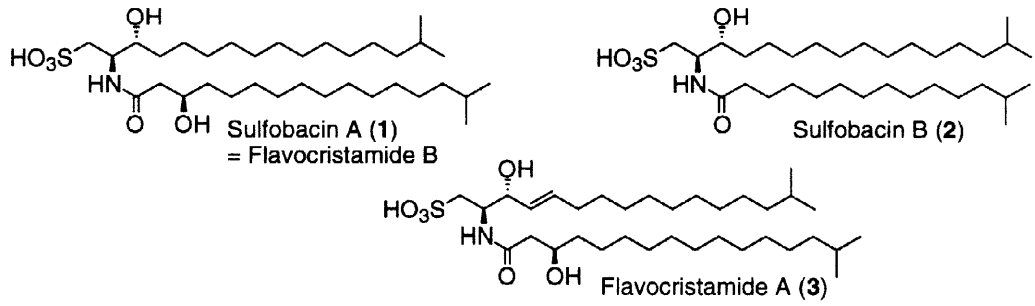
In 1995 sulfobacin A (**1**) and B (**2**), von Willebrand factor receptor antagonists, were isolated by Kamiyama et al. from the culture broth of *Chryseobacterium* sp. (*Flavobacterium* sp.).[1] Almost simultaneously, the isolation of flavocristamide A (**3**) and B (**1**), DNA polymerase α inhibitors, from the cultured mycelium of *Flavobacterium* sp. was reported by Kobayashi et al.[2] These compounds are sulfonic acids and belong to unusual sphingosine relatives. Although a structurally similar sulfonolipid was previously synthesized by Kamikawa et al.,[3] the synthesis of sulfobacins has not been reported yet. We therefore became interested in synthesizing new sulfonolipids (**1**, **2** and **3**) as a part of our works to prepare unusual sphingosine relatives.[4] In this paper, we report the synthesis of sulfobacin A (**1**) and B (**2**).



Scheme 1 shows the synthetic plan for **1**. The target compound **1** can be prepared from an aminosulfinic acid **A**, which is obtainable from the key intermediate **B**. Since the sulfone portion of **B** is a part of acetonide group, this is thought to be a sulfinic acid equivalent. The key intermediate **B** may be synthesized by diastereoselective coupling of **C** with **D**. For the preparation of optically active **E**, we adopt enzymatic resolution.

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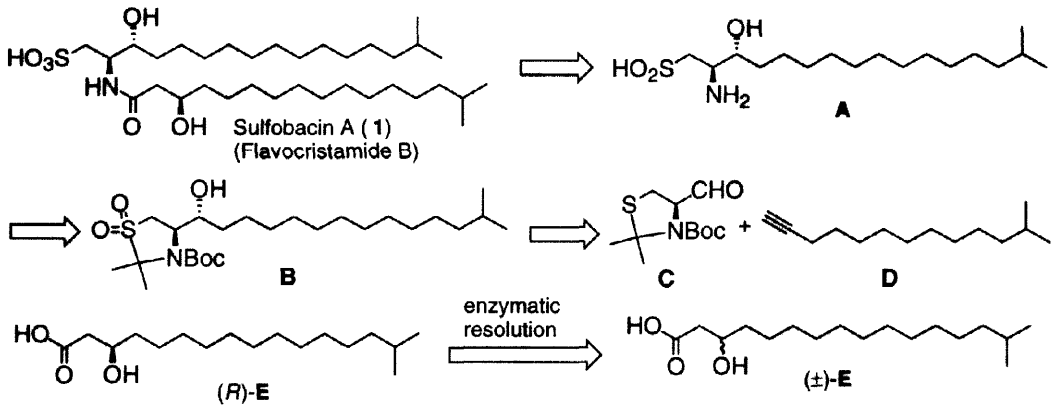


Scheme 1. Synthetic plan for **1**.

