Pergamon

Tetrahedron Letters 43 (2002) 7639–7641

TETRAHEDRON LETTERS

A short synthesis of aspergillamide B. The marine natural product from *Aspergillus* sp.

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Received 5 July 2002; accepted 26 July 2002

Abstract—A short route to the marine natural product aspergillamide **B** has been developed. The key step is the stereoselective formation of the *trans* indole–enamide pharmacophore by indole-assisted dehydration from the functionalized aminoalcohol intermediate. HPLC and ^{1}H NMR analyses show that aspergillamide **B** is more stable in the *cis* rotamer form. © 2002 Elsevier Science Ltd. All rights reserved.

During the past few years, a number of bioactive natural products featuring an indole-3-ethenamide substructure have been isolated from various sources. Among them, terpeptine,[1] chondriamides[2] and coscinamides,[3] as well as aspergillamides **A** (**1a**) and **B** (**1b**), are the most representative examples of this new class of compounds. The latters, cytotoxic peptides, have been structurally elucidated following their isolation in low yields from an *Aspergillus* sp. (Fig. 1).[4]

To date, a number of procedures allowing the formation of enamides have been developed.[5] Interestingly, a library of aspergillamide analogues were recently prepared by Dömling and co-workers[6] using the Ugi multicomponent reaction.[7] Several of these analogues were found to be more active than the natural aspergillamides. However, as a major drawback, the Ugi multicomponent reaction[7] gave in general a mixture of regio- and diastereoisomers,[6] and, stereocontrolled processes are usually required to overcome this difficulty.[8]

Herein, we describe the first stereoselective synthesis of aspergillamide **B** taking advantage of a simple dehydration of a suitably functionalized aminoalcohol intermediate as outlined in Scheme 1.

To design this sequence, we thought that the electron rich indole unit might assist water elimination to provide the enamide moiety, in its thermodynamically stable *trans* configuration (Scheme 1). Following these observations, we have examined the dehydration process starting from the aminoalcohols **3a** and **3b** (Scheme 2). These derivatives were obtained in moderate yield

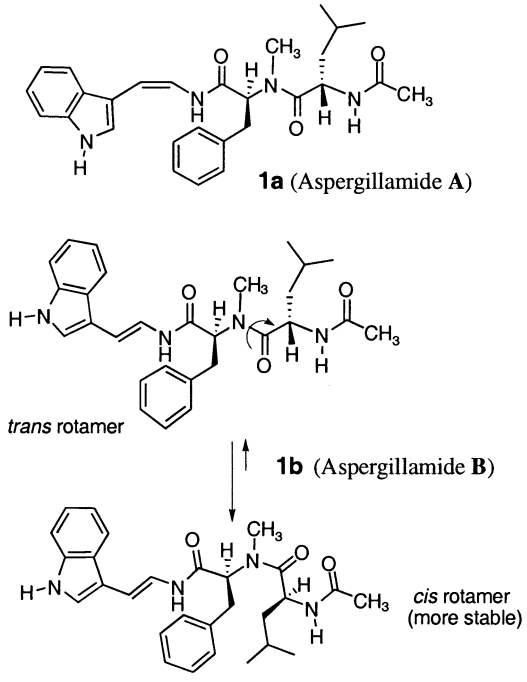

Figure 1. Structure of aspergillamides.

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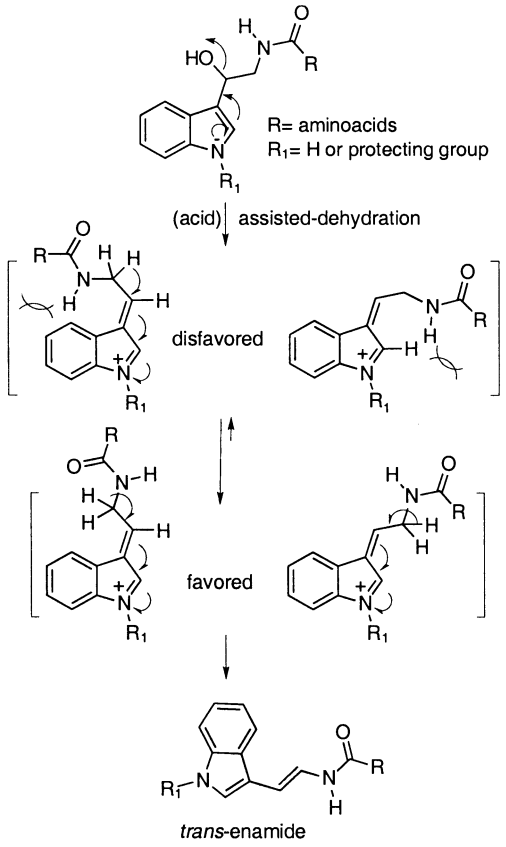
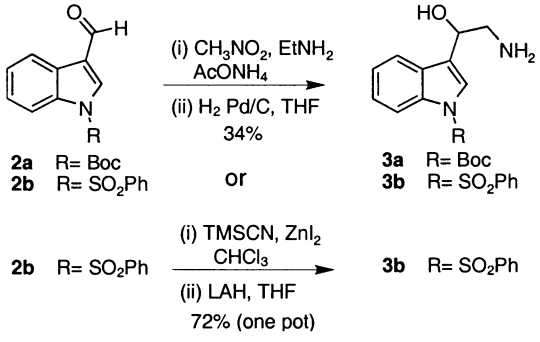
PII: S0040-4039(02)01602-7



