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Enantioselective Synthesis of Schulzeines B and C via a β-Lactone-Derived Surrogate for Bishomoserine Aldehyde

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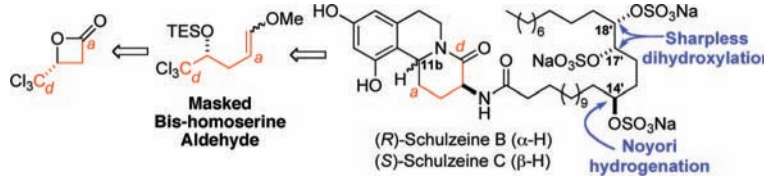
ABSTRACT



Enantioselective syntheses of the glucosidase inhibitors schulzeines B and C were achieved by employing a Pictet−Spengler reaction of a β-lactone-derived, masked bishomoserine aldehyde. Subsequent Corey−Link reaction unveiled an α-azido acid enabling cyclization to the δ-lactam fused tetrahydroisoquinoline. An efficient synthesis of the trisulfate-bearing side chain featured a Noyori hydrogenation and a Sharpless dihydroxylation. An unexpected reaction of a pendant amine during a Corey−Link process opens avenues for the synthesis of proline and related amino acid derivatives.

Schulzeines B and C (**1**/**1′**) are potent α-glucosidase inhibitors (IC_{50} 48−170 nM) and viral neuraminidase inhibitors (IC_{50} 60 μM) recently isolated by Fusetani and co-workers from the marine sponge *Penares schulzei*.[1] The structure of these marine alkaloids was determined by chemical degradation and extensive NMR analysis, while the absolute configuration was based on Mosher ester analysis of fragments from chemical degradation of the natural product.[1] The intriguing bioactivity combined with the unique structure of schulzeines aroused several synthetic efforts toward these targets.[2] Notably, all of the reported syntheses of the tricyclic isoquinoline core began with glutamic acid derivatives. Our interest in the schulzeines was sparked by their biological activity including their potential as antidiabetic agents[3] and an interest in exploiting the versatility of β-lactones and in particular the commercially available, optically active trichloromethyl-β-lactone **8**,[4] which we previously demonstrated serves as a useful masked α-azido acid via the Corey−Link process.[5]

Our synthetic strategy toward schulzeines B and C (**1**/**1′**) entailed a late stage trisulfation following amide coupling of the δ-lactam-fused tetrahydroisoquinolines **2**/**2′** and the 28-carbon side chain **3** (Figure 1). The δ-lactam would be derived from cyclization of α-azido acids derived from trichloromethyl carbinols **4**/**4′** via the Corey−Link modified Jocic reaction.[6] The diastereomeric tetrahydroisoquinolines **4**/**4′** would be formed

(1) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; Van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187.

(2) (a) Kuntiyong, P.; Akkarasamiyo, S.; Eksinitkun, G. *Chem. Lett.* **2006**, *35*, 1008. (b) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K. *J. Org. Chem.* **2007**, *72*, 6591. (c) Wardrop, D. J.; Bowen, E. G. *Abstracts of Papers*, 233rd ACS National Meeting, Chicago, March 25−29, 2007.

(3) For a review of glycosidase inhibitors, see: Jung, M.; Park, M.; Lee, H. C.; Kang, Y.-H.; Kang, E. S.; Kim, S. K. *Curr. Med. Chem.* **2006**, *13*, 1203.

(4) This δ-lactone available from Aldrich ($104/25 g, 99% ee, 2008) is prepared by the method of Wynberg. See: (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166. For preparation using in situ ketene generation, see: (b) Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248.

(5) Tennyson, R.; Cortez, G. C.; Galicia, H. J.; Kreiman, C. R.; Thompson, C. M.; Romo, D. *Org. Lett.* **2002**, *4*, 533.

