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Total synthesis of argyrins A and E

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ABSTRACT

The total synthesis of argyrins A and E were accomplished using a convergent strategy by condensation of one tripeptide and two dipeptide fragments. The synthesis strategy, which was developed for the protection of peptide fragments and identification of the optimum macrocylization site, can be applied to further synthetic studies involving other members of the argyrin family.

The proteasome, a multicatalytic proteinase complex, is responsible for the degradation of a large proportion of intracellular proteins.[1] Therefore, the proteasome is an interesting target for therapeutic agents that inhibit cell proliferation in diseases such as cancer.[2] Numerous proteasome inhibitors that have promising potential in clinical trials have been recently developed.[3] Bortezomib was approved by the U.S. food and drug administration (FDA) for treatment of multiple myeloma and mantle-cell lymphoma. However, the designing of proteasome inhibitors with high specificity and wide clinical applicability remains to be accomplished because some inhibitors display cytotoxicity, whereas others inhibit other proteases such as calpains and cathepsins.[3e]

In 2002, argyrin A and its congeners were originally isolated from *Archangium gephyra* during the screening of myxobacteria for new antibiotics (Fig. 1).[4] Recently, Malek's group found that argyrin A shows biological activity at remarkably low concentrations without significant cytotoxic effects. In addition, all antitumoral activities of argyrin A were found to depend on the prevention of $p27^{kip1}$ destruction, because loss of $p27^{kip1}$ expression confers resistance to this compound. Malek et al. hence concluded that argyrin A is a more specific proteasome inhibitor than bortezomib.[5] These excellent properties of argyrins have attracted significant attention, and the total syntheses of argyrin B and F have been accomplished by two research groups.[6,7] To further understand the structure–activity relationship of argyrin A, we here report a convergent macrocycle-assembly strategy to synthesize argyrins A and E in parallel from three fragments: two dipeptides and a tripeptide (Fig. 1).

In the retrosynthetic analyses of argyrins A and E, the macrocyclization site is so important that it can ultimately determine the success of the synthesis. Poor disconnections can lead to slow cyclization rates, facilitating side-reactions such as oligomerization and/or epimerization of the C-terminal residue.[8] Analyzing the sequences of the molecules, we chose the achiral glycine as the C-terminal end to avoid racemization during backbone macrocyclization. In addition, such disconnection makes the turn-inducing thiazole residues to be located in the middle of the linear peptide precursor, which will result in the N- and C-termini approaching each other to make the head–tail macrocyclization more robust.

The various components of argyrins A (**1**) and E (**2**) were synthesized by different routes. Our synthesis of intermediate **5** used a straightforward route from *N*-Boc-D-alanine **7** (Boc = *tert*-butyloxycarbonyl) following the procedure (Scheme 1) provided in literature.[9] The ethyl ester group of **8** was saponified with LiOH and then coupled with the methyl ester of tryptophan to provide the dipeptide **5**.

The synthesis of the key intermediate **13** started from the previously characterized compound **10**, which was obtained from commercially available 3-methoxybenzeneamine, **9** (Scheme 2). Boc-protected 3-methoxybenzeneamine **10,** was lithiated with 2.1 equiv of *tert*-butyllithium in diethyl ether, followed by iodination with molecular iodine to give *tert*-butyl (2-iodo-3-methoxyphenyl) carbamate, **11**, in 90% yield;[10] subsequent deprotection of the Boc group yielded the desired compound **12**. The key intermediate **15** was easily derived through a palladium-catalyzed heteroannulation reaction between the amine **12** and the aldehyde **14**, the latter being synthesized from the dimethyl ester of *N*-Boc-L-glutamic acid in two steps.[11,12] Bismuth–bromide-based catalytic selective deprotection[13] of the Boc group of **13,** followed by hydrolysis of the methyl ester group and coupling with glycine methyl ester, yielded the dipeptide **3**. Analogously, the dipeptide **4** was easily prepared in 82% yield by coupling Boc-protected tryptophan **16** with glycine methyl ester.

