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An asymmetric synthesis of sulfobacin A

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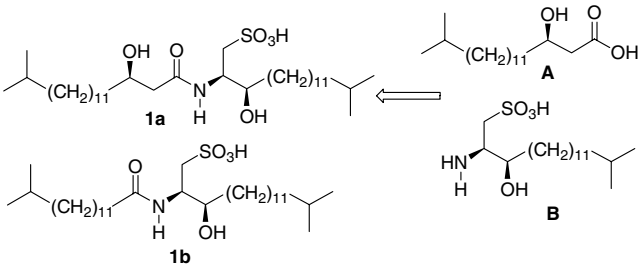
Abstract—A facile synthesis of sulfobacin A has been developed starting from (*R*)-cyclohexylideneglyceraldehyde (**11**). The key steps in the synthesis are the highly diastereocontrolled allylation of **11** and *syn*-selective reduction of a ketone derived from **11**. The other attractive features are the operational simplicity and the use of inexpensive compounds/reagents.

The development of simple and efficient strategies is a highly desirable goal for organic synthesis. Despite impressive progress,[1a] this remains a very dynamic and challenging area in asymmetric synthesis.[1b,c] The most practical methods are aimed at producing target compounds via reliable routes utilizing inexpensive and readily available materials. To this end, we have recently reported expeditious syntheses of various bioactive compounds such as prelactone B,[2a] herbarumin III,[2b] oxybutynin,[2c] safingol[2d] and hapalosin[2e,f], using easily accessible (*R*)-cyclohexylideneglyceraldehyde **11** as a chiral template. This Letter reports an efficient asymmetric synthesis of sulfobacin A starting from **11**.

Sulfobacins A and B (**1a** and **1b**) were isolated independently from the culture broth of the soil grown bacterium strain *Chryseobacterium* sp. NR 2933,[3a,b] while **1a** was also obtained from the marine bacterium *Flavobacterium* sp., isolated from the marine bivalve *Cristaria plicata*.[3c] Besides being potent DNA polymerase α inhibitors, **1a** and **1b** also show potent competitive inhibitory activity against the binding of von Willebrand factor to the GPIb/1X receptor with IC_{50} values of 0.47 μM and 2.2 μM, respectively. The compounds belong to the class of sulfonolipids having an aminosulfonic acid moiety, and are analogous to sphingosine. In view of their impressive bioactivity and unusual structures, several syntheses of sulfobacins A and B involving combinations of chemical/enzymatic asymmetric routes or chiral building blocks have been reported.[4]

The synthesis of **1a** essentially requires amidation of the chiral β-hydroxy acid **A** with amino alcohol **B**, both possessing the same long chain aliphatic moiety (Scheme 1). It was envisaged that fragment **A** could be constructed by allylation of **11**[2b] and introduction of the aliphatic chain at the acetal site. Given that amino alcohol **B** is an alkyl glycerol derivative, its synthesis from **11** also appeared straightforward. Thus, the total synthesis could be divided into the four parts discussed below.

For the syntheses of the long chain aliphatic synthons, the known ketone **3**[5] prepared from the commercially available inexpensive acid **2** was converted to ester **4** by a Wittig reaction with triphenylmethylphosphonium iodide (72%) followed by catalytic hydrogenation (∼quant.). Ester **4** was reduced with LAH to alcohol **5** (95%), which was brominated to furnish **6** (91%), the required synthon for the preparation of **A**. Likewise, C-alkylation of **7**,[6] accessible from **2**, with 2-bromopropane and subsequent depyranylation gave **8** (85% in two steps). Catalytic hydrogenation to **9** (∼quant.) followed by bromination afforded **10** (92%) (Scheme 2).



Scheme 1.

