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Total syntheses of bacillamide C and neobacillamide A; revision of their absolute configurations

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ABSTRACT

The enantiospecific syntheses of both enantiomers of bacillamide C and neobacillamide A are described, along with the measurement of their optical activities, leading to the revision of the proposed absolute configurations of these natural products.

1. Introduction

Several natural products containing 2-(1-aminoethyl)thiazole-4-carboxylic acid **1** have been isolated from microorganisms that grow in marine and terrestrial biomass (Fig. 1). This scaffold has an asymmetric carbon atom on the α-aminoethyl group that biosynthetically derives from alanine. The (*S*)-enantiomer of **1** is derived from L-(+)-alanine and the (*R*)-enantiomer from D-(−)-alanine. Despite the importance of the enantiomeric forms of bioactive natural products, there is widespread confusion in the literature on this aspect of some of the metabolites containing this moiety.

A tryptamine amide of **1**, the alkaloid **2** (Fig. 1), having local anesthetic action, was isolated from a thermophilic actinomycete from the soil *Thermoactinomyces* strain TM-64.[1] Its structure was determined on the basis of its chemical reactions and combined spectroscopy techniques (^{1}H and ^{13}C NMR, HRMS, IR). This metabolite showed $[\alpha]_D^{20} = -6.0$ while the absolute configuration of the stereogenic center was tentatively determined as (*S*) by comparison of the circular dichroism (CD) of the *N*-salicylidene derivative with *N*-salicylidenes of (*S*)-α-aryl-alkylamines (having an aryl group instead of a thiazole). The total synthesis of **2** was performed from L-(+)-alanine and its configuration was confirmed as (*S*) although the product obtained showed extensive racemization.[2]

Bacillamide C was isolated from a culture of *Bacillus endophyticus* SP31 obtained on a bioassay-guided investigation from a hypersaline microbial mat. The bacillamide C showed $[\alpha]_D^{24} = -15.2$ (*c* 0.082, MeOH).[3] The asymmetric carbon center of **3** was tentatively determinated as (*R*) by comparison of its CD spectra with that reported for **2** (Fig. 1).

Microbiaeratin was isolated from a culture of *Microbispora aerata* IMBAS-11A obtained from penguin excrements collected at the Antartic.[4] The planar structure of microbiaeratin was the same as bacillamide C comparing their spectroscopic data with those reported. However, the optical activity of microbiaretin was not reported. In a similar manner, another metabolite was isolated from a culture of Thermoactinomyces strain TA66-2 obtained from hot-spring water. This metabolite also has the planar structure of bacillamide C, but its specific rotation was not reported.[5]

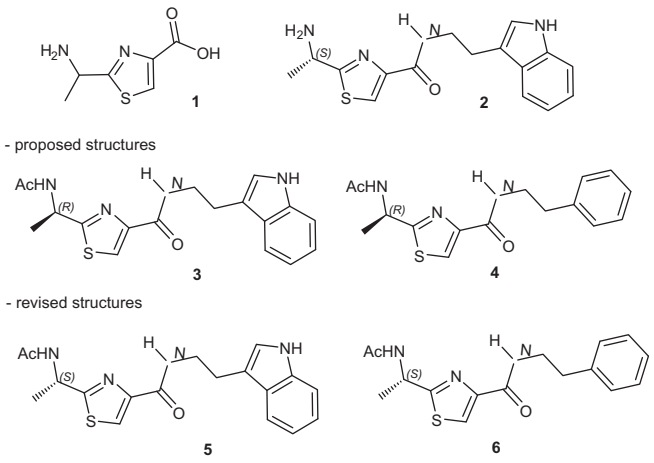

Figure 1. Metabolites containing 2-(1-aminoethyl)thiazole-4-carboxylic acid; proposed and revised structures for bacillamide C and neobacillamide A.

