

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5202

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## Asymmetric formal synthesis of schulzeines A and C†

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Received 23rd April 2012, Accepted 30th May 2012

DOI: 10.1039/c2ob25772f

The asymmetric formal synthesis of schulzeines A and C is described. Key features of the synthesis include the efficient and stereoselective construction of the benzoquinolizidine skeleton via the aza-Claisen rearrangement-induced ring expansion of the 1-vinyl-*N*-glycyl-isoquinoline, which was prepared by the highly enantioselective asymmetric allylation of the 8-benzyloxy-substituted dihydroisoquinoline and by the acid-catalyzed transannulation of the resulting 10-membered lactam.

$\alpha$ -Glucosidase plays an important role in various biological processes such as protein folding in the endoplasmic reticulum, cell surface glycoprotein stabilization, cell–cell and cell–virus recognition processes and oligosaccharide metabolism.<sup>1</sup> Thus,  $\alpha$ -glucosidase has been considered as a promising molecular target for the treatment of cancer, diabetes and viral infections.<sup>2</sup> Furthermore, some iminosugars, including the 1-deoxynojirimycin derivatives, have proven to be effective  $\alpha$ -glucosidase inhibitors for the treatment of hepatitis B infection and non-insulin-dependent type 2 diabetes.<sup>2c</sup> Recently, marine invertebrates were reported to produce novel classes of  $\alpha$ -glucosidase inhibitors that are structurally distinct from the classic glycoside derivatives.<sup>3</sup> In particular, schulzeines, isolated from the extracts of the marine sponge *Penares schulzei*, exhibited quite potent  $\alpha$ -glucosidase inhibitory activities (IC<sub>50</sub> 48–170 nM).<sup>3a</sup> Schulzeines share *O*-sulfated fatty acid structures with penasulfates<sup>3b</sup> and penarolides<sup>3c</sup> but contain a unique 3-amino-benzo[ $\alpha$ ]quinolizidine core, which is not based on a sugar scaffold. Thus, the production of schulzeines has attracted special attention from synthetic and medicinal chemists due to the novel structures and intriguing biological activities of these compounds. Several successful strategies have been introduced for the synthesis of schulzeines A–C.<sup>4</sup> We have also achieved a highly efficient asymmetric synthesis of schulzeines

A (1) and C (2) via a chiral transfer strategy that has not been previously reported. Herein, we describe the efficient and highly stereoselective formal synthesis of schulzeines A and C that employs a tandem chiral transfer strategy.

Pictet–Spengler-type cyclocondensation has been successfully utilized by several groups in the synthesis of the 3-amino-benzo[ $\alpha$ ]quinolizidine core (3) of schulzeines A and C through 1,4-asymmetric induction.<sup>4a–d</sup> Pictet–Spengler-type cyclocondensation preferentially produced the *cis*-isomer (C<sub>11b</sub>  $\alpha$ -H) over the *trans*-isomer (C<sub>11b</sub>  $\beta$ -H). However, the diastereocontrol of the two stereocenters remains a challenging task because the 1,4-asymmetric induction to form the new remote stereocenter had low or moderate stereoselectivity. As shown in Fig. 1, we

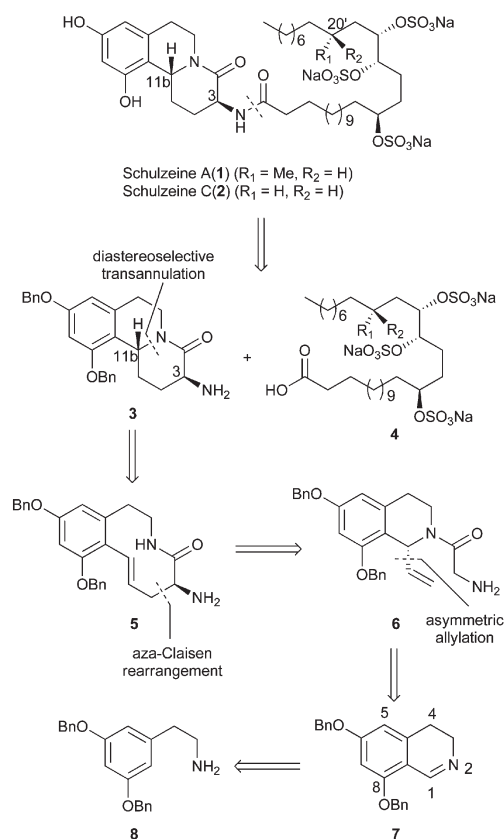


Fig. 1 Retrosynthetic analysis.

