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Total Synthesis of the α-Glucosidase Inhibitors Schulzeine A, B, and C and a Structural Revision of Schulzeine A

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Since the isolation of deoxynojirimycin in 1976,[1] glycosidase inhibitors have become the subject of intense scrutiny because of their profound effect on glycoprotein processing, oligosaccharide metabolism, and cell−cell and cell−virus recognition processes.[2] The schulzeines (**1**−**3**), a new class of marine alkaloids isolated by Fusetani and co-workers from extracts of the marine sponge Penares schulzei, display potent (IC_{50} = 48−170 nM) α-glucosidase-inhibitory activity (Figure 1).[3] While these compounds, which are comprised of a benzo[*a*]quinolizidine core with a trisulfated C_{28} amide side chain, bear little apparent resemblance to the more familiar iminosugar family of inhibitors, they are structurally related to other glucosidase inhibitors, including penasulfate[4] and the penarolides,[5] which similarly are *O*-sulfated fatty acids derivatives. The structure of **1**−**3** was elucidated by Fusetani, through a combination of spectral analysis and chemical degradation, while their absolute configuration was determined by modified Mosher analysis of the fragments obtained upon acidic hydrolysis of the lipid side chains. Herein we describe the enantioselective total synthesis of schulzeine A, B, and C, together with a revision of the previously proposed stereochemistry at the C20′ position of schulzeine A.[6]

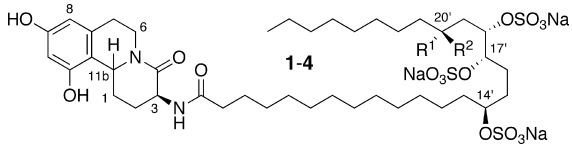
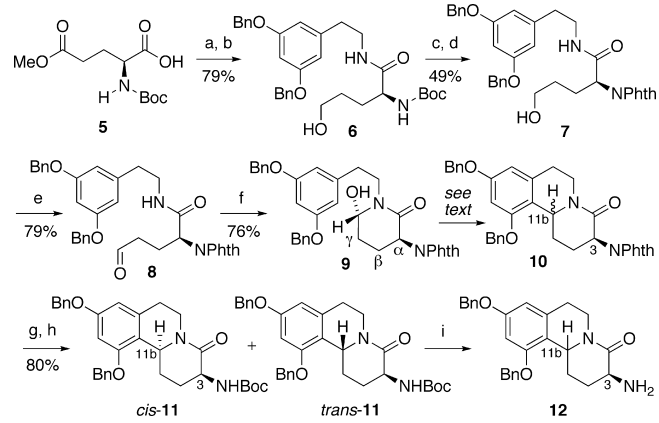


Figure 1. (+)-Schulzeine A (*revised structure*) (**1**; C11b-H_β; R^1 = Me R^2 = H); (−)-schulzeine B (**2**; C11b-H_α; R^1, R^2 = H); (+)-schulzeine C (**3**; C11b-H_β; R^1, R^2 = H); (+)-schulzeine A (*proposed structure*) (**4**; C11b-H_β; R^1 = H; R^2 = Me).

From a strategic standpoint, we envisioned that both the *trans*- and *cis*-3-aminobenzo[*a*]quinolizidine subunits present in schulzeines A and C, and B, respectively, could be constructed from L-glutamate derivative **8**, through a Pictet−Spengler-type cyclocondensation (Scheme 1). Although Lee[7] and others[8] have demonstrated that γ- and β-substituents in hydroxy lactams related to **9** can affect varying degrees of stereocontrol at the C11b ring junction, it was unclear at the outset of this study whether efficient 1,4-asymmetric induction could be achieved during the cyclization of the *N*-acyliminium ion generated from **8**.[6,9]

Our route to the schulzeines commenced from L-glutamic acid γ-methyl ester **5**,[10] which was coupled with 2-[3,5-bis(benzyloxy)phenyl]ethylamine,[11] via the mixed anhydride (Scheme 1). Chemoselective reduction of the methyl ester, using lithium chloride−sodium borohydride,[12] then proceeded smoothly to provide primary alcohol **6** as a single enantiomer.[13] Unanticipated interference of the *N*-Boc group during the subsequent Pictet−Spengler reaction now mandated the exchange of this carbamate for a more robust *N*-phthalimide group. This was accomplished by treatment of **6** with ethereal HCl and *N*-phthaloylation of the resulting primary amine with *N*-(ethoxycarbonyl)phthalimide.[14] Oxidation of alcohol **7**, under Swern conditions,[15] provided unstable aldehyde **8**, which, upon exposure to acetic acid, underwent cyclization to form hydroxy lactam **9**.[7b] Gratifyingly, exposure of either **8** or **9** to a range of Pictet−Spengler promoters, including $BF_3 \cdot Et_2O$, acetic acid, or trifluoroacetic acid, lead to the selective formation of *cis*-**10** with *cis*/*trans* selectivity ranging from 2:1 (**8**, TFA−CH_2Cl_2, −78 °C, 93%) to 9:1 (**9**, AcOH−$CHCl_3$, reflux, 72%). While *cis*- and *trans*-**10** proved to be inseparable by chromatography, diastereomer separation could be achieved after hydrazinolysis of the phthalimide group and formation of carbamates *cis*-**11** and *trans*-**11**.[16] Treatment of each diastereomer with TFA then afforded *trans*- and *cis*-**12**, the benzo[*a*]quinolizidine subunits required for the synthesis of schulzeines A and C and schulzeine B, respectively.[17]