Then, we turned our attention to the synthesis of the tripeptide **6**, which was prepared from Boc-protected D-alanine, **17**

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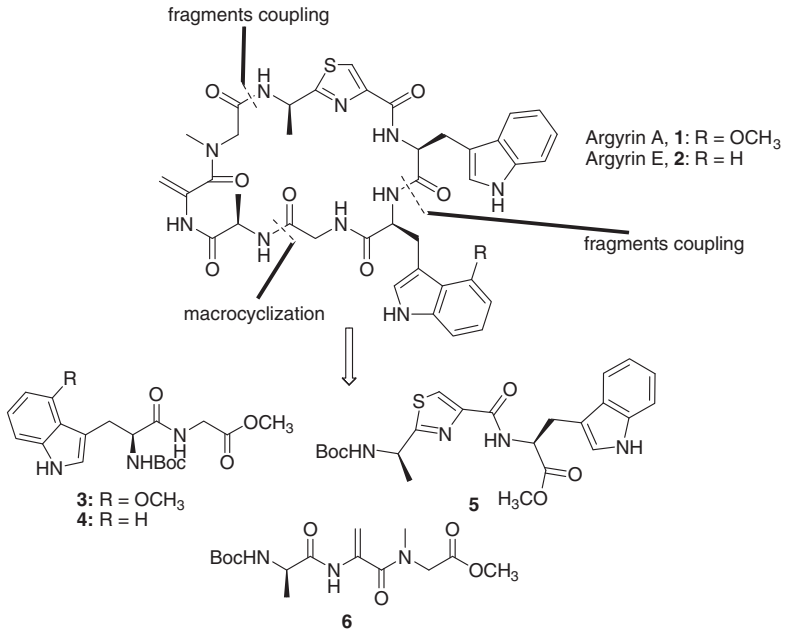
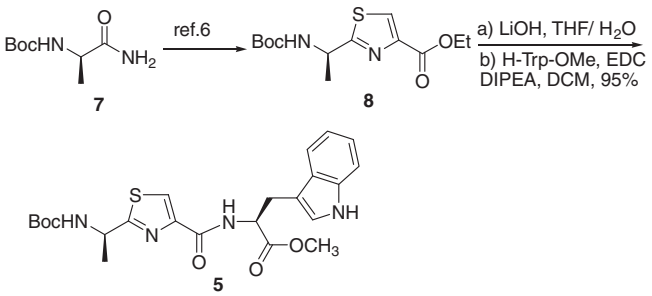


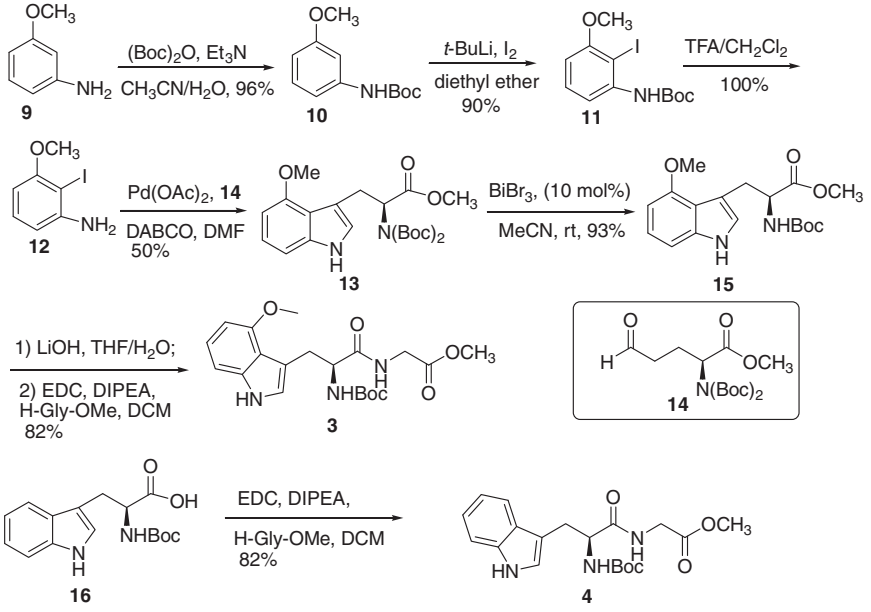
Figure 1. Structure and retrosynthetic analysis of argyrin A and E.



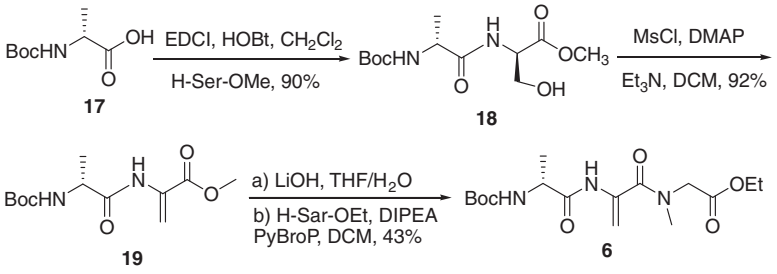
Scheme 1. Synthesis of the linear dipeptide **5**.

