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# A short total synthesis of sulfobacin A

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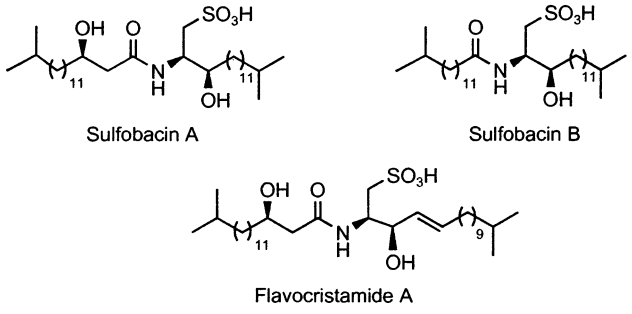
**Abstract**—A total synthesis of the von Willebrand factor receptor antagonist sulfobacin A is described. Key steps for this short route to sulfobacin A include ruthenium-catalyzed asymmetric hydrogenation and diastereoselective electrophilic amination for the construction of the three stereogenic centers.

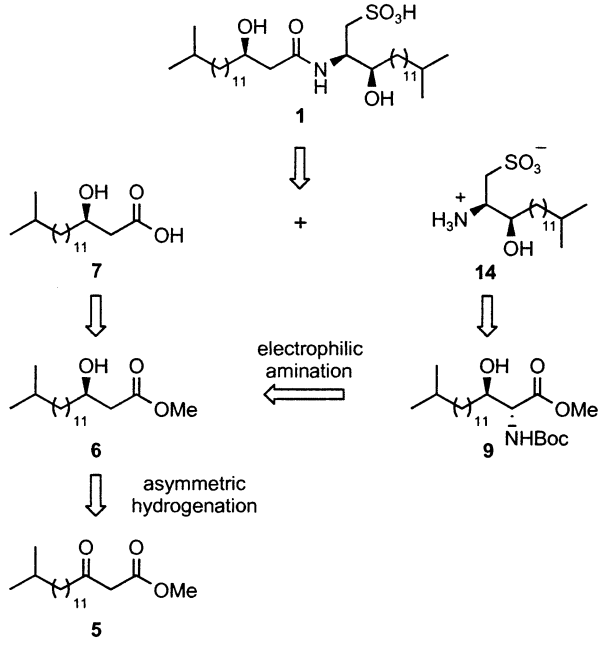

While screening for novel von Willebrand factor (vWF) receptor antagonists, Kamiyama and co-workers[1,2] isolated in 1995 sulfobacins A and B in the culture broth of *Chryseobacterium* sp. NR 2993, a strain isolated from a soil sample collected in Iriomote Island (Scheme 1). These compounds showed potent inhibitory activity against the binding of vWF to its receptor in a competitive manner with $IC_{50}$ of 0.47 μM for sulfobacin A and 2.2 μM for sulfobacin B. The same year, Kobayashi and co-workers[3] isolated sulfobacin A and flavocristamide A from a marine bacterium *Flavobacterium* sp., separated from the marine bivalve *Cristaria plicata* collected in Ishikary Bay (Scheme 1). These compounds exhibited inhibitory activity against DNA polymerase α.




**Scheme 1.** Structures of flavocristamide A and sulfobacins A and B.

Two syntheses of sulfobacin A have been reported by Shioiri[4,5] and Mori.[6,7] As part of our ongoing efforts towards the synthesis of biologically active natural products,[8–10] we report herein a short synthesis of sulfobacin A using sequential catalytic asymmetric hydrogenation[11,12] and electrophilic amination[13,14] for the construction of the three stereogenic centers.

Scheme 2 shows our retrosynthetic analysis for sulfobacin A. Our approach is based on the use of β-