Neobacillamide A, a phenethylamine amide analogue of bacillamide C, together with bacillamide C was isolated from a culture of *Bacillus atrophaeus* C89 obtained from the marine sponge *Dysidea avara*.[6] Neobacillamide A was characterized as the (*R*)-enantiomer by comparison of its specific rotation ($[\alpha]_D^{24} = -16.0$) with the specific rotation of bacillamide C previously reported.[3] The proposed structure for neobacillamide was **4** (Fig. 1).

A total synthesis of (*R*)-bacillamide C from D-(−)-alanine was performed by Xu et al.,[7] and a convergent synthesis of bacillamide

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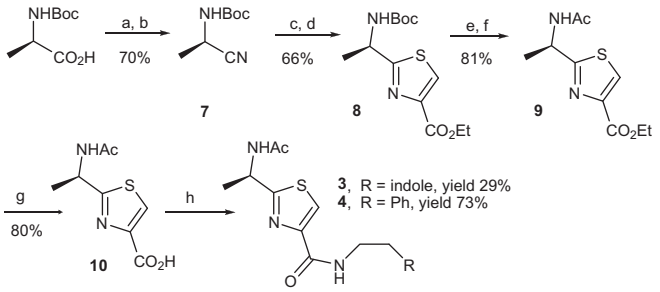

Scheme 1. Reagents and conditions: (a) NH_3 (g), $ClCO_2Et$, Et_3N, THF, −10 °C; (b) TFAA, Py, THF, rt; (c) cysteine ethylester hydrochloride, phosphate buffer pH 7, MeOH, 60 °C; (d) DBU, $BrCCl_3$, CH_2Cl_2, −10 °C; (e) TFA, CH_2Cl_2, rt; (f) Ac_2O, Py, rt; (g) 10% aqueous KOH, THF, rt; (h) tryptamine, HBTU, DIPEA, 0 °C to rt or 2-phenetylamine, $ClCO_2Et$, Et_3N, THF, −5 °C to rt.

C and analogues using a chiral auxiliary was performed by Dömling et al.[8] However in both studies, the specific rotation was not compared to the natural product nor was it reported.

In our studies on the synthesis of marine products and their analogues our aim was to obtain (*R*)-bacillamide C and (*R*)-neobacillamide A by a stereospecific route from D-(−)-alanine. The total syntheses of both via a common key intermediate **10** are described here in (Scheme 1). The signs of the specific rotation of the synthesized compounds did not match with those reported. Both (*S*)-enantiomers were also synthesized to confirm these results.

2. Results and discussion

The synthesis of the common key intermediate **10** was performed by the stereospecific sequence of reactions as shown in Scheme 1. We began this synthesis with Boc-D-(+)-alanine having the (*R*)-configuration. The Boc-D-(+)-alanine led to the amide using ethylchloroformate and ammonia at −10 °C, which was then converted into nitrile **7** by dehydration with trifluoroacetic anhydride and triethylamine. The condensation of **7** with cysteine ethylester hydrochloride under buffered conditions in an aqueous methanol medium gave the thiazoline, which then was oxidized to thiazole **8** by bromotrichloromethane and DBU.

The Boc group of **8** was hydrolyzed with trifluoroacetic acid after which the amine was acetylated by acetic anhydride in pyridine. Intermediate **10** was then obtained by alkaline hydrolysis of ethyl ester. The (*R*)-bacillamide C **3** was obtained by coupling **10** with tryptamine with an HBTU reagent. The methodology to prepare the thiazoline ring using a nitrile and cysteine is not a common method for thiazoline with an α stereogenic carbon.[9] The enantiopurity of intermediates **8** and **3** were confirmed by chiral HPLC. The ^1H NMR, ^{13}C NMR, and HRMS data of **3** were in agreement with previously reported data, however the specific rotation of this product was $[\alpha]_D^{24} = +23.1$(*c* 4.71, MeOH), which is the opposite sign of the natural product.[3]Similarly (*R*)-neobacillamide A **4** was prepared from intermediate **10** and 2-phenethylamine using ethyl chloroformate as an activating agent. The spectroscopic data of **4** were in agreement with the reported data but the specific rotation $[\alpha]_D^{24} = +22.5$(*c* 7.25, MeOH) was contrary to the natural product; lit.[4] $[\alpha]_D^{24} = -16.0$ (*c* 0.10, MeOH).

