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An efficient total synthesis of sulfobacin A

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Abstract—A short and efficient enantioselective synthesis of sulfobacin A has been achieved using the Sharpless asymmetric dihydroxylation and the regiospecific nucleophilic opening of a cyclic sulfate as the key steps.

Sulfobacins A and B were isolated for the first time in 1995 by Kamiyama et al. from the culture broth of *Chryseobacterium* sp. NR 2993, a strain isolated from a soil sample collected on Iriomote Island (Fig. 1).[1] Almost simultaneously, Kobayashi and co-workers[2] isolated flavocristamide A and sulfobacin A from the cultured mycelium of *Flavobacterium* sp. These compounds are novel sulfonolipids and are unusual sphingosine derivatives. Biological studies of these compounds were revealed to inhibit the binding of von Willebrand factor to the GPIb/IX receptors in a competitive manner with IC_{50}'s of 0.47 μM for sulfobacin A and 2.2 μM for sulfobacin B, respectively. These compounds were also found to exhibit inhibitory activity against DNA polymerase α.

In the literature, the three different synthetic approaches reported so far for sulfobacin A involve either a chiral

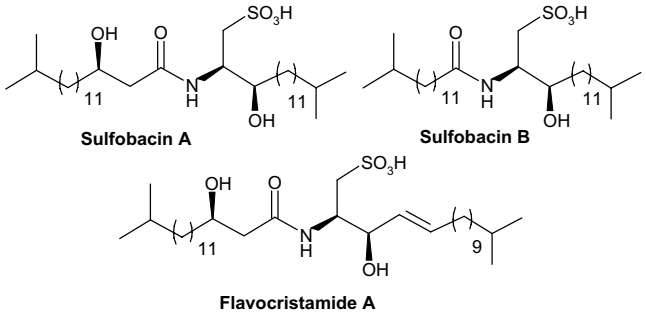

Figure 1.

building block or a chiral auxiliary to establish one or more of the stereogenic centres present in the molecule. The asymmetric aldol reaction of a Schiff's base derived from glycine ethyl ester and (+)-2-hydroxy-3-pinanone has been utilised as the key step by Shiori et al.[3] In another approach, the title compound was synthesised in a stereoselective manner using L-cysteine as a chiral building block.[4] Genet et al. have employed a ruthenium-catalysed asymmetric hydrogenation and diastereoselective electrophilic amination for the construction of the three stereogenic centres.[5]

As part of our ongoing research program aimed at developing enantioselective syntheses of naturally occurring lactones[6] and amino alcohols,[7] the Sharpless asymmetric dihydroxylation (AD) and subsequent trans- formation of diols formed via cyclic sulfites/sulfates were envisaged as powerful tools offering considerable opportunities for synthetic manipulation. Herein we report a new and highly enantioselective total synthesis of sulfobacin A employing the AD and the regioselective nucleophilic opening of a cyclic sulfate as the key steps.

Our synthetic approach for the synthesis of sulfobacin A was envisioned via the retrosynthetic route as shown in Scheme 1. The cyclic sulfate **6** was visualised as a common intermediate for the synthesis of both fragments **11** and **13**, which in turn could be obtained from the diol **5**. The diol **5** could be derived from olefin **4** through asymmetric dihydroxylation. The β-hydroxy acid **13** would be obtained by nucleophilic opening of cyclic sulfate **6** with hydride and subsequent hydrolysis, while **11** would be prepared by the nucleophilic opening of cyclic sulfate **6** with azide followed by a Mitsunobu reaction with thioacetic acid.