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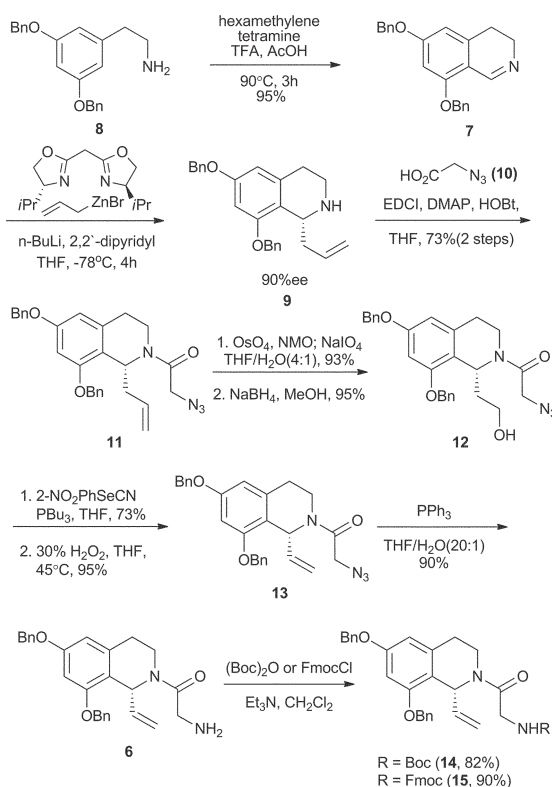
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† Electronic supplementary information (ESI) available: Experimental details, spectral data of all the new compounds and HPLC data of compounds 11 and 16. See DOI: 10.1039/c2ob25772f

envisioned that the *trans*-3-aminobenzo[ $\alpha$ ]quinolizidine skeleton of schulzeines A (**1**) and C (**2**) could be easily constructed by an aza-Claisen rearrangement (ACR)-induced ring expansion of the 1-vinyl-*N*-glycyl-isoquinoline **6** and a subsequent stereospecific transannulation of the resulting 10-membered lactam **5**. The initial C<sub>11b</sub>-chiral center of ACR precursor **6** would be introduced by the asymmetric alkylation of the 3,4-dihydroisoquinoline **7**, which could be readily prepared from the commercially available amine **8**.

The first obstacle to overcome in our synthetic approach involved the asymmetric allylation of dihydroisoquinoline **7**. Asymmetric alkylations of 8-alkoxy-substituted dihydroisoquinolines such as **7** have been limited due to low enantioselectivity.<sup>4h,5</sup> Only a few successful examples have been reported to date, and most of the reactions gave moderate or good enantioselectivities up to 82% ee.<sup>4h,5a</sup> However, we were able to achieve the highly enantioselective allylation of the 8-benzyloxy-substituted dihydroisoquinoline **7**, with a high enantioselectivity of 90% ee, by utilizing the Nakamura protocol<sup>6</sup> as shown in Scheme 1. We assumed the absolute stereochemistry of **9** as *R*-configuration based on the previous report<sup>6</sup> and confirmed it based on the optical rotation of **3**. To the best of our knowledge, we present the first application of the enantioselective allylation of an 8-alkoxy-substituted dihydroisoquinoline with high facial selectivity.

The syntheses of the ACR precursors **6** and **13–15** are shown in Scheme 1. Dihydroisoquinoline **7** was prepared by the treatment of the commercially available amine **8** with hexamethylene tetramine in TFA and acetic acid.<sup>4h,7</sup> The dihydroisoquinoline **7** was then subjected to Nakamura's asymmetric allylation<sup>6</sup> to