The reaction sequences were performed again, but this time starting from Boc-L-(−)-alanine to obtain the (*S*)-enantiomers. The specific rotation of (*S*)-bacillamide C **5** was $[\alpha]_D^{24} = -23.7$ (*c* 4.99, MeOH) while that of (*S*)-neobacillamide A **6** was$[\alpha]_D^{24} = -24.1$ (*c* 7.37, MeOH); these were in agreement with the specific rotations of the corresponding natural products.

This result is especially important when producing bacillamide C from cultures of *Bacillus atrophaeus* strain C89 to serve as a building block in potently bioactive cyclic peptides.[10] Also the revised absolute configuration of bacillamide C and neobacillamide A shows they are derived of L-(+)-alanine; and this is important for genomic studies of their biosynthesis.[11] Bacillamides-type metabolites containing the scaffold **1** derived from D-(−)-alanine have not been confirmed in the literature, however, other metabolites from microorganisms containing it, such as the argyrins, have been reported.[12]

3. Conclusion

In conclusion, our stereospecific syntheses of **5** and **6** from L-(+)-alanine via the common key intermediate **10**, showed that their spectroscopic data and optical activities were consistent with those reported for bacillamide C and neobacillamide A, respectively. These results allowed us to conclude that the absolute configuration of the natural products bacillamide C and neobacillamide A should be revised to (*S*).

4. Experimental section

4.1. General procedures

All reagents were of reagent grade and used without further purification unless specified otherwise. Solvents for the reactions were distilled prior to use: THF was distilled from Na and benzophenone, and CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere in flame-dried or oven-dried glassware with magnetic stirring. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz and 100 MHz, respectively. Spectra were recorded at 25 °C in $CDCl_3$ or DMSO-d_6. ^1H spectra were referenced internally to the solvent signal ($CHCl_3$, 7.26 ppm; DMSO, 2.50 ppm) and ^{13}C spectra to the solvent signal ($CDCl_3$, 77.00 ppm; DMSO-d_6, 39.52 ppm). The coupling constants *J* are given in Hz. The signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet, and br = broad. Optical rotations were measured on a digital polarimeter using a 0.7 mL cell with a 0.5 dm path length. Low resolution direct inlet electron impact mass spectra (EI-MS) were taken on a Shimadzu QP 2010 plus mass spectrometer, operating at 70 eV, and *m*/*z* ratios are reported as values in atomic mass units. High resolution mass analyses (HR-MS) were performed in ESI mode taken on a Bruker micrOTOF-Q. HPLC analyses were conducted with a Shimadzu instrument using a Chiralcel OD column (4.6 × 250 mm). Mobile phase for isocratic mode was a mixture of *n*-hexane and 2-propanol 90:10 (v/v) for the enantiomeric analysis of **8**. The enantiomeric analyses of the bacillamides were performed using gradient elution of *n*-hexane and 2-propanol, beginning with a mixture of 90:10 (v/v) to 40:60 (v/v). Column chromatography was carried out using silica gel (60–120 mesh or 100–200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether were used for column chromatography and were distilled prior to use.

4.2. Synthesis of *N*-Boc-(*R*)-alanine amide

To a stirred solution of *N*-Boc-(*R*)-alanine (5.0 g, 26.4 mmol) in dry THF at −10 °C, were added triethylamine (3 mL, 21.12 mmol) and ethyl chloroformate (2.5 mL, 26.4 mmol). The reaction mixture was stirred for 1 h and then NH_3 (g) was bubbled for 1.5 h. The mixture was then stirred at room temperature overnight. Next, THF was removed under reduced pressure, after which NaCl sat. sol. (40 mL) was added and extracted with EtOAc (5 × 40 mL).