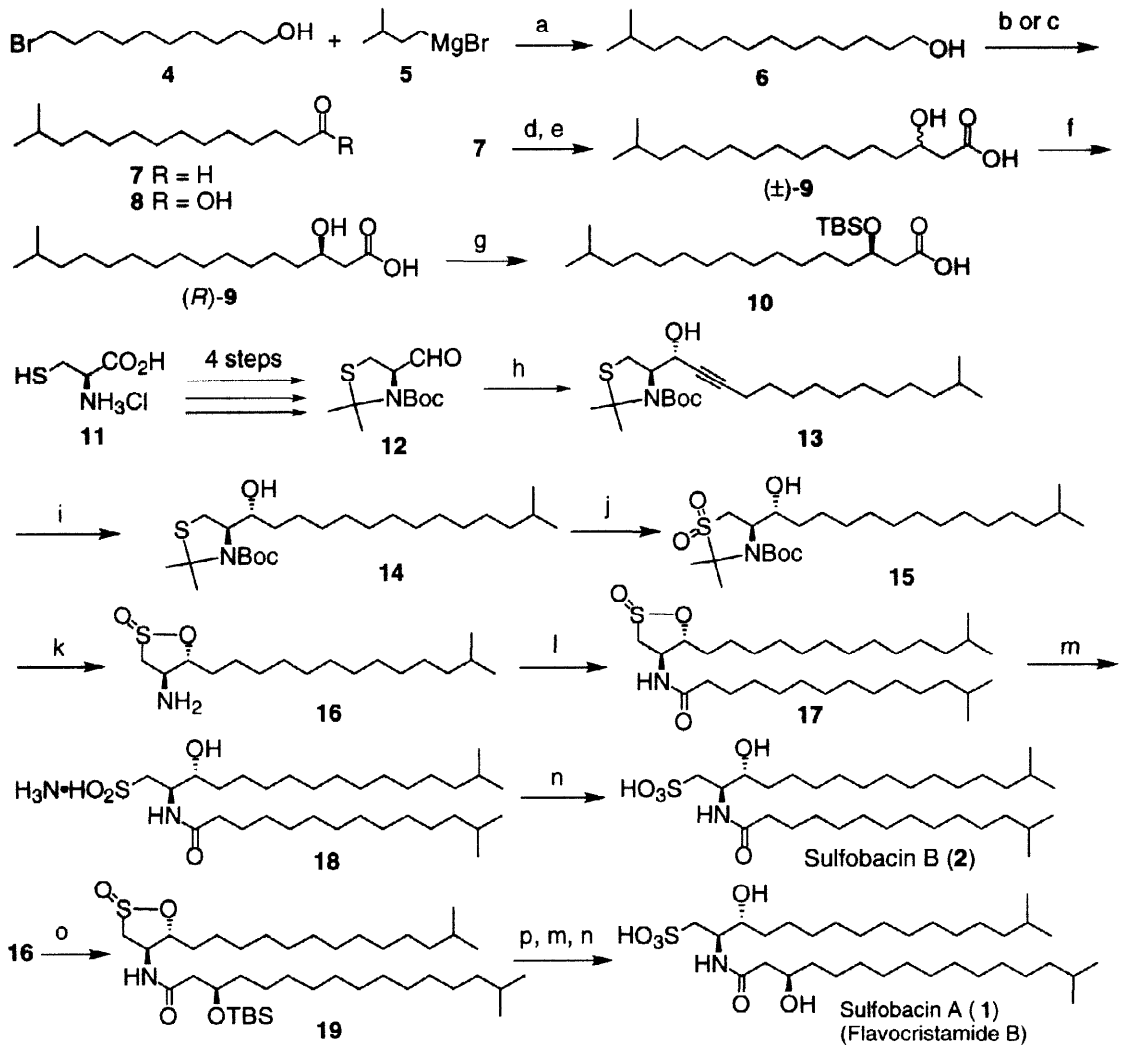
The synthesis of sulfobacin A (**1**) and B (**2**) is summarized in Scheme 2. Grignard coupling of bromo alcohol **4** with **5** gave alcohol **6**. It was then oxidized to the corresponding aldehyde **7** and carboxylic acid **8**, respectively. The aldehyde **7** was treated with lithio enolate of ethyl acetate followed by hydrolysis to give (±)-**9** (= **E**) in 68% yield. This racemate was resolved by lipase PS in the presence of vinyl acetate to afford desired (*R*)-**9** in 28% yield,[5] $[\alpha]_D^{23}$ = −12.7 (*c* = 1.02, $CHCl_3$), <lit.[6] $[\alpha]_D^{20}$ = −12.0 (*c* = 1.0, $CHCl_3$)>. The enantiomeric purity of (*R*)-**9** was estimated by GLC analysis on a chiral stationary phase to be ~100% e.e. The hydroxy acid (*R*)-**9** was then converted to the corresponding *t*-butyldimethysilyl (TBS) ether **10**.