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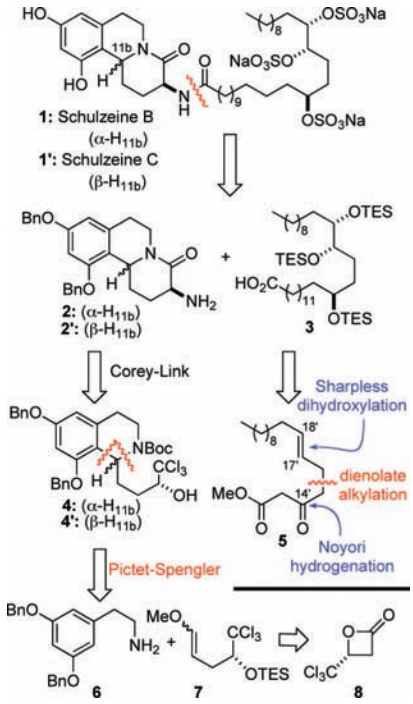
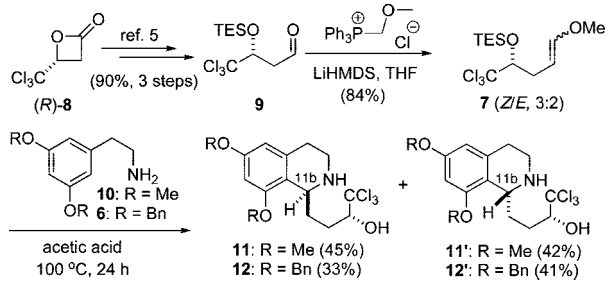


Figure 1. Retrosynthetic analysis of schulzeines B and C.

via an expected nondiastereoselective Pictet−Spengler condensation of aryl amine **6** and the masked α-amino acid aldehyde **7** ultimately derived from (*R*)-trichloromethyl-*β*-lactone **8**. Access to both diastereomers was desirable as it would enable synthesis of diastereomeric schulzeines B and C.[1] The three alcohol-bearing stereocenters would be introduced via sequential Noyori hydrogenation and a reagent-controlled Sharpless asymmetric dihydroxylation of *β*-ketoester **5** derived from methylacetoacetate dienolate alkylation.

Synthesis of the tetrahydroisoquinoline core began with conversion of commercially available *β*-lactone **8** to the vinyl ether **7** which serves as a masked aldehyde/α-amino acid for the Pictet−Spengler reaction (Scheme 1). One-carbon,

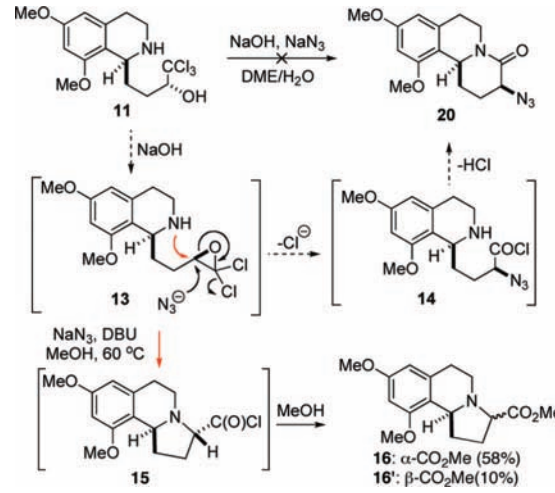
Scheme 1. Synthesis of the Masked Bishomoserine Aldehdye Tetrahydroisoquinolines **11/12**



Wittig homologation of the known aldehyde **9**,[5] gave vinyl ether **7** as an inconsequential 3:2 mixture of *E*/*Z* olefin isomers. In our initial studies of the Pictet−Spengler process, we employed the commercially available dimethyl catechol amine **10** to identify suitable Pictet−Spengler conditions. While several acids in aprotic solvents were unsuccessful (e.g., AcOH or TFA in CH_2Cl_2 or $CHCl_3$), the Pictet−Spengler process including in situ hydrolysis of the vinyl ether **7** was possible in glacial acetic acid with heating to give the tetrahydroisoquinolines **11**/**11′** in excellent yield and as a ∼1:1 mixture of diastereomers by ^{1}H NMR of the crude product. The diastereomers were readily separated by flash column chromatography and could be carried on separately in subsequent transformations.

