# A Total Synthesis of (+)-Bacillamide B

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Dedicated to Prof. Gerald Pattenden on the occasion of his 70th birthday in recognition of his elegant work on the biomimetic synthesis of natural products and his unique wit, humour, inspiration and support.

**Abstract:** A total synthesis of the halophile-derived natural product (+)-bacillamide B is described. The route relies upon a Hantzsch synthesis of ethyl (*S*)-2-acetoxyethylthiazole-4-carboxylate followed by a dipyridyl disulfide-mediated coupling between the corresponding carboxylic acid and tryptamine. This synthesis has unambiguously demonstrated that in contrast to the previous tentative stereochemical assignments the stereochemistry of the alcohol at C15 of the title compound has *S*-configuration.

**Key words:** extremophile, total synthesis, natural product, heterocycle, thiazole

Extremophiles, organisms that proliferate under conditions detrimental to the majority of life on Earth, offer us a glimpse at how life on primordial earth may have existed, or indeed, even been created. As such, there is considerable astrobiological interest in extremophiles.[1] Extremophiles also have considerable commercial significance,[2] since examination of how they have adapted, both chemically and enzymatically, to their hostile habitats may act as a catalyst for the discovery of useful new processes. For example, it was the isolation of a DNA polymerase from a thermophilic organism (later called *Thermus aquaticus*) found in a thermal pool in Yellowstone National Park that was to become the cornerstone of the polymerase chain reaction (PCR) and revolutionise genetic science.[3] Other notable applications of extremophiles in modern life include the use of ectoines in skin creams and cryophile-derived lipases in low-temperature washing detergents. Aside from the extremolytes and extremozymes, there are an ever increasing number of intriguing natural products being isolated from extremophiles.[4] Bacillamide B (**2**; Figure 1) was recently isolated from a new bacterium, *Bacillus endophyticus*, which was found living in a hypersaline microbial mat found at Salt Pond, San Salvador Island, Bahamas.[5] Also isolated were the previously identified congener bacillamide A (**1**),[6] as well as a second novel metabolite bacillamide C (**3**). Bacillamide B (**2**) is a tryptamide thiazole which may be biogenetically derived from tryptamine, cysteine and lactic acid. Its antibacterial activity was measured against an MRSA but, due to a dearth of material (only 1 mg was isolated), along with a lack of appropriate test organisms, a full analysis of bioactivity was not carried out. The stereochemistry of the alcohol at C15 of bacillamide B (**2**) was assigned as having an *R*-configuration by comparison of its circular dichroism (CD) spectrum with that of a closely related metabolite, *N*-3′-indolylethyl-2α-aminoethylthiazole-4-carboxamide (**4**).[7] The stereochemistry of this latter compound was only assigned by a second comparison of CD spectra, in this case, with those of *N*-salicylidene derivatives of some model α-arylalkylamines.[8] Since it was assumed that a thiazole would create a similar interaction with the salicylidenimino moiety to that of an aryl ring, a somewhat tenuous assumption, the authors describe their assignement as only 'tentative'. This potential uncertainty regarding the absolute stereochemistry, coupled with the fact that such small quantities of bacillamide B (**2**) were isolated among the natural products obtained from the newly discovered bacterium, *Bacillus endophyticus*, itself isolated from such an unusual source, prompted the present synthesis.