(Scheme 3). Sequential coupling with L-serine methyl ester yielded the dipeptide **18**, which was further subjected to mesylation, followed by elimination, to provide the dehydroalanine moiety **19**. The next peptide coupling was carried out after hydrolysis of the ester group with the sarcosine ethyl ester (Sar-OEt), using bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) as the coupling reagent, to provide fragment **6**.

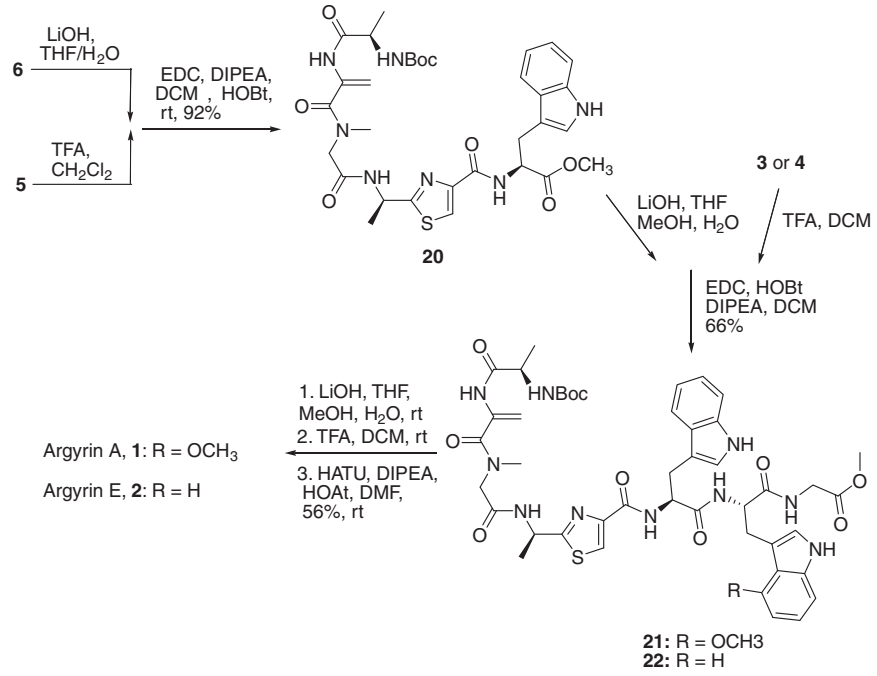
Coupling of the above three fragments and completion of the total syntheses of argyrins A and E were accomplished as shown in Scheme 4. Removal of the protective group Boc from the dipeptide **5** and coupling with the free acid from tripeptide **6** gave the product **20** in 92% yield. Subsequently, the methyl ester of **20** was cleaved by LiOH in quantitative yield. The free acid was



Scheme 2. Synthesis of the linear dipeptides **3** and **4**.



Scheme 3. Synthesis of the linear tripeptide **6**.



Scheme 4. Synthesis of argyrins A and E.

immediately coupled with the Boc-deprotected fragment from **3** or **4**, respectively, using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and HOBt, to yield the linear heptapeptides **21** and **22**, respectively, in 66% yield. Before macrocyclization, the two protecting groups were removed by hydrolysis (for the methyl ester group) and with trifluoroacetic acid (TFA) in dichloromethane (for the N-terminal Boc group). After examining several macrocyclization conditions, we successfully obtained argyrins A and E in 56% yield, respectively, using HATU as the condensation reagent in DMF solution (0.7 mM). This step was repeated three times, and in all cases, comparable chemical yields were obtained. The spectroscopic (^{1}H NMR and ^{13}C NMR) and the optical rotation data for the synthetic argyrins A and E fully matched the data published for the corresponding natural products.[14]

In summary, the total synthesis of argyrins A and E were accomplished through a convergent macrocycle-assembly strategy from a tripeptide fragment and two dipeptide intermediates (11% overall yield from 3-methoxybenzeneamine, with the longest linear sequence comprising 14 steps). The methods developed to ensure the protection of both the peptide fragments and the optimum macrocylization site are the useful outcomes of this study, which may potentially be applicable to the synthesis of other analogs of this family. Efforts toward applying these methods to other natural products are currently underway in our laboratory and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.021.