The organic layer was washed with HCl 0.5 M (2 × 30 mL) and dried over Na_2SO_4, filtered, and evaporated under vacuum, to give the amide (82% yield) as a white solid; $[\alpha]_D^{24} = +36.6$ (*c* 0.74, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.52 (br s, 1H), 6.10 (br s, 1H), 5.30 (br s, 1H), 4.21 (br s, 1H), 1.41 (s, 9H), 1.35 (d, *J* 7.07 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 175.32, 155.54, 80.18, 59.45, 28.28, 18.25.

4.3. Synthesis of *N*-Boc-(*S*)-alanine amide

The procedure 4.2 was performed using *N*-Boc-(*S*)-alanine to give the amide (89% yield); $[\alpha]_D^{24} = -37.5$(*c* 0.77, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical with those of *N*-Boc-(*R*)-alanine amide.

4.4. Synthesis of *N*-Boc-(*R*)-alanine nitrile 7

To a stirred solution of *N*-Boc-(*R*)-alanine amide (3.0 g, 15.94 mmol) in dry THF was added dry pyridine (5.15 mL, 63.76 mmol). The trifluoroacetic anhydride (4.4 mL, 31.76 mmol) was then added at 0 °C. The reaction mixture was then stirred for 2 h. Next, THF was removed under reduced pressure. The concentrate was dissolved in EtOAc (40 mL), washed with HCl 0.5 M (5 × 20 mL), half-satd aq $NaHCO_3$ solution (20 mL) and dried over Na_2SO_4. The solvent was evaporated under vacuum, to give **7** (85% yield) as a yellow solid; δ_H (400 MHz $CDCl_3$) 4.81 (br s, 1H), 4.61 (br s, 1H), 1.54 (d, *J* 7.2 Hz, 3H), 1.46 (s, 9H); δ_C (100 MHz $CDCl_3$) 154.04, 119.49, 81.27, 37.58, 28.20, 19.59.

4.5. Synthesis of *N*-Boc-(*S*)-alanine nitrile

The procedure in Section 4.4 was performed using *N*-Boc-(*S*)-alanine amide to give the corresponding nitrile (87% yield). The ^1H and ^{13}C NMR spectra were identical with those of *N*-Boc (*R*)-alanine nitrile.

4.6. Synthesis of (*R*)-ethyl 2-(1-(*tert*-butoxycarbonylamino) ethyl)thiazole-4-carboxylate 8

Cysteine ethyl ester (1.60 g, 8.68 mmol) and **7** (1.13 g, 6.63 mmol) were dissolved in a 1 M sodium phosphate buffer pH 7 (5 mL) and degassed by bubbling nitrogen for 10 min. The reaction mixture was then stirred at room temperature for 3 h. The reaction mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo, to give a crude product. The residue was purified by flash chromatography (EtOAc/PE; 40:60) to give the thiazoline. To a solution of the thiazoline (1.35 g, 4.46 mmol) in dry CH_2Cl_2 (20 mL), at −20 °C was added $BrCCl_3$ (1.7 mL, 16.96 mmol) and the reaction mixture was stirred for 15 min. The DBU (2.5 mL, 19.96 mmol) was then added and the reaction mixture was stirred for an additional 2 h. The CH_2Cl_2 was evaporated under vacuum, to give a crude product, which was purified by flash chromatography (EtOAc/PE; 40:60) to give **8** (79% yield), as a brown oil; $[\alpha]_D^{24} = +11.3$ (*c* 0.65, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.06 (s, 1H), 5.25 (s, 1H), 5.08 (m, 1H), 4.39 (q, *J* = 7.12 Hz, 2H), 1.60 (d, *J* = 6.91 Hz, 3H), 1.42 (s, 9H), 1.37 (t, *J* = 7.13 Hz, 3H); δ_C (100 MHz, $CDCl_3$): 174.93, 161.35, 154.88, 147.17, 127.16, 80.24, 61.43, 48.92, 28.30, 21.75, 14.36; MS ID 300.10, found 300.11

4.7. Synthesis of (*S*)-ethyl 2-(1-(*tert*-butoxycarbonylamino) ethyl)thiazole-4-carboxylate

The procedure in Section 4.6 was performed using *N*-Boc-(*S*)-alanine nitrile to give the corresponding thiazole (95% yield) as a brown oil; $[\alpha]_D^{24} = -11.7$ (*c* 1.05, MeOH). The ^1H and ^{13}C NMR spectra were identical with those of **8**.

