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ORIGINAL PAPER

Total synthesis of racemic 1-aryl-tetrahydroisoquinoline alkaloids

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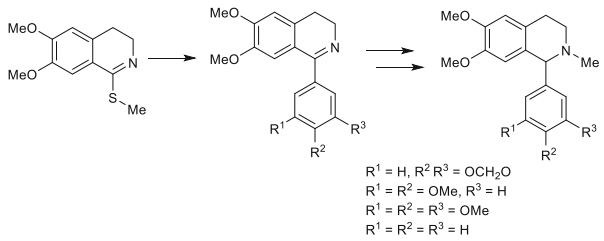
Abstract A new synthetic route was developed for the preparation of natural products cryptostyline I, II, III and 1-phenyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. The Liebeskind–Srogl palladium-catalyzed carbon–carbon cross-coupling protocol was used in the key step of the total synthesis.

Graphical abstract



Keywords Natural products · Heterocycles · Catalysis · Thionation · Liebeskind–Srogl reaction

Introduction

Cryptostylines (**1a**–**1c**) are rarely occurring tetrahydroisoquinoline alkaloids that contain variously substituted phenyl ring at position C-1 (Fig. 1). (+)-Cryptostyline I–III have been isolated from *Cryptostylis fulva* [1, 2]. Later, the absolute configuration of these compounds was determined [3, 4]. In 1974, Agurell et al. isolated (−)-cryptostyline I, II, and III from *Cryptostylis erythroglossa* [5]. The unsubstituted variation, the 1-phenyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline alkaloid (**1d**) (unnamed trivially), was isolated from *Adhatoda vasica* in 1998 [6].

The 1,2,3,4-tetrahydroisoquinoline ring is an important scaffold in organic and medicinal chemistry [7–12]. Accordingly, various methodologies have been described for the preparation of alkaloids **1a**–**1d** in both racemic [13–18] and enantiopure forms [19–28]. The retrosynthetic approaches to the construction of alkaloids **1a**–**1d** as the key step are outlined in Fig. 1. The most common procedures are the Pictet–Spengler condensation and the Bischler–Napieralski reaction (Fig. 1, Pathways A [15, 16] and B [18, 19, 21, 25, 28]). Takano et al. described the aryl radical-initiated cyclization for the synthesis of racemic cryptostylines I–III (**1a**–**1c**) (Fig. 1, Pathway C [17]). Another ring closure reaction has been described for the construction of the isoquinoline skeleton. For example, in the asymmetric synthesis of (*S*)-(+)-cryptostyline II, intramolecular lactamization was applied (Fig. 1, Pathway D [20, 26]). The C-1 arylation of *N*-alkyltetrahydroisoquinolines was reported as the key step of the synthesis of cryptostyline alkaloids **1a**–**1c** (Fig. 1, Pathway E [13, 14, 22–24, 27]).

The simple one-pot preparation of (±)-cryptostylines I–III (**1a**–**1c**) was described by Ruchiravat et al. starting from homoveratrylamine (**2**) and the appropriate aromatic aldehydes **3a**–**3c** (Scheme 1) [16]. The Pictet–Spengler condensation was carried out in formic acid. After that, formaldehyde was added to this mixture and the reaction continued. The products were obtained in good yields.

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The same synthetic route was applied for the preparation of racemic alkaloids **1a**, **1b**, and **1d** [15]. In this case, the Pictet–Spengler reaction was performed in boiling benzene catalyzed by triflouroacetic acid. Subsequent reductive methylation of the 1-aryl-1,2,3,4-tetrahydroisoquinoline intermediates (**4a**, **b**, **d**) with formaldehyde and $NaBH_4$ furnished compounds **1a**, **1b**, and **1d** in 62, 46, and 58 % yield, respectively.

Takano and co-workers reported an interesting synthesis of (±)-cryptostylines I–III (**1a**–**1c**) (Scheme 2) [17]. The Schiff base **5** was used as the starting material, which was treated with Bu_3SnH and azobisisobutyronitrile (AIBN). In the next step, a reductive methylation of intermediate **4a**–**4c** using formaldehyde and $NaBH_4$ gave the desired products in reasonable overall yields.

Recently, Singh et al. utilized the direct C-1 arylation of 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6**) in the synthesis of natural products (±)-**1a**–**1d** (Scheme 3). The target molecules were obtained by the reaction of in situ-prepared α-amino carbanion and appropriate aryl chloride [13] or direct arylation of **6** with aryl Grignard reagents via diethyl azodicarboxylate (DEAD)-mediated oxidative C–H activation [14].

