Short Synthetic Route toward the Tricyclic Core of Schulzeines

Punlop Kuntiyong,* Sunisa Akkarasamiyo, and Gedsirin Eksinitkun
Department of Chemistry, Faculty of Science, Silpakorn University, Rajamanka Nai Rd., Muang Nakhon Pathom 73000, Thailand

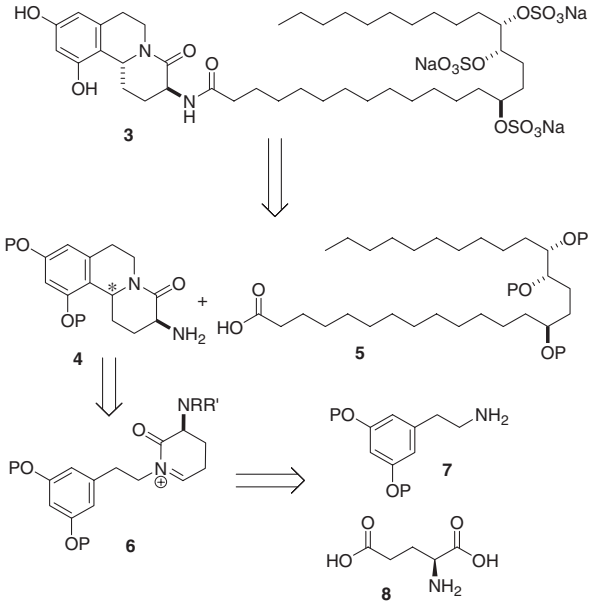
(Received May 16, 2006; CL-060576; E-mail: punlop@su.ac.th)

The tricyclic core of marine natural products schulzeines was synthesized using *N*-acyliminium ion cyclization. The intermediate *N*-acyliminium ion was generated from treatment of α-hydroxy-δ-lactam with a Lewis acid. The tricyclic products were obtained as a mixture of 2 diastereomers at the C-11b stereocenter. The diastereomeric ratios were low and dependent on the Lewis acid used in the reaction.

Schulzeines are a new class of marine natural products, isolated from a marine sponge, *Penares schulzei* (Figure 1). They exhibit potent α-glucosidase inhibitory effects making them promising leads for drug development for diseases such as cancers, diabetes, and viral infections.[1]

The structure of schulzeines can be divided into two major components, namely, the tricyclic core **4** containing tetrahydro isoquinoline fused with δ-lactam and the C28 fatty acid side chain **5**. The tricyclic core bears two stereogenic centers at C-3 and C-11b. The stereocenter at C-3 is assigned as S in all members of this family whereas schulzeines A and C have 11b R, and schulzeine B has 11b S configuration. The C28 fatty acid side chain of schulzeines bear three stereogenic centers at C-14, C-17, and C-18 as sodium sulfate salts with the configurations assigned as S, S, S. Schulzeine A has an extra stereogenic center at C-20 bearing a methyl substituent.

Retrosynthetically, the tricyclic core of schulzeines can be derived from cyclization of *N*-acyliminium ion **6**.[2] This in turn can be synthesized from 2-(3,5-dihydroxyphenyl)ethylamine and L-glutamic acid derivatives (Scheme 1).



Scheme 1. Retrosynthetic analysis of schulzeines.

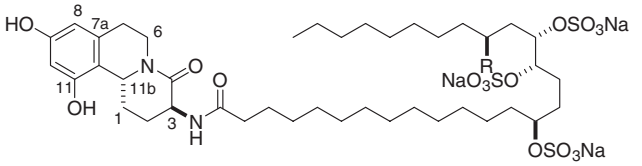
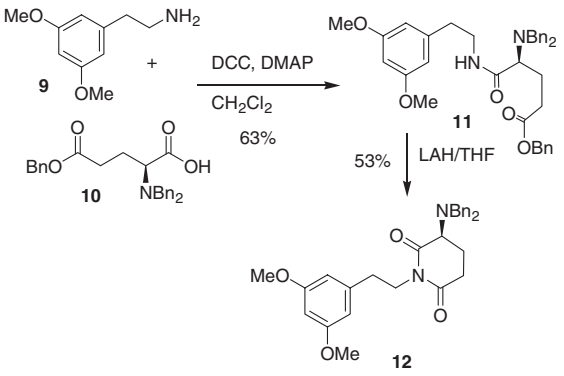