In our initial strategy, we envisoned a one-pot conversion of the trichloromethyl carbinol to the *δ*-lactam **20** (Scheme 2). While several substrates have been utilized in the

Scheme 2. Attempted One-Pot Strategy to the Tricyclic Core Leading to a Proline Derivative Synthesis



Corey−Link process, amine-containing substrates have rarely been studied. Treatment of the trichloromethylcarbinol **11** was expected to provide dichlorooxirane intermediate **13** as previously proposed for this process,[6c] which upon epoxide cleavage by azide with inversion would provide acid chloride **14** that could be trapped by the pendant piperidine nitrogen to provide *δ*-lactam **20**. However, despite extensive experimentation, this strategy was unsuccessful.[7]

Under one set of conditions employing DBU as base, pyrrolidines **16**/**16′** were isolated as a ∼6:1 mixture of separable diastereomers (68%, combined yield). These products presumably arise from attack of the piperidine

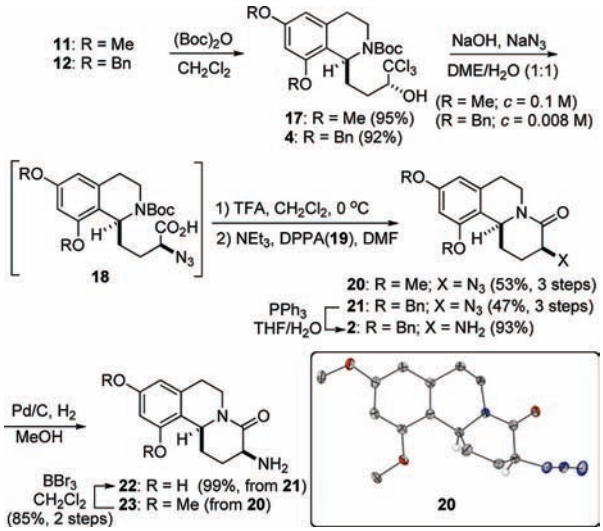
(6) (a) Jocic, Z. *Z. Zh. Russ. Fiz. Khim. Ova.* **1897**, *29*, 97. (b) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906 For mechanistic studies of the Jocic reaction, see: (c) Reeve, W.; Wood, C. W. *Can. J. Chem.* **1980**, *58*, 485 For recent applications of Jocic-type reactions, see: (d) Shamshina, J. L.; Snowden, T. S. *Org. Lett.* **2006**, *8*, 5881.

(7) Solubility issues with the N-unprotected isoquinoline **11** under typical Corey−Link conditions (0.1 M, H_2O/DME) which only gave recovered starting material led us to study high dilution conditions (0.008 M). However, this gave multiple polar products which were not readily identified. IR analysis of the crude reaction mixture showed no azide-containing products. Other unsuccessful conditions studied include nonprotic solvents (THF, DMF) with strong bases (NaH, NaHMDS, KO^{t}Bu) which mainly led to recovered starting material.

nitrogen onto the intermediate dichloroepoxide **13** as shown (Scheme 2). In the presence of MeOH, the methyl ester is generated from the presumed acid chloride intermediate **15**. This unexpected intramolecular capture of the presumed dichloroepoxide **13** with the pendant amine suggests a potential new strategy for the synthesis of proline, pipecolinic acid, and other cyclic amino acid derivatives.

To avoid the observed premature cyclization, the amine **11** was protected as the corresponding *t*-butyl carbamate (Boc) and then subjected to standard Corey−Link conditions which now proceeded smoothly to give the α-azido acid **17** (R = Me; Scheme 3). Direct Boc deprotection and cycliza-

Scheme 3. Synthesis of Core Structures **20**/**21** from a Dimethyl and a Dibenzyl Catechol Substrate (Inset: ORTEP of Azide **20**)