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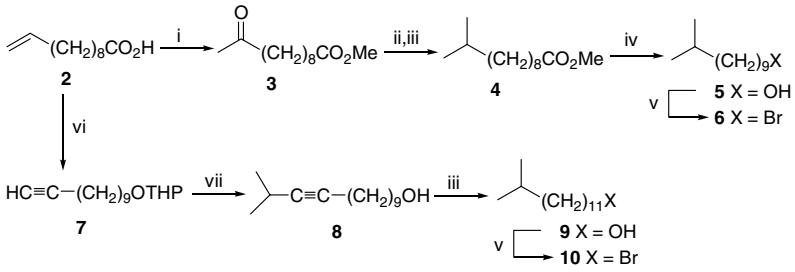
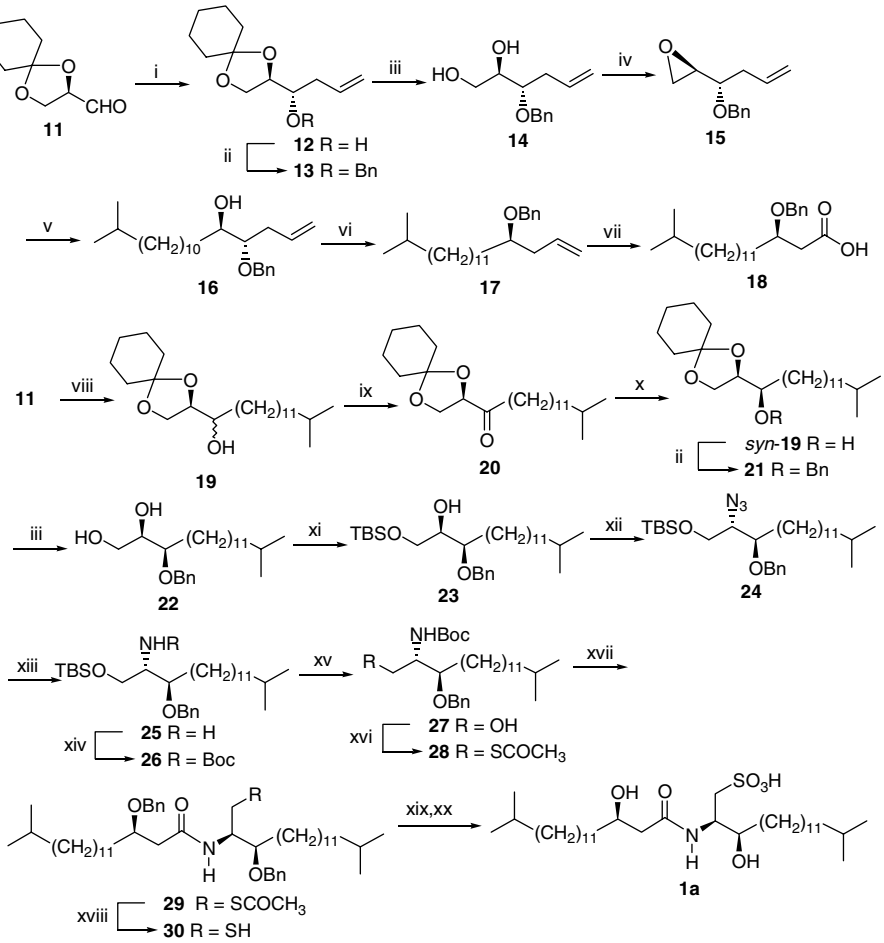


Scheme 2. Reagents and conditions: (i) Ref. 5, (ii) $MePPh_3I/n$-BuLi/THF/−20 °C (72%), (iii) H_2/10% Pd–C/EtOH/rt (∼quant.), (iv) LAH/Et_2O/Δ (95%), (v) Ph_3P/Br_2/pyridine/CH_2Cl_2 (91%), (vi) Ref. 6, (vii) n-BuLi/THF/HMPA/$(CH_3)_2CHBr$/−78 °C; MeOH/PTS/Δ (85%).

For the preparation of synthon **A**, homoallylic alcohol **12** obtained almost exclusively (91%, *syn*:*anti* = 3:97) by allylation[7] of aldehyde **11** was benzylated to give **13** (93%). Deacetalization with aqueous trifluoroacetic acid (TFA) gave diol **14** (72%), which was converted into epoxide **15** (86%) via regioselective monotosylation and base treatment. The Cu^+-catalyzed reaction of **15** with the Grignard reagent prepared from **6** proceeded smoothly to furnish **16** (84%). Mesylation of **16** followed by LAH reduction gave **17** (81%). This was converted to acid **18** (92%) by $NaIO_4/RuCl_3$-catalyzed oxidative cleavage[8] of the alkene function (see Scheme 3).

To prepare synthon **B**, the Grignard reagent prepared from **10** was reacted with **11** to give alcohol **19** with a predominance of the *anti*-isomer (81:19 *anti*:*syn*). Since