Mollov's group reported a new synthetic method for the preparation of racemic cryptostiline III (**1c**) by the following route (Scheme 4) [18]. The treatment of (3,4-dimethoxyphenyl)acetic acid (**7**) and 3,4,5-trimethoxy-*N*-methylbenzamide (**8**) with $POCl_3$ produced isoquinoline derivative **9**. After this, intermediate **9** was transformed to (±)-cryptostyline III (**1c**) by a two-step reduction and the product was obtained in 31 % overall yield.

In continuation of our efforts in the field of alkaloid chemistry [29–31], we now describe a new synthesis of natural products (±)-**1a**–**1d**. In this approach, our earlier results were used for the preparation of 1-aryl-3,4-dihydroisoquinoline intermediates [32].

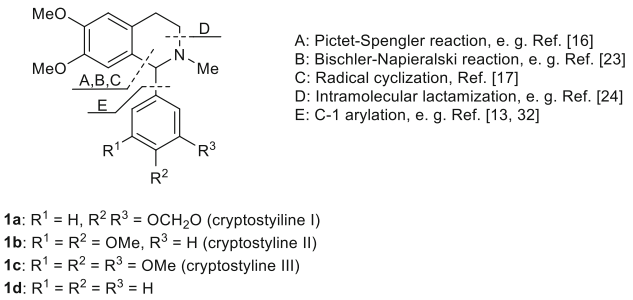
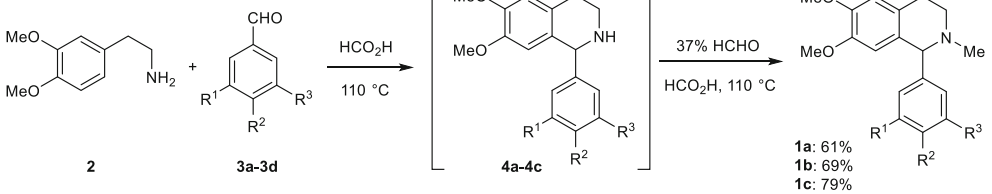


Fig. 1 Structure of the cryptostyline derivatives **1a**–**1d** described and the disconnection approaches leading to them

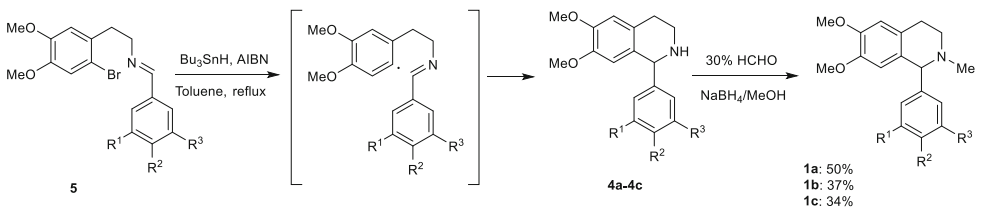
Results and discussion

The starting material for the synthesis of alkaloids **1a**–**1d** was 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**). This compound was prepared in acid-catalyzed Pictet–Spengler reaction according to literature procedure from 2-(3,4-dimethoxyphenyl)ethylamine and paraformaldehyde in a yield of 94 % [33]. The tetrahydroisoquinoline derivative **11** was then thionated with elemental sulfur according to our earlier microwave-assisted procedure in dimethylformamide at 170 °C [34] (Scheme 5). Thioamide **12** was obtained in 63 % yield after purification by chromatography. The key intermediate, 6,7-dimethoxy-(1-