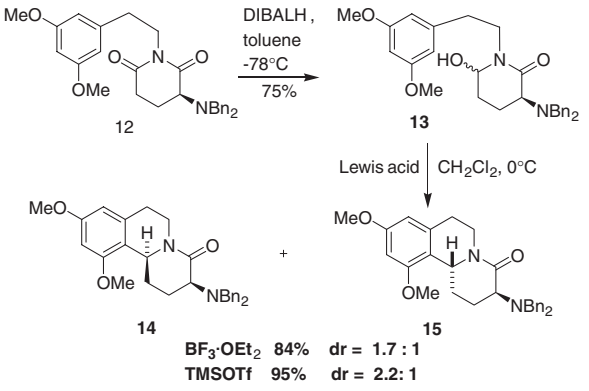
Figure 1. Schulzeines A (1) R = CH_3, B (2) R = 11b-*epi*-schulzeine C, C (3) R = H.

2-(3,5-Dimethoxyphenyl)ethylamine (**9**) was prepared in a straightforward fashion in 5 steps from 3,5-dihydroxybenzoic acid. Amide formation of this amine with 5-benzyl-*N*,*N*-dibenzyl-L-glutamate gave amide–ester **11**. Initially, we planned to reduce the benzyl ester to the corresponding primary alcohol. We envisioned that oxidation of such alcohol would give an α-hydroxy-δ-lactam. Treatment of this intermediate with a Lewis acid should give an *N*-acyliminium ion which should promptly cyclize to give the tricyclic product with a certain level of diastereoselectivity induced by the existing stereogenic center. However, a reaction of this compound with lithium aluminum hydride in THF at 0 °C gave imide **12** in 53% yield. This apparently resulted from abstraction of the amide's N–H proton by LAH and subsequent attack to the benzyl ester carbonyl. The corresponding alcohol from reduction of the benzyl ester was not detected (Scheme 2).

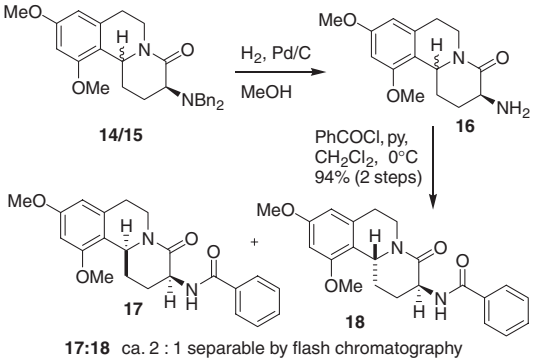
However, there are several precedents where addition of a nucleophile to an unsymmetrical imide delivers α-hydroxylactam intermediate with good regiocontrol. Sodium borohydride in ethanol gives a reduction product in which a more hindered carbonyl group is reduced[3] whereas DIBALH in toluene gives the complimentary product.[4] Thus treatment of imide **12** with DIBALH in toluene at −78 °C gave α-hydroxy-δ-lactam **13** in a good yield. This compound was treated with $BF_3 \cdot OEt_2$ in dichloromethane to give tricyclic cores **14** and **15** of schulzeines as



Scheme 2. Amide **11** formation and subsequent reaction with lithium aluminum hydride.



Scheme 3. Reduction of imide **12** with DIBALH and subsequent treatment of the α-hydroxy-δ-lactam with Lewis acids.



Scheme 4. Debenzylation of **14** and **15** and their conversion to benzamide derivatives **17** and **18**.

an inseparable mixture of two diastereomers at the C-11b. The diastereomeric ratio was determined to be 1.7:1 from ^{1}H NMR data. The configuration at C-11b of the major diastereomer **14** is assigned as S according to the NOESY experiment of the product mixture which shows correlation between the H-11b and H-3 indicating their cis relationship.[5] This correlation is absent in the minor diastereomer **15**. The diastereomeric ratio of the products showed some dependence on the nature of the Lewis acid used in this reaction where TMSOTf gave slightly better selectivity of 2.2:1 (Scheme 3).[6,7]