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14. *Spectroscopic data of argyrin A* (**1**): ^{1}H NMR (400 MHz, $CDCl_3$) 10.68 (*s*, 1 H), 9.47 (s, 1 H), 8.82 (d, *J* = 8.4 Hz, 1 H), 8.60 (d, *J* = 1.6 Hz, 1 H), 8.57 (d, *J* = 7.2 Hz, 1 H), 8.52 (d, *J* = 2.0 Hz, 1 H), 8.05 (s, 1 H), 7.33–7.31 (m, 2 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.97 (d, *J* = 2.4 Hz, 1 H), 6.91–6.86 (m, 3 H), 6.82 (d, *J* = 2.4 Hz, 1 H), 6.34 (t, *J* = 7.2 Hz, 1 H), 5.51–5.44 (m, 1 H), 5.40 (d, *J* = 7.6 Hz, 1 H), 5.08–5.04 (m, 1 H), 5.01 (d, *J* = 1.6 Hz, 1 H), 4.95 (d, *J* = 16.8 Hz, 1H), 4.71 (d, *J* = 1.2 Hz, 1 H), 4.54–4.50 (m, 1 H), 4.33 (s, 3 H), 4.26–4.21 (m, 2 H), 3.54–3.46 (m, 3 H), 3.40 (d, *J* = 16.8 Hz, 1 H), 3.32 (dd, *J* = 14.8, 4.0 Hz, 1 H), 3.07 (s, 3 H), 2.84 (dd, *J* = 15.2, 3.2 Hz, 1 H), 1.73 (d, *J* = 7.2 Hz, 3 H), 1.42 (d, *J* = 7.2 Hz, 3 H), 1.05 (dd, *J* = 17.4, 5.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) 172.9, 171.0, 170.9, 170.1, 169.8, 168.3, 166.8, 159.8, 152.3, 150.4, 138.4, 136.8, 134.7, 126.5, 125.5, 123.7, 123.6, 122.9, 121.2, 119.2, 117.4, 116.0, 111.3, 108.2, 106.6, 105.7, 101.2. 99.7, 57.7, 56.1, 52.1, 51.0, 48.4, 45.3, 40.5, 37.4, 26.9, 26.6, 20.3, 13.9. MS (ESI, *m*/*z*) found 847.3 ($[M+Na]^+$). $[\alpha]_D^{25}$ = +140.9 (*c* 0.1, $CHCl_3$); Lit. [7]: $[\alpha]_D^{25}$ = +145.2 (*c* 0.91, $CHCl_3$).
Argyrin E (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) 10.59 (br, 1H), 9.40 (s, 1H), 8.86–8.83 (m, 2H), 8.65 (d, *J* = 7.6 Hz, 1H), 7.97 (s, 1H), 7.51–7.48 (m, 2H), 7.28–7.24 (m, 3H), 7.15–7.12 (m, 1H), 7.09–7.07 (m, 1H), 6.97–6.96 (m, 1H), 6.93–6.90 (m, 1H), 6.86–6.84 (m, 1H), 6.45–6.39 (m, 2H), 5.51–5.43 (m, 1H), 5.20–5.17 (m, 1H), 5.05–5.02 (m, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 4.86 (br, 1H), 4.73 (s, 1H), 4.30–4.23 (m, 2H), 3.56–3.33 (m, 4H), 3.26–3.14 (m, 2H), 3.11 (s, 3H), 1.71 (d, *J* = 7.2 Hz, 3H), 1.37 (d, *J* = 7.2 Hz, 3H), 1.27–1.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 172.8, 171.2, 170.8, 170.5, 169.9, 168.3, 167.0, 160.2, 150.0, 136.8, 136.6, 134.9, 127.4, 126.5, 125.3, 123.4, 123.0, 121.6, 120.4, 119.7, 118.1, 115.9, 111.8, 111.6, 109.1, 106.0, 100.0, 56.2, 52.2, 51.1, 48.3, 45.4, 41.2, 37.5, 27.0, 26.5, 20.5, 14.0. MS (ESI, *m*/*z*) found 817.2 ($[M+Na]^+$). $[\alpha]_D^{25}$ = + 123.2 (*c* 0.2, acetone); Lit. [4]: $[\alpha]_D^{25}$ = +127 (*c* 0.73, acetone).