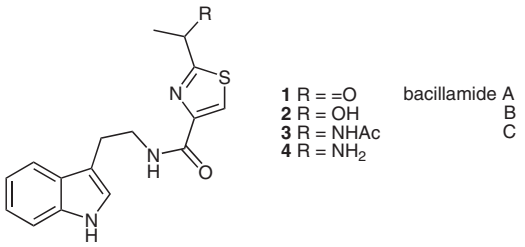


**Figure 1**

We sought to synthesise bacillamide B (**2**) by coupling tryptamine with the appropriate thiazole carboxylic acid. Our synthesis began with commercially available (*S*)-2-acetoxypropionyl chloride (**5**),[9] which was readily converted into amide **6** in 88% yield by treatment with $NH_3$ gas in $CH_2Cl_2$ (Scheme 1). Subsequent treatment with Lawesson's reagent in 1,4-dioxane gave the corresponding thioamide **7** in 69% yield, following flash column chromatography. Traditional Hantzsch synthesis of thiazoles bearing α-chiral centres can result in complete racemisation.[10] However, Schmidt and co-workers have reported that addition of ethyloxirane, which traps the HBr generated in situ forming a bromohydrin, serves to prevent epimerisation in such reactions.[11] Thus, reaction of thioamide **7** with ethyl bromopyruvate in the presence of ethyloxirane gave an intermediate hemiaminal which was subsequently dehydrated with neat trifluoroacetic anhydride to give ethyl (*S*)-2-acetoxyethylthiazole-4-car-

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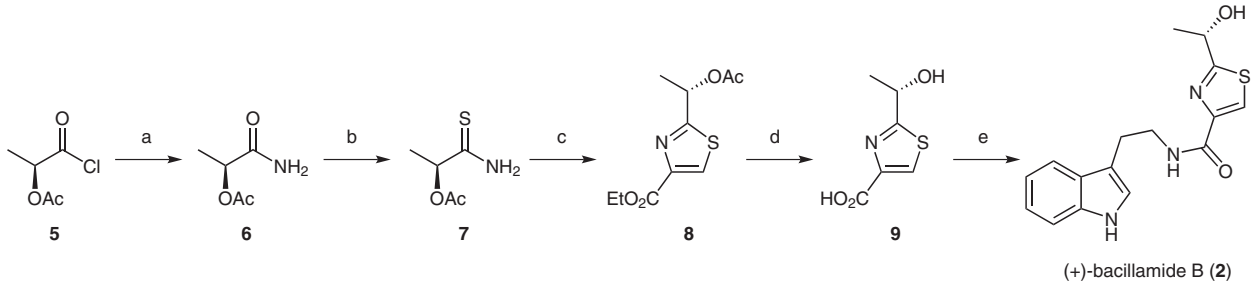


**Scheme 1** *Reagents and Conditions*: (a) $NH_3$, $CH_2Cl_2$, 20 °C, 1 h, 88%; (b) Lawesson's reagent (2 equiv), 1,4-dioxane, 20 °C, 16 h, 69%; (c) (i) ethyl bromopyruvate, ethyloxirane, *i*-PrOH, 60 °C, 30 min; (ii) $(CF_3CO)_2O$, 20 °C, 30 min, 58% (2 steps); (d) 2 M LiOH, THF–MeOH; 20 °C, 24 h, 80%; (e) dipyridyl disulfide, $Ph_3P$, tryptamine, $CH_2Cl_2$, 20 °C, 16 h, 54%.

boxylate (**8**), in 58% yield over two steps. Saponification of diester **8** with 2M LiOH in THF/MeOH gave thiazole carboxylic acid **9** in 80% yield.[12] Finally, a dipyridyl disulfide-mediated coupling[13] of thiazole carboxylic acid **9** with tryptamine furnished bacillamide B (**2**) in 54% yield.[14]

The NMR and IR spectra for synthetic bacillamide B (**2**) matched those reported for the natural compound,[5] as did the sign of the specific rotation and the characteristics of the CD spectrum, indicating that we had indeed synthesised natural (+)-bacillamide B (**2**). However, we had begun our synthesis with (*S*)-2-acetoxypropionyl chloride (**5**) which, on the basis of the original stereochemical assignment,[5] should have given (–)-bacillamide B (**2**). Thus, our synthesis demonstrates that the proposed stereochemical assignment of the alcohol at C15 of (+)-bacillamide (**2**) was incorrect, and that, in fact, this centre has an *S*-configuration. The stereochemical assignment of bacillamide C and also the recently isolated natural product neobacillamide A[15] should thus also be called into question. Assuming that the biosynthetic origin of (+)-bacillamide B (**2**) is indeed as described above, then D-(+)-lactic acid, the natural and biologically more relevant isomer, is a precursor, rather than the unnatural (–)-antipode, which the original stereochemical assignment of **2** would have implied.