Scheme 1. Synthesis of the Benzo[*a*]quinolizidine Subunit[a]



[a] Conditions: (a) *i*-BuOCOCl, NMM, CH_2Cl_2, −35 °C, 15 min, then 2-[3,5-bis(benzyloxy)phenyl]ethylamine, DMF, CH_2Cl_2, rt, 12 h; (b) $NaBH_4$, LiCl, THF, MeOH, 0 °C, 5.5 h; (c) HCl−Et_2O, CH_2Cl_2, rt, 2 h; (d) $PhthCO_2Et$, Na_2CO_3, THF, rt, 16 h; (e) Swern oxidation; (f) AcOH, CH_2Cl_2, rt, 2 h; (g) H_2NNH_2, EtOH, rt, 24 h; (h) $Boc_2(O)$, CH_2Cl_2, rt, 1 h, *cis*-**11** (57%), *trans*-**11** (26%); (i) TFA, CH_2Cl_2, 0 °C, 1 h *cis*-**12** (C11b-H_α, 98%), *trans*-**12** (C11b-H_β, 85%)

Construction of the proposed C_{28} trisulfate side chain of **1** began from hydroxy ester **13**,[18] which was converted to the corresponding aldehyde via Swern oxidation.[15] The C14 stereocenter was then introduced by asymmetric allylation under Keck's conditions,[19] which afforded **14** in high enantiomeric excess (>98% ee).[13] After silylation of the hydroxyl group, a sequence of hydroboration−oxidation, Mitsunobu reaction of the primary alcohol with 1-phenyl-1*H*-tetrazole-5-thiol, and S-atom oxidation provided sulfone **15** in excellent overall yield. Assembly of the complete lipid subunit was now accomplished using the Julia−Kocienski protocol.[20] Thus, selective deprotonation of **15** with KHMDS followed by treatment of the sulfone anion with (*S*)-3-methylundecanal furnished *E*-alkene

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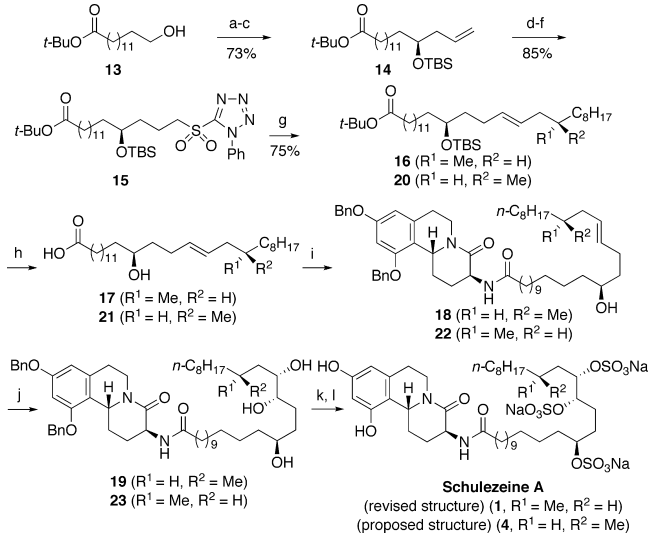
16 with high diastereoselectivity, albeit in moderate yield. Treatment of **16** with HF−TBAF and then aqueous NaOH resulted in the sequential deprotection of the *O*-TBS ether and *tert*-butyl ester. Carboxylic acid **17** was then coupled with *trans*-**12** using EDC to afford compound **18**. Sharpless asymmetric dihydroxylation in the presence of the $(DHQ)_2PHAL$ ligand[21] then provided 1,4,5-triol **19** as a 4:1 mixture of diastereomers.

Persulfation of **19** was accomplished by treatment with excess sulfur trioxide−pyridine complex in DMF for 2 h.[22] Purification of the resulting trisulfate by reversed phase chromatography and hydrogenolysis of the benzyl ethers now provided *epi*-C20′-schulzeine A (**4**). Unfortunately, the ^1H and ^{13}C NMR spectra of this material, although similar to the natural product, were not identical.[3] That these discrepancies were restricted to those resonances from and near the C20′ stereocenter of the lipid side chain prompted us to the postulate that the original stereochemical assignment at this position should be reevaluated.