**Scheme 2.** Retrosynthetic analysis for sulfobacin A.

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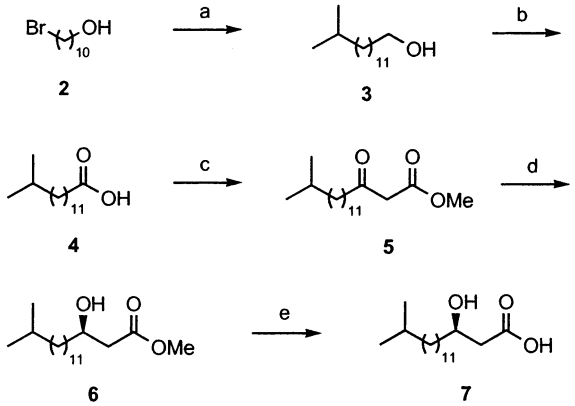
hydroxy ester **6** as a key intermediate for the synthesis of both fragments **7** and **14** whose coupling reaction would afford the desired sulfobacin A (**1**). Thus, β-hydroxy acid **7** would be obtained from **6** by simple alkaline treatment while **14** would be prepared via compound **9**, easily obtainable by diastereoselective electrophilic amination of **6**. Asymmetric hydrogenation of β-keto ester **5** using chiral ruthenium complexes would furnish the key intermediate **6** with high enantiomeric excess.

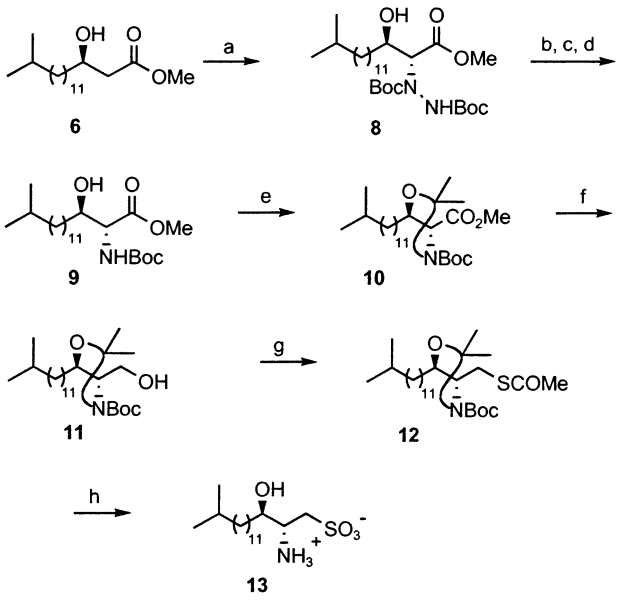
The synthesis of the desired β-hydroxy ester **6** began with the commercially available 10-bromodecan-1-ol **2** which was converted into alcohol **3** by treatment with isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate[7] in 95% yield (Scheme 3). Oxidation of **3** using Jones' reagent then furnished the corresponding carboxylic acid **4**, which was converted into the β-keto ester **5** using Masamune's procedure.[15]

Thus, the addition of carbonyl diimidazole to **4** followed by treatment with the magnesium salt of monomethyl malonic acid gave the requisite β-keto ester **5** in 81% yield. For the asymmetric hydrogenation of **5**, we used our recently reported simple procedure for the in situ preparation of chiral ruthenium catalysts starting directly from anhydrous $RuCl_3$.[16] Thus, hydrogenation of **5** was carried out at 80°C in methanol under a low pressure of hydrogen (6 bar), using 1 mol% of the $RuCl_3$/(*R*)-MeO-BIPHEP system.

Under these conditions, β-hydroxy ester **6** was obtained in 96% yield and excellent enantiomeric excess (e.e. >99%, determined by HPLC analysis, Chiralcel OD-H column, hexane/propan-2-ol: 99/1, flow rate: 1.0 mL/min, detection: 215 nm), $[\alpha]_D^{25}$ −14.3 (*c* 0.51, $CHCl_3$), lit.[2] $[\alpha]_D^{20}$ −12.7 (*c* 0.52, $CHCl_3$). Finally, alkaline treatment of **6** furnished the corresponding β-hydroxy carboxylic acid **7**, $[\alpha]_D^{25}$ −11.6 (*c* 1.0, $CHCl_3$), lit.[17] $[\alpha]_D^{20}$ −12.0 (*c* 1.0, $CHCl_3$).



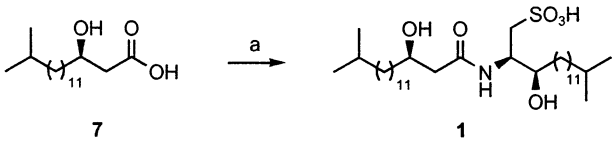

**Scheme 3.** *Reagents and conditions*: (a) $Me_2CH(CH_2)_2MgBr$, $Li_2CuCl_4$ (1 mol%), THF, −78°C to rt, 12 h, 95%; (b) Jones' reagent, acetone, rt, 1 h, 88%; (c) carbonyl diimidazole, THF, rt, 6 h; $Mg(O_2CCH_2CO_2Me)_2$, THF, rt, 16 h, 81%; (d) $H_2$ (6 bar), $RuCl_3$/(*R*)-MeO-BIPHEP (1 mol%), MeOH, 80°C, 23 h, 96%, e.e. >99%; (e) 1N NaOH, MeOH, 0°C, 30 min, then rt, 3 h, 89%.