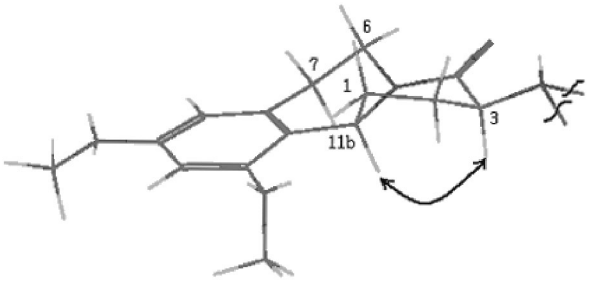
Our initial hypothesis was that the aromatic moiety of the molecule would approach the *N*-acyliminium ion from the opposite face to the *N*,*N*-dibenzylamino substituent leading to the product **15** with 11b R configuration as the major diastereomer. However, the observed selectivity in favor of **14** does not support this speculation. The two diastereomers at C-11b can be separated by flash column chromatography after conversion to their benzamide derivatives **17** and **18** (Scheme 4).

In summary, we have synthesized the tricyclic core of schulzeines. Albeit low diastereoselectivity was achieved, each diastereomer can be proceeded to make the natural products. The rationale for the selectivity is not clear to us at the moment and is being investigated. The synthesis of C28 fatty acid side chains of schulzeines is well underway in our laboratory. The completion of these fatty acids and their union with the tricyclic core to give the complete skeleton of schulzeines will be reported in due course.

PK would like to thank Prof. Boonsong Kongkathip, Prof. Pittaya Tuntiwachwuttikul, and Prof. Surachai Nimgirawath for helpful discussions and guidance. Dr. Somkiat Thadaniti is acknowledged for assistance with NMR experiments. Mrs. Panit Vedchakanchana is acknowledged for assistance with GC-MS analysis. Financial supports are provided by the Thailand Research Fund (TRF) and National Science and Technology Development Agency (NSTDA) of Thailand.

References and Notes

1 K. Takada, T. Uehara, Y. Nakao, S. Matsunaga, R. W. M. van Soest, N. Fusetani, *J. Am. Chem. Soc.* **2004**, *126*, 187.
2 B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431.
3 N. S. Simpkins, C. D. Gill, *Org. Lett.* **2003**, *5*, 535.
4 W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367.
5 NOESY experiment shows correlation between H-11b and H-3 in **14**. The 1D NOE difference experiments also show signal enhancement of H-3 (δ 3.55 ppm) when H-11b (δ 4.57 ppm) was irradiated.



6 Y. S. Lee, D. J. Cho, S. N. Kim, J. H. Choi, H. Park, *J. Org. Chem.* **1999**, *64*, 9727.
7 Data for **14**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.50 (m, Ph $\times$ 2), 6.34 (d, $J = 2.0$, H-10), 6.29 (d, $J = 2.1$, H-8), 4.85 (dd, $J = 10.3$, 3.9, H-6α), 4.57 (dd, $J = 10.9$, 3.2, H-11b), 4.26 (d, $J = 14.6$, N-CH_2-Ph), 3.89 (d, $J = 14.6$, N-CH_2-Ph), 3.81 (s, O-CH_3), 3.79 (s, O-CH_3), 3.55 (dd, $J = 9.9$, 9.1, H-3), 2.78 (m, H-6β), 2.72 (m, H-7), 2.35 (m, H-1α), 2.17 (m, H-2β), 1.90 (m, H-2α), 1.40 (m, H-1β); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5 (C-4), 159.2 (Ph), 157.5 (C-9), 157.0 (C-11), 141.2 (C-11a), 137.6 (C-7a), 128.4 (Ph), 128.1 (Ph), 126.6 (Ph), 104.3 (C-10), 96.9 (C-8), 56.7 (C-3), 55.3 (OCH_3), 55.2 (OCH_3), 49.6 (C-11b), 38.1 (C-6), 29.5 (C-7), 29.3 (C-1), 23.6 (C-2); HRMS (ES) m/z 457.2487, calcd for $C_{29}H_{33}N_2O_3$ m/z 457.2491 $(M + H)^+$.
8 Full experimental procedures and spectroscopic data of compounds **11**, **12**, **13**, **14**, **15**, **17**, and **18** are provided. This material is available free of charge at www.csj.jp/journals/cl/.

Published on the web (Advance View) July 29, 2006; doi:10.1246/cl.2006.1008