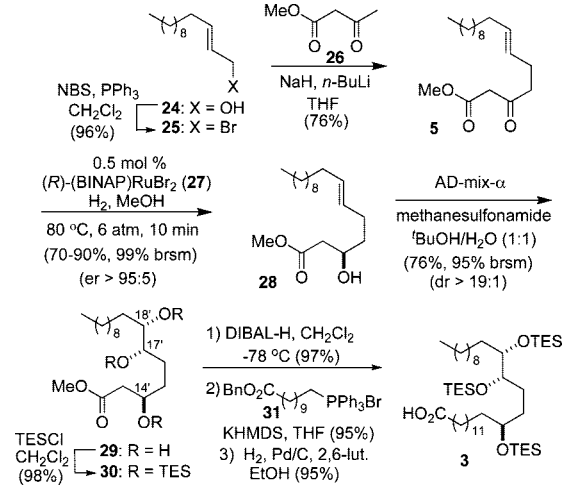
tion to the δ-lactam with diphenylphosphoryl azide (DPPA)[8] in DMF gave the azido tricycle **20**, and the relative stereochemistry of this intermediate was confirmed by X-ray crystallography (inset, Scheme 3). Following azide reduction and demethylation of the protected catechol, the known amino tricycle **22** was obtained, and all spectroscopic data matched those previously reported for the same compound derived from schulzeine degradation.[1]

In a second-generation strategy to the isoquinoline core with an eye toward simplifying final deprotection of the catechol, we employed a dibenzyl-protected catechol **6** in the Pictet−Spengler reaction to enable a late stage hydrogenation (Scheme 1). The required phenethyl amine **6** was prepared by reduction of a known cyanide precursor using a slight modification of a literature procedure.[9,10] Pictet−Spengler condensation of vinyl ether **7** and β-aryl amine **6** gave the tetrahydroisoquinolines **12**/**12′** (dr ∼1:1) which were readily separable and could be processed separately to schulzeines B and C.

Following the same process developed in the dimethyl series, amine protection of trichloromethyl carbinol **12** was followed by subjection of Boc-protected isoquinoline **4** to the previously employed Corey−Link conditions (Scheme 3). However, with this dibenzyl substrate, no reaction was observed under these reaction conditions. We reasoned that this was likely due to a solubility issue of this more hydrophobic substrate in the DME/H_2O reaction medium. Thus, the concentration of reagents (NaOH/NaN_3) was maintained (0.4 M/0.2 M), while substrate concentration was significantly lowered (0.008 M). Under these conditions, the Corey−Link reaction proceeded efficiently to give the desired azido acid **18** (R = Bn) which was directly transformed to the tricyclic structure **21** by Boc deprotection and lactamization. Hydrogenolysis of the benzyl ethers with concomitant reduction of the azide enabled correlation to the previously prepared amino catechol **22** and confirmed relative and absolute stereochemistry identical to the previous sequence. Selective azide reduction of tricycle **21** with PPh_3 gave the primary amine **2** readied for coupling to the side chain.

The synthesis of the side chain began with alkylation of the dienolate of methylacetoacetate with allyl bromide **25** prepared by bromination of the commercially available allylic alcohol **24** (Scheme 4). The derived β-ketoester **5** was

Scheme 4. Synthesis of the Side Chain Carboxylic Acid **3**



subjected to Noyori hydrogenation[11] to give optically active β-hydroxy ester in good yield and excellent enantioselectivity (er > 95:5, Mosher ester[10,12]). To avoid reduction of the olefin, the hydrogenation was terminated prior to reaching completion, and the starting material was readily separated and recycled. The C17′, C18′ diol was then introduced via

(8) Qian, L.; Sun, Z.; Deffo, T.; Mertes, K. B. *Tetrahedron Lett.* **1990**, *31*, 6469.

(9) The addition of 1 equiv of sulfuric acid to the $LiAlH_4$ reduction led to greatly improved yields versus $LiAlH_4$. See: Brown, H. C; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.

(10) See Supporting Information for details.