**Scheme 4.** *Reagents and conditions*: (a) MeZnBr (1 equiv.), 0°C, 1 h; LDA (2 equiv.), −78°C, 1 h; DTBAD (2 equiv.), −78°C, 2 h, 72%, d.e. >95%; (b) TFA, $CH_2Cl_2$, rt, 3 h; (c) $H_2$ (1 atm), Raney Ni, MeOH, ultrasound, rt, 14 h; (d) $Boc_2O$, $NaHCO_3$, MeOH, ultrasound, rt, 3.5 h, 80% from **8**; (e) $Me_2C(OMe)_2$, $Et_2O{\cdot}BF_3$, $CH_2Cl_2$, rt, 1 h, 93%; (f) $Ca(BH_4)_2$, THF, EtOH, −15°C to rt, 22 h, 94%; (g) $CH_3COSH$, $^iPrOCON{=}NCO_2{}^iPr$, $PPh_3$, THF, 0°C, 1 h, then rt, 16 h, 95%; (h) $H_2O_2$, TFA, rt, 1 h.

The synthesis of **13** involved again β-hydroxy ester **6** as shown in Scheme 4. The *anti*-*N*,*N*-Boc-α-hydrazino-β-hydroxy ester **8** was readily obtained from **6** by electrophilic amination with di-*tert*-butylazodicarboxylate (DTBAD).[18,19] Treatment of **6** with methylzinc bromide followed by lithium diisopropylamide at −78°C furnished the resulting zinc enolate which was reacted with DTBAD to give **8** in 72% yield and with high diastereoselectivity (d.e. >95%, determined by $^1H$ NMR). After deprotection of the hydrazine function, the N–N bond was cleaved by hydrogenolysis using Raney nickel and ultrasound.[20] Subsequent protection of the resulting amine with di-*tert*-butyl dicarbonate and ultrasound[21] afforded compound (2*R*,3*R*)-**9** in 80% overall yield starting from **8**.

Protection of **9** was performed using 2,2-dimethoxypropane with a catalytic amount of $Et_2O{\cdot}BF_3$, and the resulting oxazolidine **10** was then reduced to the primary alcohol **11**[22] by treatment with calcium borohydride. After conversion of **11** into the corresponding mesylate, all attempts to perform nucleophilic substitution with sodium sulfite failed to afford the expected sulfonic acid. Finally, Mitsunobu[23,24] reaction of **11** with thioacetic acid afforded thioester **12**[25] in 95% yield and subsequent oxidation with hydrogen peroxide in trifluoroacetic acid led to the target compound **13**.




7 1

**Scheme 5.** *Reagents and conditions*: (a) HONB, DCC, THF/dioxane, 0°C, 40 min, rt, 24 h then **13**, $NaHCO_3$, dioxane/$H_2O$, rt, 20 h, 20% from **12**.

Coupling of **13** with carboxylic acid **7** was carried out using HONB and DCC to form the corresponding active ester of **7**, which was coupled with the sodium salt of **13** in a mixture of dioxane and water at room temperature (Scheme 5).[26] After treatment with Amberlite IR-120B ($H^+$ form), sulfobacin A (**1**) was obtained in 20% yield from **12**. Spectral data of **1**[27] were found to be in agreement with those reported,[2,5,6] $[\alpha]_D^{25}$ −15.5 (*c* 0.14, MeOH) {lit.[1] $[\alpha]_D^{24}$ −35 (*c* 0.14, MeOH), lit.[3] $[\alpha]_D^{20}$ −7.9 (*c* 0.18, MeOH), lit.[6] $[\alpha]_D^{25}$ −15 (*c* 0.14, MeOH)}.[28]

In summary, in spite of the moderate yield obtained in the final coupling reaction between compounds **7** and **13**, our route to sulfobacin A is a very short one and compares favorably with the other reported syntheses. The ruthenium-catalyzed asymmetric hydrogenation of β-keto ester **5** followed by diastereoselective electrophilic amination allowed the stereocontrolled construction of the three stereogenic centers. Preparation of analogs of sulfobacin A is currently underway in our laboratory and will be reported in due course.