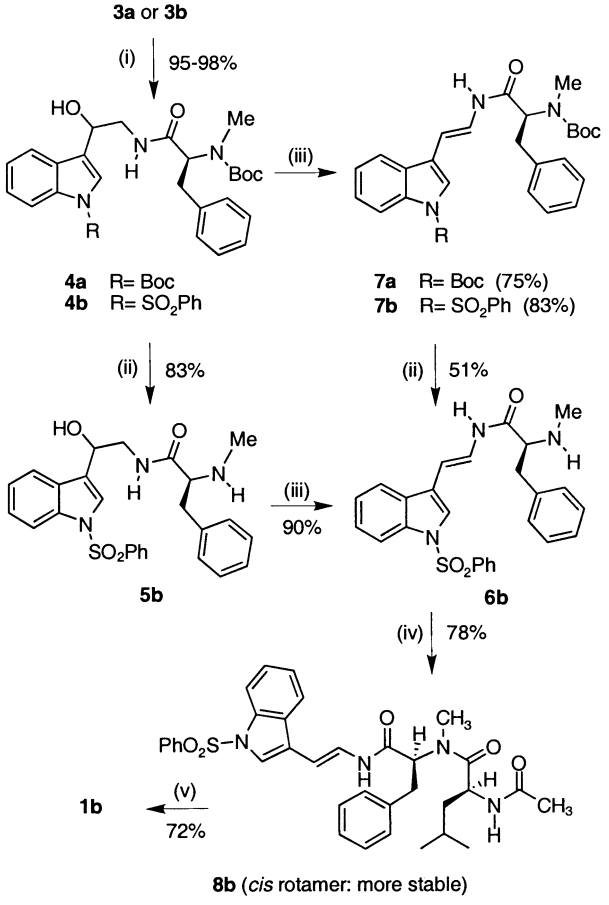
Scheme 1. The proposed synthetic pathway allowing to the *trans*-enamide products.



Scheme 2. Synthesis of aminoalcohols **3a** and **3b**.

(34%) from aldehydes **2a** and **2b**, respectively, following: (i) Henry reaction[9] using nitromethane aldol condensation and (ii) subsequent hydrogenolysis of the nitroalcohol intermediates. Interestingly, cyanosilylation of the same starting material (**2b**) using ZnI_2 as catalyst[10] afforded quantitatively the cyanohydrine intermediate which was then reduced with LAH in THF into compound **3b** in 72% overall yield.[11]

The coupling of aminoalcohol **3a** or **3b** with *N*-Boc,*N*-Me-phenylalanine[12] (HOBT/EDC) was achieved in quantitative yield affording compounds **4a** and **4b** (95–98%), respectively, as equimolar mixture of two diastereoisomers (Scheme 3). Removal of the Boc-protecting group of compound **4b** provided the aminoalcohol **5b**.



Scheme 3. Synthesis of aspergillamide **B**. *Reagents and conditions*: (i) HOBT, EDC, DMF, *N*-Boc,*N*-Me-phenylalanine; (ii) dioxane–HCl; (iii) APTS, toluene, 60°C; (iv) *N*-Ac-leucine, HOBT, EDC, DMF, DIEA; (v) 6% Na–Hg, Na_2HPO_4, dioxane–methanol.

Interestingly, as expected, upon acidic treatment (APTS-toluene) **5b** underwent a clean conversion into the single *trans*-enamide product **6b**, as confirmed by ^{1}H NMR [δ (H-enamide) = 6.24 ppm and J = 14.6 Hz].[13] Alternatively, **6a** and **6b** were obtained from **4a** and **4b**, respectively, using the same dehydration process which led to the Boc-protected enamides **7a** and **7b**, followed by Boc-deprotection (**7b**→**6b**, 51%). The coupling of **6b** and the commercially available *N*-acetyl-leucine under standard conditions yielded the protected aspergillamide **8b** in 78% yield. The benzenesulfonyl protecting group of compound **8b** was cleanly removed by treatment with Na–Hg[14] to give aspergillamide **1b** in 72% yield.[15] In the present case, this protecting group was found to be more resistant to the cleavage when using more conventional procedures.[16] Finally, HPLC analysis[17] of aspergillamide **1b** showed a mixture of *cis*- and *trans*-amide rotational isomers (see Fig. 1) which equilibrated in favour of the stable *cis* rotamer. The *cis* conformation was evidenced by the high field signal (δ_H at −0.16 ppm) of one of the two hydrogens of the leucine methylene group facing the phenyl ring (Ph-shielding effect, see ^{1}H NMR),[15] in line with literature.[4]

In conclusion, we have realized the first stereoselective synthesis of aspergillamide **B**, in short linear steps. In vitro cytotoxicity assays of aspergillamide **B** and the intermediates **6b** and **8b** were evaluated against the KB cell line. These products were found to be active in a micromolar range [IC_{50}: 10 μM for **1b**, 3 μM for **6b** and 2.3 μM for **8b**]. The application of this strategy to the synthesis of other enamide-natural products and analogues (in indole and non-indole series) together with the photoisomerization aspergillamide **A**→aspergillamide **B** is in progress and will be given in due course.