The known aldehyde **12** (= **C**) was prepared from L-cysteine hydrochloride **11**.[7] Diastereoselective addition of lithium alkynide derived from 12-methyl-1-tridecyne (**D**) to **12** was performed by Fujisawa's procedure[7] to give the desired *anti*-adduct **13** in 82% yield (*anti* : *syn* = 90 : 10). After reduction of the triple bond, the sulfur atom at the thiazolidine ring was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to afford the key intermediate **15** in 99% yield.[8]

The cleavage of *t*-butoxycarbonyl (Boc) and acetonide protecting groups of **15** by treatment with hydrochloric acid gave aminosultine **16** (= **B**) in 99% yield.[9] The amino group of **16** was acylated with **8** in the presence of DCC to give amide **17** in 79% yield. Hydrolysis of the sulfinate portion with aqueous ammonia was followed by oxidation with hydrogen peroxide to furnish sulfobacin B (**2**) in 94% yield, $[\alpha]_D^{20}$ = −8.6 (*c* = 0.14, MeOH), <lit.[1] $[\alpha]_D^{23}$ = −19 (*c* = 0.14, MeOH)>. The ^{1}H-NMR, IR and mass spectra of synthetic **2** were in good accord with those reported.[10]

Sulfobacin A (**1**) was also synthesized as follows. The aminosultine **16** was acylated with **10** to give **19**. The resulting amide **19** was converted in 3 steps (deprotection, hydrolysis and oxidation) to sulfobacin A (**1**), $[\alpha]_D^{25}$ = −15 (*c* = 0.14, MeOH), <lit.[1] $[\alpha]_D^{24}$ = −35 (*c* = 0.14, MeOH), lit.[2] $[\alpha]_D^{20}$ = −7.9 (*c* = 0.18, MeOH)>. The ^{13}C-NMR, IR and mass spectra of synthetic **1** were in good accord with those of natural **1**.[11] The ^{1}H-NMR data of synthetic **1**, however, was slightly different from that reported.[1] We therefore remeasured ^{1}H-NMR spectra of the natural and our synthetic **1** under almost the same conditions. These two spectra were superimposable[11] to support the conclusion that synthetic **1** was identical with natural **1**.[12]

In summary, the synthesis of new sulfonolipids sulfobacin A (**1**) and B (**2**) were achieved by starting from L-cysteine.[13] Our synthetic strategy might be applicable for the synthesis of flavocristamide A (**3**), which will be the subject of our future communication.



Scheme 2. Synthesis of sulfobacin A (**1**) and B (**2**).

Reagents: (a) Li_2CuCl_4/THF (96%); (b) PCC, MS 4A/CH_2Cl_2 (78%); (c) Jones' CrO_3/acetone (70%); (d) EtOAc, LDA/THF (79%); (e) LiOH/aq MeOH-THF (86%); (f) lipase PS, vinyl acetate, BHT, 60°C (28%, ~100% e.e.); (g) TBSCl, imid./DMF, then dil. HCl (82%); (h) *n*-BuLi, 12-methyl-1-tridecyne (**D**), HMPA/THF (82%, and 70%); (i) PtO_2, H_2/EtOAc (98%); (j) *m*-CPBA/$CHCl_3$ (99%); (k) 6 M HCl/MeOH (99%); (l) **8**, DCC, DMAP/$CHCl_3$ (74%); (m) aq NH_3/$CHCl_3$-MeOH; (n) aq H_2O_2 (94% for **2** and 90% for **1**, 2 steps); (o) **10**, DCC, DMAP/$CHCl_3$ (78%); (p) TBAF/THF (69%).

Acknowledgement

We thank Dr. T. Kamiyama (Nippon Roche) for his kind supply of natural sulfobacins and the copies of various spectra of them. Our thanks are due to Prof. T. Sugai (Keio University) for his suggestion concerning the enzymatic resolution. We thank Amano Pharmaceutical Co. for the gift of enzyme. This work was supported by the Grant-in-Aid for Scientific Research on Priority Area No. 08245103 from the Ministry of Education, Science, Sports and Culture, of Japanese Government.

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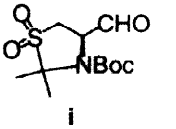
8. In our attempt to explore an alternative route to **15**, addition of lithium 12-methyl-1-tridecynide to **i** was executed. The addition took place to give **15** (70% yield) with almost perfect diastereoselection (*anti* : *syn* = ~100 : ~0 ; determined by HPLC analysis of **15**). The extremely high tendency of **i** to suffer racemization, however, precluded the use of **i** as the intermediate better than **12**.