In light of these findings, we undertook the synthesis of compound **1**, the C20′ diastereomer of **4** (Scheme 2). Returning to the Julia−Kocienski olefination, the six-step sequence to the target was now repeated using sulfone **15** and (*R*)-3-methyl-undecanal, in place of the (*S*)-enantiomer, to provide schulzeine A (**1**). Gratifyingly, the ^1H and ^{13}C NMR spectra of **1** were found to be consistent with those reported by Fusetani for the natural product,[3] thus supporting our earlier premise that the stereochemistry at C20′ should be reassigned as the *R*-configuration.

Following the same strategy employed in the assembly of **1**, the total synthesis of schulzeines B (**2**) and C (**3**) was also completed.[23] In the case of target **2**, the use of *cis*-**12**, the 3-aminobenzo[*a*]quinolizidine derived from compound *cis*-**11**, was mandated. Notably, the ^1H and ^{13}C NMR spectra of synthetic **2** and **3** closely matched the data reported for the natural products.

Scheme 2. Total Synthesis of Schulzeine A (**1**)[a]



[a] Conditions: (a) Moffat−Swern oxidation; (b) (*R*)-(+)-1,1′-bi-2-napthol (10 mol%), Ti(O-*i*-Pr)$_4$, 4 Å m.s., CH_2Cl_2, reflux 1 h; then −78 °C, allyltri-*n*-butylstannane, −20 °C, 5 d; (c) TBSCl, imd, CH_2Cl_2, 0 °C→rt, 18 h; (d) 9-BBN, THF, 0 °C→rt, 14 h, then H_2O_2, NaOH, $B(OH)_3$, rt °C, 1 h; (e) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, Ph_3P, THF, 0 °C→rt, 12 h; (f) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (20 mol%), H_2O_2, EtOH, 0 °C→rt, 14 h; (g) KHMDS, DME, −60 °C, 30 min, then (*S*)-3-methylundecanal, −60 °C→rt, 16 h, **16**, 45%; KHMDS, DME, −60 °C, 30 min, then (*R*)-3-methylundecanal, −60 °C→rt, 16 h, **20**, 75%, d.r. > 20:1; (h) HF, TBAF, THF, rt, 48 h; NaOH (1 M), EtOH, THF, reflux, 48 h, **17**, 70%; **21**, 84%; (i) EDC, CH_2Cl_2, rt, 16 h, **18**, 73%; **22**, 80%; (j) AD-mix α, $MeSO_2NH_2$, *t*-BuOH−*t*-BuOMe−H_2O−THF, 0 °C (1:1:1:1), 18 h, **19**, 83%, d.r. = 4:1; AD-mix α, $MeSO_2NH_2$, *t*-BuOH−*t*-BuOMe−H_2O (1:1:1), 0 °C, 48 h, **23**, 77%, dr = 91:9; (k) SO_3-pyr, DMF, rt, 2 h; (l) H_2, Pd/C, EtOH, rt, 8 h, **4**, 88% (two steps); **1**, 75% (two steps).

In summary, the total asymmetric synthesis of the α-glucosidase inhibitors schulzeine A, B, and C has been completed, and the absolute configuration of the C20′ stereocenter of schulzeine A has been reassigned. In addition to providing material for further biological evaluation, our findings serve to reaffirm the key role that total synthesis plays in establishing the actual structure of promising natural products.

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Note Added after ASAP Publication. Reference 6b was added April 10, 2009.

Supporting Information Available: Experimental details and spectroscopic data. This material is free of charge via the Internet at http://pubs.acs.org.

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(16) Since epimerization at the C(3) center of *cis*-**11**, under basic conditions (MeONa, MeOH, reflux), generates a 1.5:1 mixture of *cis* and *trans* isomers, which can be separated and recycled, *trans*-**11** is available with greater selectivity from the D-enantiomer of **5**, by way of *ent-cis*-**10**.
(17) Assignment of relative stereochemistry to *cis*- and *trans*-**10** was achieved through NOESY experiments; a clear cross-peak between C11b-H and C3-H was observed in *cis*-**10** but not in the *trans* isomer. Further confirmation of this assignment was secured by conversion of *cis*- and *trans*-**11** to their respective (*R*)- and (*S*)-MTPA amide derivatives, which were prepared by Fusetani as part of a degradation study of **1**−**3**: see ref 3. For a tabular comparison of the spectral properties of these Mosher amides, see Supporting Information.
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(23) For full details concerning of the total synthesis of schulzeine B (**2**) and C (**3**), see Supporting Information.

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