Scheme 3. Reagents and conditions: (i) Allyl bromide/Zn/aqueous NH_4Cl/0 °C (91%), (ii) NaH/BnBr/THF/Δ (93%), (iii) aqueous TFA/rt (72%), (iv) *p*-TsCl/pyridine; K_2CO_3/MeOH (86%), (v) **6**/Mg/THF/CuBr/−78 °C (84%), (vi) MsCl/pyridine/CH_2Cl_2/0 °C; LAH/Et_2O/Δ (81%), (vii) $NaIO_4/RuCl_3$,H_2O (cat.)/CCl_4–CH_3CN–H_2O (92%), (viii) **10**/Mg/THF/0 °C–rt (86%), (ix) PCC/NaOAc/CH_2Cl_2/rt (92%), (x) K-Selectride/THF/−78 °C (93%), (xi) TBSCl/triethylamine/4,4-dimethylaminopyridine/CH_2Cl_2/rt (91%), (xii) MsCl/pyridine/0 °C–rt; NaN_3/DMF/Δ (86%), (xiii) Ph_3P/MeOH/Δ (87%), (xiv) Boc_2O/triethylamine/4,4-dimethylaminopyridine/THF/rt (93%), (xv) TBAF/THF/−78 °C (97%), (xvi) MsCl/triethylamine/CH_2Cl_2; CH_3COSK/DMF/rt (89%), (xvii) aqueous HCl–dioxane; **18**/DCC/DMAP/TEA/DMF/−10 °C–rt (79%), (xviii) LAH/Et_2O/0 °C (80%), (xix) H_2/10% Pd-C/EtOH/rt (95%), (xx) 30% aqueous H_2O_2/TFA/rt (39%).

the *syn*-isomer was required for the synthesis, the diastereomeric mixture of **19** was oxidized with pyridinium chlorochromate (PCC, 92%) to afford ketone **20**. Reduction of **20** with K-Selectride proceeded with absolute diastereocontrol to afford pure *syn*-**19** in 93% yield.[9] Benzylation to **21** (95%) followed by TFA-catalyzed deacetalization gave diol **22** (81%). Regioselective silylation of the primary hydroxyl group gave **23** (91%), which on mesylation and subsequent azidation with inversion afforded **24** (86%).[9] Reduction of the azide function with Ph_3P gave amine **25** (87%), Boc-protection of which afforded **26** (93%). Desilylation with tetrabutylammonium fluoride (TBAF) furnished alcohol **27** (97%), which on mesylation and subsequent reaction with CH_3COSK afforded **28** (89%).

Synthesis of the target compound **1a** was achieved as follows. N-deprotection of **28** followed by a dicyclohexyl carbodiimide (DCC)-catalyzed condensation with **18** gave amide **29** (79%). This was converted to thiol **30** (80%) by reduction with LAH at low temperature. This on debenzylation (95%) by catalytic hydrogenation followed by oxidation with H_2O_2–TFA led to the target compound **1a** in 39% yield.

In conclusion, an efficient asymmetric synthesis of sulfobacin A has been developed from easily available (*R*)-cyclohexylideneglyceraldehyde using a set of diastereoselective transformations.

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7. Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104, The *syn*- and *anti*-isomers of **12** could be easily separated by normal chromatography (silica gel, 0–15% EtOAc/hexane).
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9. All the compounds were fully characterized from their spectral, optical and microanalytical data. Representative data is included. Data for *syn*-**19**: colourless oil; $[\alpha]_D^{25}$ +12.4 (*c* 0.9, $CHCl_3$); IR: 3456, 1478, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.85 (d, $J = 6.8$ Hz, 6H), 1.23 (s, 17H), 1.26–1.50 (m, 8H), 1.58–1.62 (m, 8H), 2.23 (br s, 1H), 3.45–3.49 (m, 1H), 3.58–3.75 (m, 1H), 3.90–4.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.4, 23.5, 23.7, 23.8, 24.9, 25.3, 27.2, 27.7, 29.4, 29.7, 33.5, 34.6, 36.1, 38.8, 65.6, 72.2, 78.6, 109.6. Anal. Calcd for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03. Found: C, 75.12; H 12.12. Data for **24**: colourless oil; $[\alpha]_D^{25}$ +8.2 (*c* 1.22, $CHCl_3$); IR: 3065, 3031, 2096 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.08 (s, 6H), 0.86 (d, $J = 6.8$ Hz, 6H), 0.91 (s, 9H), 1.26 (s, 18H), 1.43–1.58 (m, 5H), 3.48–3.55 (m, 2H), 3.71–3.77 (m, 2H), 4.53 (d, $J = 11.4$ Hz, 1H), 4.61 (d, $J = 11.4$ Hz, 1H), 7.25–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.5, 18.2, 22.7, 25.1, 25.3, 25.8, 27.4, 28.0, 29.7, 30.0, 30.8, 39.1, 63.3, 65.4, 72.4, 78.0, 127.7, 127.9, 128.4, 138.2. Anal. Calcd for $C_{30}H_{55}N_3O_2Si$: C, 69.58; H, 10.70; N, 8.11. Found: C, 69.48; H, 10.84; N, 8.27.