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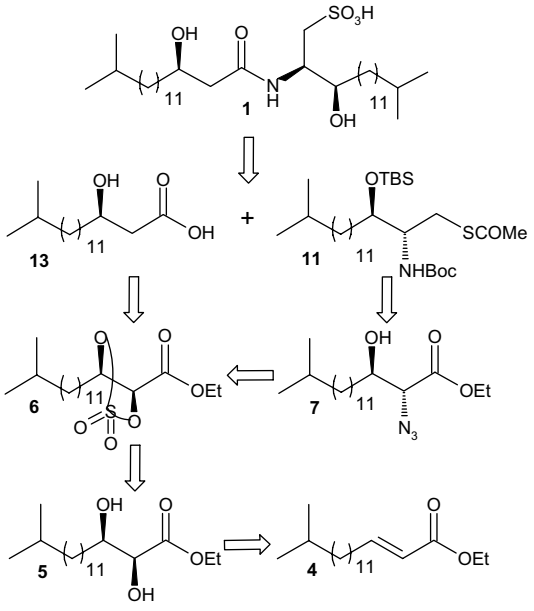
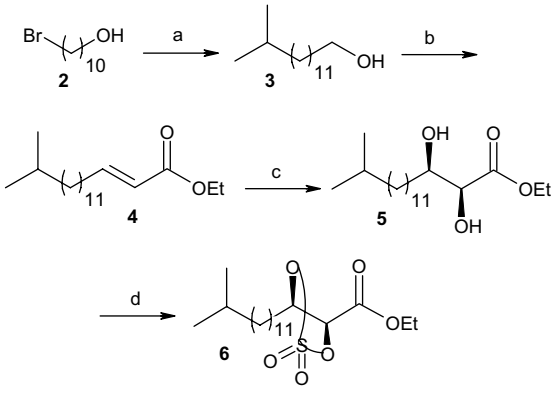
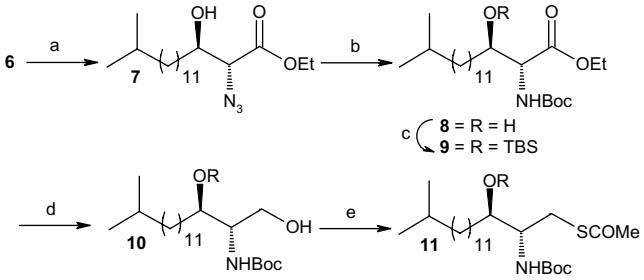


Scheme 1. Retrosynthetic route to sulfobacin A.

The synthesis of cyclic sulfate **6** commenced from 10-bromodecan-1-ol **2**, a commercially available material, as illustrated in Scheme 2. Thus treatment of **2** with isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate[4b] gave the alcohol **3** in excellent yield. Compound **3** was oxidised to the corresponding aldehyde under standard Swern conditions[8] followed by Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate to give the (*E*)-α,β-unsaturated ester **4** in 86% yield. The dihydroxylation of **4** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2$ PHAL ligand under the AD conditions[9] gave the diol **5**[10] in 95% yield with >96% ee; $[\alpha]_D^{25}$ +7.91 (*c* 1.34, $CHCl_3$). Treatment of diol **5** with thionyl chloride and triethylamine in CH_2Cl_2 gave the cyclic sulfite, which was further oxidised using



Scheme 2. Reagents and conditions: (a) $Me_2CH(CH_2)_2$ MgBr, Li_2CuCl_4 (1 mol%), THF, −78 °C to rt, 12 h, 94%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, (ii) $Et_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt, overnight, 86%; (c) $(DHQD)_2$PHAL (1 mol%), 0.1 M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 °C, 24 h, 95%; (d) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 20 min; (ii) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; 2:2:3, 0 °C, 2 h, 100%.



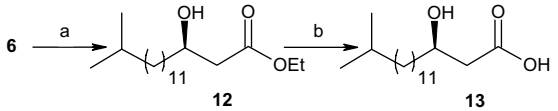
Scheme 3. Reagents and conditions: (a) NaN_3, H_2O–acetone (1:10), 1.5 h, then 20% aq H_2SO_4, Et_2O, 24 h, 92%; (b) $(Boc)_2O$, 10% Pd/C, H_2, EtOAc, 4 h, 98%; (c) TBSCl, imidazole, DMF, rt, 20 h, 98%; (d) $Ca(BH_4)_2$, THF, EtOH, −15 °C to rt, 20 h, 96%; (e) CH_3COSH, $^iPrOCON = NCO_2\,^iPr$, PPh_3, THF, 0 °C, 1 h, then rt, 16 h, 92%.

$NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **6**[11] in quantitative yield.

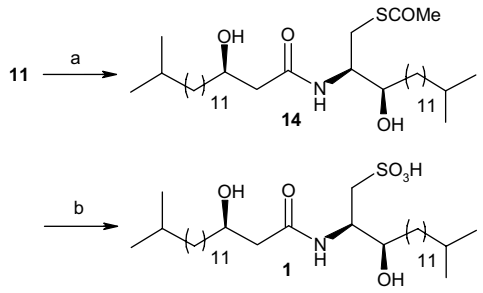
Scheme 3 summarises the synthesis of thioester **11** from **6**, a common intermediate for both fragments **11** and **13**. The essential feature of our strategy was based on the presumption that the nucleophilic opening of the cyclic sulfate **6** would occur in a regioselective manner at the α-carbon. Indeed the cyclic sulfate **6** on treatment with NaN_3 furnished the azido alcohol **7** with apparent complete selectivity for attack at the α-position. The carbonyl group must be responsible for the increased activity at the α-position.[12] Compound **7**[13] on hydrogenation in the presence of $(Boc)_2O$ gave the Boc protected amino alcohol **8** in essentially quantitative yield. The free hydroxyl group of **8** was protected with TBSCl to give **9**. Reduction of the ester group with calcium borohydride produced the alcohol **10** in excellent yield. Finally Mitsunobu reaction[14] of **10** with thioacetic acid afforded the desired thioester **11** in 92% yield.

For the synthesis of β-hydroxy acid **13**, the cyclic sulfate **6** was opened similarly with hydride in a regioselective manner to give the β-hydroxy ester[15] **12**, which on alkaline treatment furnished the corresponding β-hydroxy carboxylic acid **13** in excellent yield (Scheme 4).

After deprotection of Boc and TBS groups of **11** with hydrogen chloride in dioxane, the coupling of both the fragments **11** and **13** was smoothly achieved with diethyl phosphonocyanidate (DEPC). The thioacetate **14** thus obtained was subjected to pertrifluoroacetic acid oxidation to achieve the target molecule **1** in moderate yield (Scheme 5). The physical and spectroscopic data of **1** were in full agreement with the literature data.[1]



Scheme 4. Reagents and conditions: (a) $NaBH_4$, DMAC, 25 °C, 30 min, then 20% aq H_2SO_4, Et_2O, 12 h, 90%; (b) 1 N NaOH, MeOH, 0 °C, 30 min, then rt, 4 h, 90%.



Scheme 5. Reagents and conditions: (a) (i) 4 N HCl–dioxane, rt, 3 h, (ii) **13**, DEPC, Et_3N, DMF, −10 °C, 1 h, then rt, 20 h, 84%; (b) 30% aq H_2O_2, TFA, rt, 1 h, 30%.

In conclusion, an enantioselective synthesis of sulfobacin A has been realised for the first time using the Sharpless asymmetric dihydroxylation as the source of chirality. Thus the results described herein constitute a short, efficient and highly enantioselective route to sulfobacin A. The synthetic strategy described here has significant potential for further extension to the synthesis of other analogues. Currently studies are in progress in this direction.