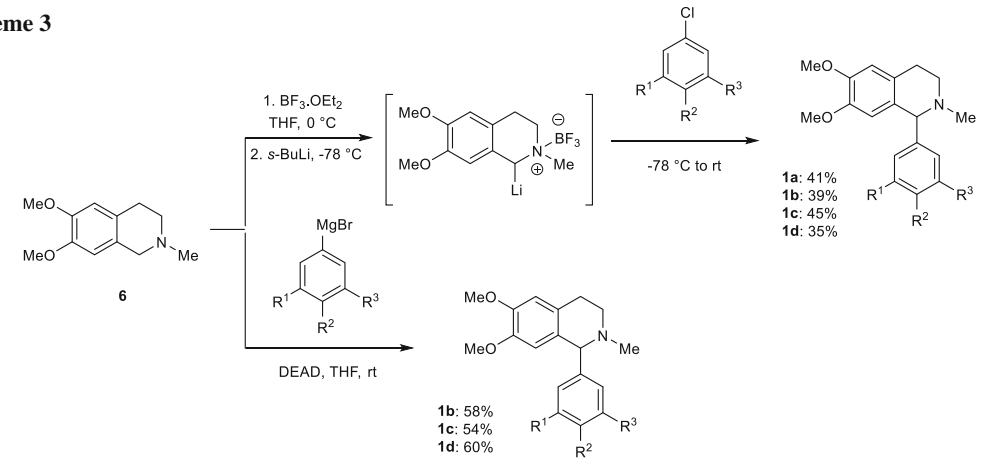
Scheme 1



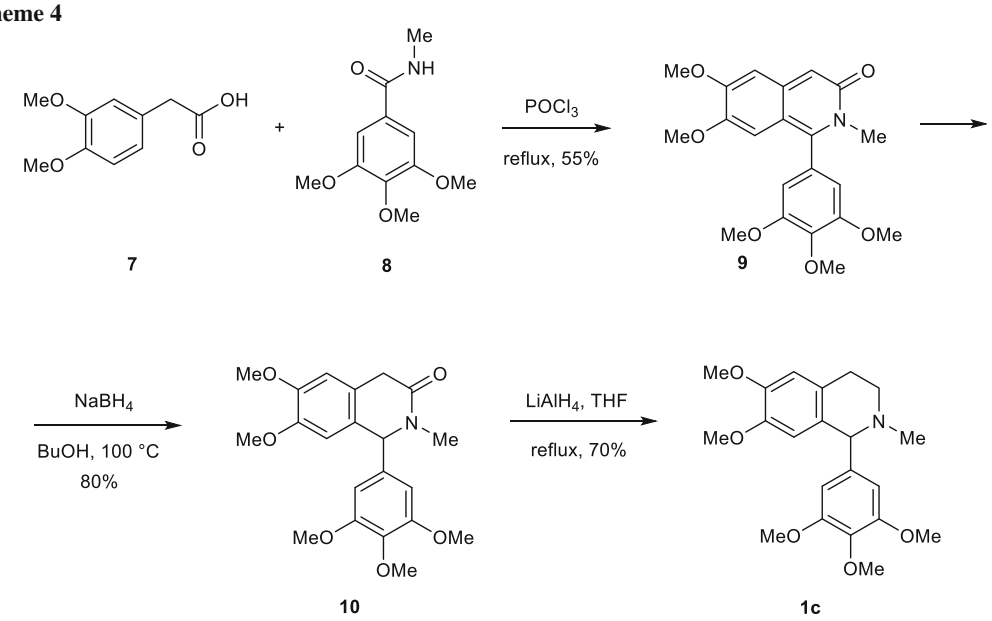
Scheme 2



Scheme 3



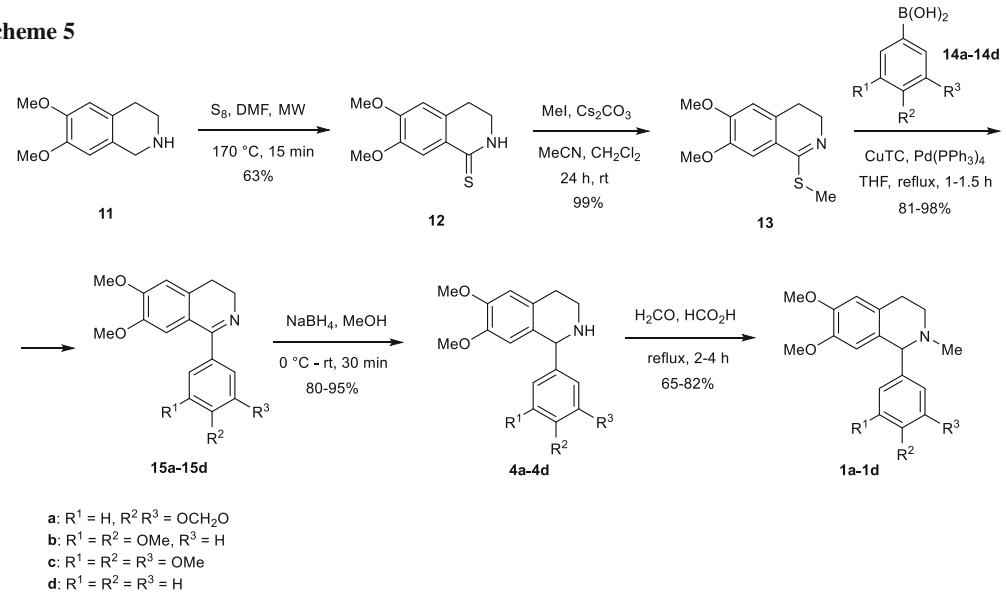
Scheme 4



methylsulfanyl)-3,4-dihydroisoquinoline (**13**) was prepared by solid–liquid phase S-methylation of the thioamide **12** with 1.1 equivalent of methyl iodide using Cs_2CO_3 in acetonitrile/dichloromethane at room temperature for 24 h [35] and was obtained in a yield of 99 %. The next step of the synthesis was the palladium-catalyzed Liebeskind–Srogl cross-coupling [32] with the appropriate boronic acids, 3,4-(methylenedioxy)phenylboronic acid (**14a**), 3,4-dimethoxyphenylboronic acid (**14b**), 3,4,5-trimethoxyphenylboronic acid (**14c**), and phenylboronic acid (**14d**). In this reaction, 10 mol% of $Pd(PPh_3)_4$ and 3 equivalents of copper(I)-thiophene-2-carboxylate (CuTC) cofactor were used. Intermediates **15a**–**15d** were isolated in excellent yields. 1-Aryl-3,4-dihydroisoquinoline derivatives **15a**–**15d** were then reduced by $NaBH_4$ in methanol [36] to give products **4a**–**4d** in a yield of 80–95 %. Finally, the racemic cryptostyline I, II, III and 1-phenyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline alkaloids (**1a**–**1d**) were synthesized by Eschweiler–Clarke methylation of amines **4a**–**4d**, respectively [11]. The products were obtained in reasonable yields (65–82 %). Compound **1a** was prepared only in 44 % yield, when the N-alkylation was carried out with CH_3I in the presence of Cs_2CO_3 using CH_3CN.

The reactions were followed by thin layer chromatography (TLC) and HPLC–MS. The intermediates and

Scheme 5



compounds prepared were identified and characterized by IR and ^{1}H and ^{13}C NMR spectroscopy.

Conclusion

In conclusion, a new synthetic route was developed for the preparation of 1-aryl-tetrahydroisoquinoline alkaloids **1a**–**1d**. The thionation of the starting material, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**) with elemental sulfur and the Liebeskind–Srogl cross-coupling reaction were used as the pivotal steps in the total synthesis. The natural products **1a**–**1d** were obtained in five steps in good overall yields.

Experimental