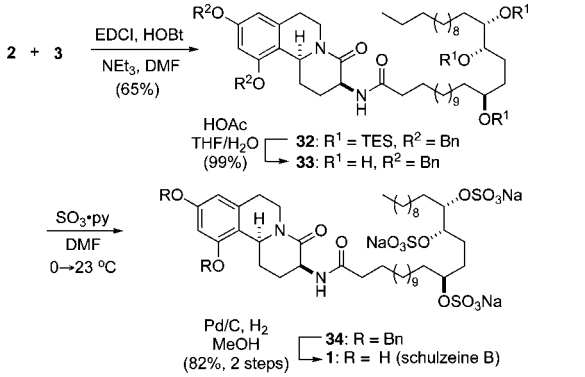
(11) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

reagent-controlled Sharpless dihydroxylation in excellent yield and diastereoselectivity (>19:1 dr, ^{1}H NMR). To confirm the relative stereochemistry, the triol **29** was peracylated with *p*-bromobenzoyl chloride to give a crystalline tribenzoate (not shown)[10] enabling confirmation of the relative and absolute stereochemistry by X-ray crystallographic analysis to be as shown based on heavy atom (Br) anomalous dispersion. Protection of the triol ester **29** as the corresponding tris-triethylsilyl ether **30** and half-reduction gave an intermediate aldehyde that was directly subjected to olefination with the Wittig reagent derived from phosphonium salt **31**. Simultaneous alkene hydrogenation and benzyl hydrogenolysis in the presence of 2,6-lutidine, to avoid TES deprotection, gave the carboxylic acid side chain **3**.

Under typical carbodiimide coupling conditions, the carboxylic acid side chain **3** and the amino tetrahydroisoquinoline core **2** were joined to give amide **32** (Scheme 5).

Scheme 5. Completion of the Synthesis of Schulzeine B



Cleavage of the TES ethers under mild acidic conditions gave triol **33** which was subjected to sulfation with the SO_3•pyridine complex[13] to provide the trisulfate **34**. This material was of sufficient purity following rapid purification through silica gel to carry on to the final step. Hydrogenolysis of the benzyl groups and filtration to remove the Pd catalyst led to schulzeine B (**1**) of high purity that was identical in all respects to the natural product including optical rotation (lit. $[\alpha]_D^{22}$ −23 (*c* 0.1, MeOH);[1] syn. $[\alpha]_D^{23}$ −23.5 (*c* 0.68, MeOH). Following the same sequence, schulzeine C (**1′**, not shown)[10] was also synthesized from the diastereomeric core structure **12′**, and data for the synthetic material matched those previously reported for the diastereomeric natural product including optical rotation (lit. $[\alpha]_D^{22}$ +33 (*c* 0.1, MeOH);[1] syn. $[\alpha]_D^{23}$ +38.0 (*c* 0.42, MeOH).

In summary, we have accomplished the total synthesis of the naturally occurring, α-glucosidase inhibitors schulzeines B and C in a highly convergent manner employing a masked, α-amino acid aldehyde synthon derived from a *β*-lactone. Key features of the synthesis include a tetrahydroisoquinoline synthesis via a Pictet−Spengler reaction of a masked bishomoserine aldehyde, a Corey−Link process to unmask the α-amino acid, and a highly efficient synthesis of the required optically active, sulfated triol side chain employing a Noyori hydrogenation and Sharpless dihydroxylation sequence. An unexpected pyrrolidine product was obtained under modified Corey−Link conditions with a substrate bearing a pendant amine and suggests the possiblity of capturing the dichloroepoxide intermediate by other tethered nucleophiles leading to proline and other amino acid derivatives. This synthesis further demonstrates the utility of *β*-lactones as intermediates in natural product total synthesis, and in particular application of the readily available trichloromethyl *β*-lactone **8** which, in this instance, leads to a versatile masked surrogate for bishomoserine aldehyde.

Acknowledgment. We thank the Welch Foundation (A-1208) for generous support of this work. We thank Dr. Nattamai Bhuvanesh (TAMU) for obtaining X-ray crystallographic data for azide **20** and the tribenzoate ester derived from triol **29**.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**7**, **9**, **11**, **12**, **16**, **17**, **20**−**22**, **25**, **28**−**30**, **32**−**33** (and the diastereomeric series leading to schulzeine C), X-ray crystallographic data including cif files for tricyclic azides **20** and **20′**, and the tribenzoate derived from triol **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802992M

(13) For a lead reference to sulfation methods, see: Simpson, L. S.; Widlanski, T. S. *J. Am. Chem. Soc.* **2006**, *128*, 1605.