4.8. Synthesis of (*R*)-ethyl 2-(1-acetamidoethyl)thiazole-4-carboxylate 9

The *N*-Boc deprotection of **8** was performed using TFA according to the established literature method and the crude product was acetylated with acetic anhydride and pyridine to give product **9** (84% yield last 2steps) as a brown oil; $[\alpha]_D^{24} = +29.1$ (*c* 0.47, $CHCl_3$); ν_{max} (NaCl) 3264 (br), 2985, 1720, 1655, 1373, 1219, 1022, 764 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.09 (s, 1H), 6.66 (m, 1H), 5.42 (p, *J* 7.05 Hz, 1H), 4.41 (q, *J* 7.11 Hz, 2H), 2.05 (s, 3H), 1.63 (d, *J* 6.93 Hz, 3H), 1.39 (t, *J* 7.11 Hz, 3H), δ_C (100 MHz, $CDCl_3$): 172.67, 170.22, 161.13, 146.81, 127.37, 61.55, 47.20, 22.97, 21.72, 14.28.

4.9. Synthesis of (*S*)-ethyl 2-(1-acetamidoethyl)thiazole-4-carboxylate

The procedure in Section 4.8 was performed using (*S*)-**8** to give the corresponding acetamide (91% yield last 2 steps) as a brown oil; $[\alpha]_D^{24} = -50.5$ (*c* 0.45, $CHCl_3$). The IR spectra, ^1H and ^{13}C NMR spectra were identical to those of **9**.

4.10. Synthesis of (*R*)-2-(1-acetamidoethyl)thiazole-4-carboxylic acid 10

To a solution of thiazole **9** (0.085 g, 0.35 mmol) in THF (2 mL), was added KOH 10% (2 mL), and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated in vacuo. To the resulting solution was added H_2O (5 mL), after which it was acidified to pH 1–2 with HCl (6 M) and extracted with EtOAc (15 mL × 3), dried over Na_2SO_4, and evaporated under vacuum, to give **10** (74% yield) as a yellow oil; δ_H (400 MHz, $(CD_3)_2CO$) 8.29 (s, 1H); 7.90 (m, 1H), 5.32 (m, 1H), 1.97 (s, 3H), 1.57 (d, *J* = 7.04 Hz, 3H); δ_C (100 MHz, $(CD_3)_2CO$) 176.68, 171.04, 163.21, 148.85, 129.65, 48.84, 23.66, 21.71.

4.11. Synthesis of (*S*)-2-(1-acetamidoethyl)thiazole-4-carboxylic acid

The procedure in Section 4.10 was performed using (*S*)-thiazole **9** to give the corresponding acid (*S*)-**10** (72% yield) as a yellow oil. The ^1H and ^{13}C NMR spectra were identical with those of (*R*)-**10**.