i

9. For latest works of synthesis of sultines, see: (a) Yolka, S.; Fellous, R.; Lizzani-Cuvelier, L.; Loiseau, M. *Tetrahedron Lett.*, **1998**, *39*, 991–992. (b) Connolly, T. J.; Durst, T. *Tetrahedron Lett.*, **1997**, *38*, 1337–1340. (c) Marson, C. M.; Giles, P. R. *J. Org. Chem.*, **1995**, *60*, 8067–8073.
10. Properties of synthetic **2**: m.p. 201–203°C; $[\alpha]_D^{21}$ = –8.6 (*c* = 0.14, MeOH); IR (KBr) ν_{max} 3300, 2940, 1650, 1550, 1470, 1200, 1060 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.83 (d, *J* = 6.6 Hz, 12H, 16, 14'-H), 1.14 (m, 4H, 14, 12'-H), 1.23 (m, 36H, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 4', 5',6', 7', 8', 9', 10', 11'-H), 1.38 (m, 2H, 3'-H), 1.49 (m, 2H, 15, 13'-H), 2.02 (t, *J* = 7.2 Hz, 2H, 2'-H), 2.64 (dd, *J* = 14.2, 4.2 Hz, 1H, 1-H), 2.77 (dd, *J* = 14.2, 6.2 Hz, 1H, 1-H), 3.51 (m, 1H, 3-H), 3.86 (m, 1H, 2-H), 4.84 d, *J* = 5.5 Hz, 1H, O-H), 7.63 (d, *J* = 8.1 Hz 1H, N-H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 22.5, 25.2, 25.4, 26.8, 27.3, 28.6, 28.9, 29.04, 29.07, 29.19, 29.3, 33.3, 35.8, 38.5, 51.3, 51.8, 71.7, 171.6; negative HR FABMS *m/z* (M–H) 574.4506 (Calcd. for $C_{32}H_{65}NO_5S$ 574.4505).
11. Properties of synthetic **1**: m.p. 233–235°C; $[\alpha]_D^{25}$ = –15 (*c* = 0.14, MeOH); IR (KBr) ν_{max} 3320, 2940, 1640, 1550, 1465, 1190, 1060 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 0.84 (d, *J* = 6.4 Hz, 12H, 16, 16'-H), 1.13 (m, 4H, 14, 14'-H), 1.23 (m, 38H, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 5', 6', 7', 8', 9', 10', 11', 12', 13'-H), 1.35 (m, 2H, 4'-H), 1.49 (m, 2H, 15, 15'-H), 2.08 (dd, *J* = 13.7, 6.1 Hz, 1H, 2'-H), 2.14 (dd, *J* = 13.7, 7.0 Hz, 1H, 2'-H), 2.66 (dd, *J* = 14.0, 3.9 Hz, 1H, 1-H), 2.75 (dd, *J* = 14.0, 6.7 Hz, 1H, 1-H), 3.47 (m, 1H, 3-H), 3.74 (m, 1H, 3'-H), 3.89 (m, 1H, 2-H), 4.67 (d, *J* = 4.3 Hz, 1H, O-H), 4.78 (d, *J* = 5.5 Hz, 1H, O-H), 7.60 (d, *J* = 8.5 Hz, 1H, N-H); ^{13}C-NMR (125 MHz,DMSO-d_6) δ = 22.5, 25.1, 25.4, 26.8, 27.3, 29.09, 29.19, 29.23, 29.3, 33.3, 36.5, 38.5, 44.7, 51.0, 51.7, 67.5, 71.8, 170.2; negative HR FABMS *m/z* (M–H) 618.4771 (Calcd. for $C_{34}H_{69}NO_6S$ 618.4768).
^{1}H-NMR (500 MHz, DMSO-d_6) data of natural **1** remeasured by us: δ = 0.84 (d, *J* = 6.7 Hz, 12H, 16, 16'-H), 1.13 (m, 4H, 14, 14'-H), 1.23 (m, 38H, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 5', 6', 7', 8', 9', 10', 11', 12', 13'-H), 1.35 (m, 2H, 4'-H), 1.49 (m, 2H, 15, 15'-H), 2.08 (dd, *J* = 13.4, 5.8 Hz, 1H, 2'-H), 2.13 (dd, *J* = 13.4, 7.3 Hz, 1H, 2'-H), 2.67 (dd, *J* = 14.0, 3.7 Hz, 1H, 1-H), 2.75 (dd, *J* = 14.0, 6.7 Hz, 1H, 1-H), 3.46 (m, 1H, 3-H), 3.74 (m, 1H, 3'-H), 3.90 (m, 1H, 2-H), 4.67 (d, *J* = 4.3 Hz, 1H, O-H), 4.78 (d, *J* = 5.5 Hz, 1H, O-H),7.63 (d, *J* = 8.9 Hz, 1H, N-H);
12. The specific rotation values of **1** and **2** seem to fluctuate as effected by the concentration or the pH of the solution, etc. For example, the specific rotation of Dr. Kamiyama's sample of the naturally occurring **1** was $[\alpha]_D^{24}$ = –8.1 (*c* = 0.10, MeOH) <lit.[1] $[\alpha]_D^{24}$ = –35 (*c* = 0.14, MeOH)>, when remeasured by us.
13. T. Shioiri et al. (Nagoya City University) announced their independent synthesis of sulfobacins (May 21, 1998 in Sendai).