All melting points were determined on a Büchi B-540 capillary melting point apparatus. IR spectra were obtained on a Bruker Vector 22 FT spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 303 K on a Varian Unity Inova 500 (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or a Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or with a Bruker Avance III HD (600 and 150 MHz for ^{1}H and ^{13}C NMR spectra, respectively) spectrometer. DMSO-d_6 or $CDCl_3$ was used as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. The reactions were monitored by analytical TLC on silica gel 60 F_{254} and LC–MS chromatography. The purifications by flash column chromatography were carried out using Merck 107736 silica gel 60 H and applying hexane–dichloromethane or dichloromethane–methanol solvent systems. All reagents were purchased from commercial sources. Analytical samples of new compounds were obtained by recrystallization from the solvents or solvent mixtures given below in parentheses.

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2H)-thione (**12**)

A mixture of 1.00 g of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**, 5.17 mmol) and 0.33 g of sulfur (2 equiv., 10.34 mmol) in 20 cm^3 of DMF was kept in a vial that was placed in the MW reactor and irradiated at 170 °C for 15 min. The mixture was cooled and concentrated under reduced pressure. Purification by flash column chromatography afforded 0.73 g (63 %) **12**. M.p.: 223–224 °C ($CHCl_3$–EtOH 1:3) (Ref. [37] 223 °C).

6,7-Dimethoxy-1-(methylsulfanyl)-3,4-dihydroisoquinoline (**13**)

To a solution of 1.00 g of 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**12**, 4.48 mmol) and 1.75 g of Cs_2CO_3 (1.2 equiv., 5.38 mmol) in a mixture of 40 cm^3 of acetonitrile and 20 cm^3 of dichloromethane, 0.70 g of methyl iodide (1.1 equiv., 4.93 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. Then, the inorganic salts were filtered off, and the filtrate was concentrated. The residue was taken up in 30 cm^3 dichloromethane and the mixture was washed with 30 cm^3 water. Finally, the organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Yield: 1.05 g (99 %); m.p.: 91–92 °C (EtOH) (Ref. [37] 94–96 °C).