Acknowledgements

We are grateful to Christiane Tempete for the biological evaluation, to Marie-Thérèse Adeline for HPLC analysis and to CONACYT (Mexico) for a research grant to L. Rivas (Grant 121999).

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11. Compound **3a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.10 (d, $J=8.1$ Hz, 1H), 7.50 (m, 2H), 7.20 (m, 2H), 4.90 (m, 1H), 3.00 (m, 2H), 2.60 (bs, 3H), 1.60 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 149.60, 135.70, 128.40, 124.40, 122.60, 122.50, 121.99, 119.50, 115.30, 83.60, 66.20, 47.33, 27.74. HRMS calcd for $C_{15}H_{20}N_2O_3$: 276.147. Found: 276.148. Compound **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, $J=8.4$ Hz, 1H), 7.86 (m, 2H), 7.71 (d, 1H, $J=8.0$ Hz), 7.68 (s, 1H), 7.47–7.33 (m, 3H), 7.26 (t, 1H, $J=7.7$ Hz), 7.14 (t, 1H, $J=7.7$ Hz), 6.7 (br s, 3H), 5.12 (dd, 1H, $J=3.3$ and 4.0 Hz), 3.46–3.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.69, 135.43, 134.26, 129.46, 128.49, 126.95, 125.44, 124.98, 123.82, 120.69, 119.69, 113.81, 71.59, 64.79. MS (ESI$^+$): m/z 633 (2M+1), 317 (MH^+), 299 (MH^+-H_2O).
12. *N*-Boc,*N*-Me-phenylalanine was prepared in quantitative yield from *N*-Boc-phenylalanine (NaH, CH_3I, DMF): $[\alpha]_D=-28.2°$ (*c* 1, EtOH), lit. −28.1° (*c* 1, EtOH). See: Omamoto, K.; Abe, H.; Kuromizu, K.; Izumiya, N. *Mem. Fac. Sci. Kyushu Univ. Ser. C* **1974**, *9*, 131–138.
13. Compound **6b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (d, 1H, $J=11.0$ Hz), 8.01 (d, 1H, $J=8.1$ Hz), 7.85 (m, 2H), 7.69 (d, 1H, $J=7.7$ Hz), 7.54–7.45 (m, 2H), 7.38–7.15 (m, 10H), 6.24 (d, 1H, $J=14.6$ Hz), 3.90 (bs, 1H), 3.39 (dd, 1H, $J=4.4$ and 7.0 Hz), 3.22 (dd, 1H, $J=4.4$ and 7.0 Hz), 2.82 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.03, 138.06, 137.00, 135.60, 133.93, 129.36, 129.18, 128.08, 127.21, 126.81, 125.16, 123.69, 123.37, 122.26, 120.46, 119.49, 113.87, 104.09, 65.78, 38.90, 35.38. MS (ESI$^+$): m/z 482 (M+Na), 460 (M+1), 148.
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15. Synthetic aspergillamide **1b**: ^{1}H NMR (400 MHz, acetone-d_6): δ 10.25 (bs, 1H), 7.81–7.74 (m, 2H), 7.60–7.22 (m, 9H), 7.16–7.05 (m, 2H), 6.69 (d, 1H, $J=14.6$), 4.99 (dd, 1H, $J=3.6$ and 10.6 Hz), 4.60 (m, 1H), 3.31 (dd, 1H, $J=3.6$ and 14.3 Hz), 3.14 (dd, 1H, $J=11.0$ and 14.3 Hz), 2.88 (s, 3H), 2.01 (s, 3H), 1.60 (m, 1H), 1.19 (m, 1H), 0.80–0.68 (2d, 6H, $J=6.8$ Hz), −0.16 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 172.86, 171.56, 166.18, 138.66, 137.38, 129.87, 129.28, 128.89, 128.32, 126.72, 125.61, 122.97, 121.78, 120.30, 119.48, 119.40, 112.79, 106.98, 62.54, 47.03, 38.01, 33.84, 28.62, 23.96, 22.67, 21.78, 19.75. MS (EI): m/z 474 (M^+), 317.
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17. The reverse-phase HPLC analysis was carried out using a Waters Symmetry (4.6×250 mm) column and heptane–isopropanol (95/5, v/v) as eluant (1 mL/min).