In conclusion, a six-step synthesis of (+)-bacillamide B (**2**) has been accomplished which relies upon a Hantzsch synthesis of ethyl (*S*)-2-acetoxyethylthiazole-4-carboxylate (**8**), followed by a dipyridyl disulfide/$Ph_3P$-mediated coupling between the corresponding carboxylic acid **9** and tryptamine. This synthesis has unambiguously demonstrated the stereochemistry of the alcohol at C15 is of *S*-configuration. The synthesis serves to demonstrate that stereochemical assignment based upon multiple comparisons of CD spectra is not reliable, particularly when there is only marginal analogy between the substituents in question.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) (*S*)-2-Hydroxyethylthiazole-4-carboxylic acid (**9**): Ethyl (*S*)-2-acetoxyethylthiazole-4-carboxylate[11] (**8**; 121 mg, 0.50 mmol) was stirred in a solution of 2 M LiOH (1 mL), MeOH (1 mL) and THF (1 mL) at 20 °C for 18 h. After this time the mixture was diluted with water (5 mL) and shaken with acidified IR-120 ion-exchange resin (3 mL) for 2 min. The ion-exchange resin was filtered and the filtrate was evaporated to give ethyl (*S*)-2-hydroxyethylthiazole-4-carboxylic acid (**9**; 69 mg, 88%) as a yellow oil. IR (film): 3301, 1703, 1495, 1195 $cm^{-1}$; $^1H$ NMR (270 MHz, acetone-$d_6$): δ = 1.55 (d, *J* = 6.7 Hz, 3 H, $CH_3$), 5.09 (q, *J* = 6.7 Hz, 3 H, C*H*OH), 8.30 (s, 1 H, SCH); $^{13}C$ NMR (67.5 MHz, acetone-$d_6$): δ = 24.8 ($CH_3$), 68.9 (CHOH), 128.9 (C5), 148.3 (C4), 162.8 ($CO_2H$), 179.8 (C2).
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(14) (+)-Bacillamide B (**2**): A solution of tryptamine (6.4 mg, 0.04 mmol) and $Ph_3P$ (10.5 mg, 0.04 mmol) in $CH_2Cl_2$ (2

mL) was added dropwise over 5 min to a solution of (*S*)-2-hydroxyethylthiazole-4-carboxylic acid (**9**; 6.9 mg, 0.04 mmol) and dipyridyl disulfide (8.8 mg, 0.04 mmol) in $CH_2Cl_2$ (2 mL) at 20 °C. After 24 h, the supernatant solvent was removed and evaporated in vacuo. The residue was purified by flash column chromatography ($SiO_2$; 2% MeOH–$CHCl_3$) to give bacillamide B (**2**; 6.8 mg, 54%) as a light-yellow amorphous solid. $[\alpha]_D^{20}$ +10.1 (*c* 0.10, MeOH) [Lit.[5] +7.4 (*c* 0.095, MeOH)]; IR (film): 3411bw, 3293bw, 2923w, 1642s, 1546s, 1492m, 1456m, 1250w, 1187w, 1103m, 1009w $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 10.81 (s, 1 H), 8.35 (t, *J* = 6.0 Hz, 1 H), 8.13 (s, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.18 (d, *J* = 1.7 Hz, 1 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.97 (t, *J* = 7.4 Hz, 1 H), 6.24 (d, *J* = 5.0 Hz, 1 H), 4.94 (dq, *J* = 6.5, 5.2 Hz, 1 H), 3.54 (dd, *J* = 7.0, 6.5 Hz, 2 H), 2.93 (t, *J* = 7.5 Hz, 2 H), 1.47 (d, *J* = 6.5 Hz, 3 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 178.6, 160.5, 149.9, 136.2, 127.2, 123.0, 122.5, 120.9, 118.40, 118.20, 111.7, 111.3, 66.6, 25.3, 24.1; MS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}N_3O_2S$: 316.1120; found: 316.1128.

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