4.12. Synthesis of (*R*)-(*N*-(2-(1H-indol-3-yl)ethyl)-2-(1-acetamidoethyl)thiazole-4-carboxamide 3

To a solution of **10** (0.081 g, 0.38 mmol) and tryptamine (0.073 g, 0.45 mmol) in dry CH_2Cl_2, at 0 °C were added HBTU (0.171 g, 0.45 mmol), DIPEA (0.15 mL, 0.84 mmol), and 4-DMAP (cat.). The reaction mixture was then warmed up to room temperature, and stirred for 6 h. To the resulting solution was added HCl 5% (10 mL) and it was extracted with EtOAc (20 mL × 3). The organic layer was washed with $NaHCO_3$ solution, dried over Na_2SO_4, and the solvent was evaporated under vacuum to give the crude product, which was purified by flash chromatography (EtOAc/PE/MeOH; 30:70:5) to give **3** (29%) as a light brown oil; $[\alpha]_D^{24} = +23.1$ (*c* 4.71, MeOH); ν_{max} (NaCl) 3283 (br), 2978, 1928, 1655, 1547, 1493, 1439, 1265, 1042, 741 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 10.83 (s, 1H), 8.71 (d, *J* 7.6 Hz, 1H), 8.40 (t, *J* 6.0 Hz, 1H), 8.12 (s, 1H), 7.61 (d, *J* 7.9 Hz, 1H), 7.33 (d, *J* 8.05 Hz, 1H), 7.18 (d, *J* 2.3 Hz, 1H), 7.06 (m, 1H), 6.98 (m, 1H), 5.15 (p, *J* 7.1 Hz, 1H), 3.54 (dd, *J* 14.6, 6.6 Hz, 2H), 2.94 (m, 2H), 1.90 (s, 3H), 1.50 (d, *J* 7.0 Hz, 3H); δ_χ (100 MHz, DMSO-d_6) 175.02, 169.04, 160.29, 149.68, 136.18, 127.15, 123.12, 122.50, 120.88, 118.32, 118.14, 111.65, 111.28, 46.66, 39.78, 25.23, 22.40, 20.38; HRMS ESI: MH+, found 357.1387. $C_{18}H_{21}N_4O_2S$ requires 357.1385.

4.13. Synthesis of bacillamide C, (*S*)-(*N*-(2-(1*H*-indol-3-yl)ethyl)-2-(1-acetamidoethyl)thiazole-4-carboxamide 5

The procedure in Section 4.12 was performed using acid (*S*)-**10** to give **5** (68%) as light brown oil; $[\alpha]_D^{24} = -23.6$ (*c* 4.99, MeOH). The IR, HRMS ESI, ^{1}H, and ^{13}C NMR spectra were identical with those of **3** and with those reported for bacillamide C.

4.14. Synthesis of (*R*)-(*N*-(2-phenethyl)-2-(1-acetamidoethyl) thiazole-4-carboxamide 4

To a solution of **10** (0.15 g, 0.55 mmol) in dry THF at −5 °C, were added Et_3N (0.08 mL, 0.55 mmol) and ethyl chloroformate (0.05 mL, 0.55 mmol). The reaction mixture was then stirred for 1 h, and warmed to room temperature. The 2-phenylethanamine (0.08 g, 0.66 mmol) was added and the reaction mixture was stirred at room temperature overnight. The EtOAc (15 mL) was added, and washed with $KHCO_3$ 5% (15 mL), H_2O (15 mL), HCl 5% (15 mL), and H_2O (15 mL), dried over Na_2SO_4 and the solvent was evaporated under vacuum to give the crude product, which was purified by flash chromatography (EtOAc/PE; 30:70), to give **4** (73%) as a light brown oil; $[\alpha]_D^{24} = +22.5$ (*c* 7.25, MeOH); ν_{max} (NaCl) 3267 (br), 2932, 2859, 1655, 1543, 1493, 1447, 1254, 1042, 748 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.02 (s, 1H), 7.34 (m, 3H), 7.26 (m, 3H), 6.12 (d, *J* 7.9 Hz, 1H), 5.36 (m, 1H), 3.70 (ddd, *J* 13.3, 7.1, 2.1 Hz, 2H), 2.93 (t, *J* 7.1 Hz, 2H), 2.06 (s, 3H), 1.59 (d, *J* 6.9 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 172.41, 169.46, 160.89, 149.66, 138.82, 128.83, 128.62, 126.54, 123.16, 47.02, 40.55, 35.84, 23.23, 21.38. HRMS ESI: MH^-, found 316.11224. $C_{16}H_{18}N_3O_2S$ requires 316.11197.

4.15. Synthesis of neobacillamide A, (*S*)-(*N*-(2-phenethyl)-2-(1-acetamidoethyl)thiazole-4-carboxamide 6

The procedure 4.14 was performed using the acid (*S*)-**10** to give **6** (94%) as a light brown oil; $[\alpha]_D^{24} = -24.1$ (*c* 7.37, MeOH). The IR, HRMS ESI, ^{1}H, and ^{13}C NMR spectra were identical with those of **4** and with those reported for neobacillamide A.

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