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References and notes

1. (a) Kamiyama, T.; Umino, T.; Sawairi, S.; Shirane, M.; Ohshima, S.; Yokose, K. *J. Antibiot.* **1995**, *48*, 924–928; (b) Kamiyama, T.; Itezono, Y.; Nakamura, Y.; Satoh, T.; Yokose, K. *J. Antibiot.* **1995**, *48*, 929–936.
2. Kobayashi, J.; Mikami, S.; Shigemori, H.; Takao, T.; Shimonishi, Y.; Izuta, S.; Yoshida, S. *Tetrahedron* **1995**, *51*, 10487–10490.
3. (a) Irako, N.; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 5793–5796; (b) Shiori, T.; Irako, N. *Tetrahedron* **2000**, *56*, 9129–9142.
4. (a) Takikawa, H.; Muto, S.; Nozawa, D.; Kayo, A.; Mori, K. *Tetrahedron Lett.* **1998**, *39*, 6931–6934; (b) Takikawa, H.; Nozawa, D.; Kayo, A.; Muto, S.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2467–2477.
5. (a) Labeeuw, O.; Phansavath, P.; Genêt, J.-P. *Tetrahedron Lett.* **2003**, *44*, 6383–6386; (b) Labeeuw, O.; Phansavath, P.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2004**, *15*, 1899–1908.
6. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445–13450; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349–4356; (c) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921–2923; (d) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149–6151; (e) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849–851.
7. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447–3449; (b) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425–4426; (c) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309–10312; (d) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035–1037; (e) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957–1958; (f) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231–4232; (g) Kondekar, N. B.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5477–5479; (h) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877–5879.
8. For reviews on the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857–870; (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297–572.
9. (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448–451; (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (c) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, *61*, 3055–3060.
10. For the measurement of enantiomeric excess, the diol **5** was converted into its dibenzoate. The enantiomeric purity of the dibenzoate was estimated to be 96% by chiral HPLC analysis using Lichocart 250-4 (4 mmID × 25 cm) HPLC-Cartridge (R.R.-Whelk-01), 1% *i*-PrOH in hexane, 1 mL/min. Spectral data of compound **5**: white solid, mp 56 °C, $[\alpha]_D^{25}$ +7.91 (*c* 1.34, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3493, 3019, 2927, 2855, 2400, 1732, 1467, 1401, 1368, 1216, 1135, 1086, 1026 cm^{-1}: ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (d, J = 6.6 Hz, 6H), 1.17 (m, 2H), 1.26 (br s, 21H), 1.52 (m, 3H), 3.68 (m, 1H), 4.08 (m, 1H), 4.27 (q, J = 7.2 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.59, 73.25, 72.54, 61.74, 39.00, 33.57, 29.85, 29.57, 29.48, 27.86, 27.31, 25.67, 22.52, 14.04; Anal. Calcd for $C_{19}H_{38}O_4$ (330.50): C, 69.05; H, 11.59. Found: C, 69.28; H, 11.42.
11. For reviews on cyclic sulfites/cyclic sulfates, see: (a) Lohray, B. B. *Synthesis* **1992**, 1035–1052; (b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051–7091.
12. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, third ed.; Harper & Row: New York, 1987, p 321 and references cited therein.
13. Spectral data of compound **7**: light yellow oil, $[\alpha]_D^{25}$ +27.72 (*c* 1.24, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3469, 2926, 2855, 2111, 1736, 1466, 1370, 1216, 1038, 758, 668, 521 cm^{-1}: ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (d, J = 6.6 Hz, 6H), 1.14 (m, 2H), 1.26 (br s, 21H), 1.53 (m, 3H), 2.06 (br s, 1H), 2.20 (m, 1H), 3.95 (m, 1H), 4.32 (q, J = 7.04 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.89, 71.78, 66.16, 61.86, 52.96, 38.92, 32.85, 29.80, 29.51, 29.44, 29.29, 27.82, 27.27, 25.87, 25.28, 22.49, 14.00: Anal. Calcd for $C_{19}H_{37}N_3O_3$ (355.28): C, 64.19; H, 10.49; N, 11.82. Found: C, 64.31; H, 10.21; N, 11.64.
14. (a) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119–3122; For a review, see: (b) Mitsunobu, O. *Synthesis* **1981**, 1–28.
15. Gaw, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.