## Acknowledgements

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22. Characteristic data for compound **11**: $R_f$ 0.29 (20% AcOEt in cyclohexane); $[\alpha]_D^{25}$ −6.5 (*c* 0.79, $CHCl_3$); IR $\nu_{max}$ ($CH_2Cl_2$): 3459, 2927, 2852, 1680 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, 50°C) $\delta$ = 4.05–3.95 (m, 2H), 3.81 (m, 1H), 3.65 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.49 (s, 9H), 1.60–1.15 and 1.25 (m and bs, 23H), 0.86 (d, 6H, *J* = 6.6 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ = 155.0, 92.5, 81.0, 75.6, 63.2, 61.1, 38.9, 29.8, 29.5, 28.8, 28.3, 27.8, 27.3, 26.8, 26.3, 24.4, 22.5; MS (CI, $NH_3$): *m*/*z* (%) 428 [$M^+$+1] (100); $C_{25}H_{49}NO_4$ (427.6) calcd C, 70.21; H, 11.55; N, 3.28; found C, 70.30; H, 11.57; N, 3.18.
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25. Characteristic data for compound **12**: $R_f$ 0.66 (20% AcOEt in cyclohexane); $[\alpha]_D^{25}$ +3.0 (*c* 1.11, $CHCl_3$); IR (film) 2925, 2854, 1702, 1455, 1379 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$), major conformer, $\delta$ = 4.12 (m, 1H), 4.00 (m, 1H), 3.19 (dd, 1H, *J* = 13.7 and 6.6 Hz), 3.06 (dd, 1H, *J* = 13.7 and 4.1 Hz), 2.33 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.48 (s, 9H), 1.39–1.03 and 1.25 (m and bs, 23H), 0.85 (d, 6H, *J* = 6.6 Hz); minor conformer, $\delta$ = 4.12 (m, 1H), 3.94 (m, 1H), 3.25 (dd, 1H, *J* = 13.5 and 6.3 Hz), 3.02 (dd, 1H, *J* = 13.5 and 5.5 Hz), 2.31 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.48 (s, 9H), 1.39–1.03 and 1.25 (m and bs, 23H), 0.85 (d, 6H, *J* = 6.6 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$), two conformers: $\delta$ = (195.0, 194.6), (152.3, 151.6), (92.9, 92.5), (80.2, 80.0), (58.5, 57.8), 39.0, 30.5, 30.1, 29.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.9, 28.7, 28.3, 27.9, 27.6, 27.4, 26.9, 26.8, 26.4, 24.6, 23.3, 22.6; MS (CI, $NH_3$): *m*/*z* (%) 486 [$M^+$+1] (100).
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27. Characteristic data for compound **1**: $R_f$ 0.22 (low layer of $CHCl_3$–MeOH–$H_2O$/65:25:10); $[\alpha]_D^{25}$ −15.5 (*c* 0.14, MeOH); IR $\nu_{max}$ (KBr) 3356, 2950, 2850, 1642, 1554, 1467, 1198, 1054 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta = 7.66$ (d, 1H, $J = 8.8$ Hz), 4.79 (d, 1H, $J = 5.6$ Hz); 4.68 (d, 1H, $J = 4.4$ Hz), 3.91 (m, 1H), 3.75 (m, 1H), 3.47 (m, 1H), 2.74 (dd, 1H, $J = 14.1$ and 6.7 Hz), 2.69 (dd, 1H, $J = 14.1$ and 4.3 Hz), 2.13 (dd, 1H, $J = 13.5$ and 6.7 Hz), 2.09 (dd, 1H, $J = 13.5$ and 5.5 Hz), 1.45 (m, 2H), 1.35 (m, 2H), 1.23 (m, 38H), 1.13 (m, 4H), 0.83 (d, 12H, $J = 6.6$ Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 170.4, 72.1, 67.8, 52.0, 51.3, 45.0, 38.7, 36.8, 33.5, 29.6, 29.5, 29.4, 29.3, 27.6, 27.0, 25.7, 25.4, 22.7.

28. As mentioned earlier by Mori[6] the specific rotation value of sulfobacin A seems to fluctuate depending on the concentration or the pH of the solution.