**Scheme 1** Preparation of ACR precursors **6** and **13–15**.

**Table 1** ACR of cyclic glycinamides **6** and **13–15**

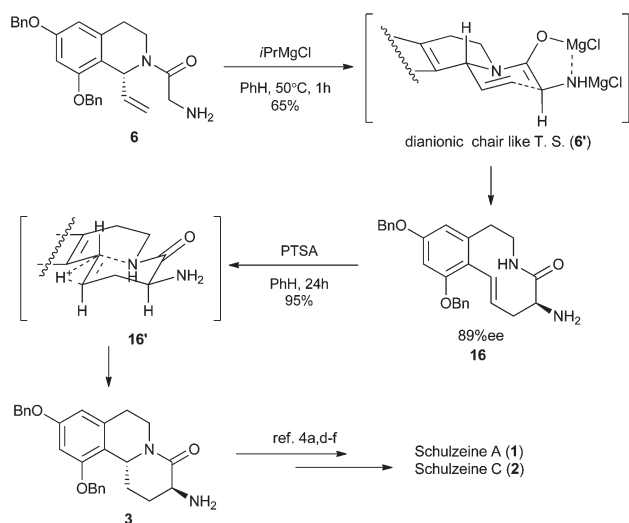
Entry	X	Solvent	Base (equiv.)	Temp.	Yield <sup>a</sup> (%)
1	N <sub>3</sub>	PhMe	LHMDS (3)	Reflux	NR <sup>b</sup>
2	N <sub>3</sub>	PhMe	iPrMgCl (3)	Reflux	NR
3	NHBoc	PhMe	LHMDS (3)	Reflux	NR
4	NH <sub>2</sub>	PhMe	LHMDS (4)	Reflux	10
5	NH <sub>2</sub>	PhMe	iPrMgCl (4)	Reflux	22
6	NH <sub>2</sub>	PhH	LHMDS (4)	Reflux	18
7	NH <sub>2</sub>	PhH	iPrMgCl (4)	Reflux	64
8	NH <sub>2</sub>	PhH	iPrMgCl (4)	50 °C	65
9	NH <sub>2</sub>	PhH	iPrMgCl (4)	25 °C <sup>c</sup>	50
10	NHFmoc	PhH	iPrMgCl (4)	Reflux	40 <sup>d</sup>

<sup>a</sup> Isolated yield by flash column chromatography. <sup>b</sup> No reaction. <sup>c</sup> Room temperature. <sup>d</sup> See text.

afford the homoallylic amine **9** with an excellent enantioselectivity of 90% ee. The secondary amine **9** was coupled with 2-azidoacetic acid **10**, which was prepared from glycine,<sup>8</sup> to provide amide **11**. Subsequent oxidative cleavage of the terminal olefin followed by reduction of the resulting aldehyde with NaBH<sub>4</sub> in methanol afforded alcohol **12**. Alcohol **12** was converted into olefin **13** using the Grieco procedure.<sup>9</sup> Reduction of azide **13** using the Staudinger reaction<sup>10</sup> gave the free amine **6**. The reaction of amine **6** with (Boc)<sub>2</sub>O or FmocCl produced the *N*-protected glycinamides **14** and **15**.

With three types of ACR precursors (**6**, **13–15**) in hand, we carried out the pivotal ACR-induced ring expansion as summarized in Table 1. As the Tsunoda group proposed, the reaction seemed to proceed through a dianionic transition state, which rendered the desired rearrangement feasible even at room temperature.<sup>11</sup> The free amine **6** proved to be the most appropriate for the ring expansion reaction, whereas the *N*-Boc-protected glycinamide **14** did not undergo ACR (entry 3). Despite our extensive efforts, the ACR of the *N*-Fmoc-protected glycinamide **15** provided the free amine product **16**, possibly due to the *in situ* generation of the ACR precursor **6** (entry 10). The use of isopropyl magnesium chloride as a base provided higher yields than did LHMDS, and the use of toluene as a solvent significantly reduced the chemical yields compared with the use of benzene (entries 4–7). The ACR of the free amine **6** was successful even at room temperature although the yield slightly decreased (entries 7–9). The plausible transition state (**6'**) of the ACR-induced ring expansion is shown in Scheme 2.

Finally, the acid-promoted highly stereoselective transannulation of **16** afforded the desired benzoquinolizidine **3**, which can be efficiently transformed into schulzeines A and C according to previous reports.<sup>4a,d-f</sup> The structure of **3** was confirmed by comparison of its spectral data including <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and HRMS with the data for an authentic sample. The stereochemistry of **3** was also confirmed by comparison of the optical



rotation of **3** ( $[\alpha]_D^{24} +170.8$ ,  $c$  0.50,  $\text{CHCl}_3$ ) with the reported one (lit.  $[\alpha]_D^{24} +182.4$ ,  $c$  2.10,  $\text{CHCl}_3$ ).<sup>4a</sup>

## Conclusions

In conclusion, we have achieved a highly stereoselective formal synthesis of schulzeines A and C in 10 steps with a 24% overall yield starting from the commercially available amine **8**. The key features of our synthesis are the highly enantioselective Nakamura's asymmetric allylation of the 8-benzyloxy-substituted dihydroisoquinoline, the ring expansion of 1-vinyl-*N*-glycyl-isoquinoline through amide enolate-induced ACR and stereospecific transannulation for the efficient construction of the benzoisoquinolizidine scaffold.

## Acknowledgements

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MEST) (No. 2011-0030635) and a National Research Foundation of

Korea grant funded by the Korean government (MEST) (NRF-C1ABA001-2011-0018561).

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