General procedure for the preparation of 1-aryl-3,4-dihydroisoquinolines: synthesis of compounds 15a–15d

To the stirred solution of 0.50 g 6,7-dimethoxy-1-(methylsulfanyl)-3,4-dihydroisoquinoline (**13**, 2.11 mmol) in 20 cm^3 abs. THF under argon atmosphere, the appropriate arylboronic acid (**14a–14d**, 1.2 equiv., 2.52 mmol), 1.21 g CuTC (3 equiv., 6.33 mmol), and 0.24 g $Pd(PPh_3)_4$ (10 mol%, 0.21 mmol) were added. The mixture was refluxed until the starting material disappeared (1–1.5 h). After cooling, the solvent was evaporated and a $CHCl_3$–MeOH (7:1) mixture (25 cm^3) was added. The crude reaction mixture was subsequently washed with 25 % aq NH_3 (2 × 30 cm^3). The aqueous layer was extracted with a $CHCl_3$–MeOH (7:1) mixture (2 × 25 cm^3). The combined organic phase was dried ($MgSO_4$), filtered, and the solvent evaporated. The crude material was purified by flash column chromatography.

1-(1,3-Benzodioxol-5-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**15a**)
Yield: 0.64 g (98 %). The product was characterized as the hydrochloride salt. M.p.: 219–221 °C (*i*-PrOH) (Ref. [38] 228 °C).

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**15b**)
Yield: 0.64 g (92 %); m.p.: 167–168 °C (MeCN) (Ref. [26] 168–169 °C).

6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline (**15c**)
Yield: 0.61 g (81 %); m.p.: 156–158 °C (EtOH–H_2O) (Ref. [39] 160 °C).

6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline (**15d**)
Yield: 0.52 g (93 %). The product was characterized as the hydrochloride salt. M.p.: 214–216 °C (MeCN, decomp.) (Ref. [40] 212–213 °C).

General procedure for the preparation of 1-aryl-1,2,3,4-tetrahydroisoquinolines: synthesis of compounds 4a–4d

To the stirred solution of 1-aryl-3,4-dihydroisoquinoline derivatives **15a–15d** (1.40 mmol) in 30 cm^3 MeOH at 0 °C, 0.16 g $NaBH_4$ (3 equiv., 4.20 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min and room temperature for 15 min. The solvent was removed under reduced pressure, and the reaction mixture was diluted with 20 cm^3 saturated aqueous $NaHCO_3$ and extracted with EtOAc (2 × 20 cm^3). The combined organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated. The crude material was purified by flash column chromatography.

1-(1,3-Benzodioxol-5-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**)
Yield: 0.39 g (90 %); m.p.: 128–129 °C (EtOH) (Ref. [41] 122–124 °C).

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4b**)
Yield: 0.42 g (90 %); m.p.: 101–102 °C (EtOH) (Ref. [21] 104–105 °C).

6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**4c**)
Yield: 0.40 g (80 %); m.p.: 106–108 °C (Et_2O) (Ref. [4] 108–110 °C).

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**4d**)
Yield: 0.36 g (95 %); m.p.: 111–113 °C (EtOH) (Ref. [42] 110–111 °C).

General procedure for the preparation of 1-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines: synthesis of compounds 1a–1d

The compounds **4a–4d** (0.80 mmol), 1.03 cm^3 formaldehyde (35 %, 13.1 mmol), and 1.60 cm^3 formic acid (98 %, 42.4 mmol) were stirred at reflux under argon atmosphere until the starting material disappeared (2–4 h). After cooling, the reaction mixture was concentrated. 10 % $NaHCO_3$ solution (15 cm^3) was added and the mixture was extracted with CH_2Cl_2 (2 × 15 cm^3). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by recrystallization or flash column chromatography.

1-(1,3-Benzodioxol-5-yl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (±)-cryptostyline I (**1a**)
Yield: 0.18 g (68 %); m.p.: 115–117 °C (EtOH) (Ref. [13] 116–117 °C).

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (±)-cryptostyline II (**1b**)
Yield: 0.18 g (65 %); m.p.: 88–89 °C (hexane) (Ref. [43] 89–90 °C).

6,7-Dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, (±)-cryptostyline III (**1c**)
Yield: 0.22 g (72 %); m.p.: 137–139 °C (MeOH) (Ref. [18] 137–138 °C).

1-Phenyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1d**)
Yield: 0.19 g (82 %); m.p.: 75–76 °C (hexane) (Ref. [44] 74–76 °C).

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