Asymmetric synthesis of (+)- and (−)-dihydropinidines: diastereoselective addition to chiral imine or 1,3-oxazolidine derived from (*R*)-phenylglycinol as a single starting material with organometallic reagents

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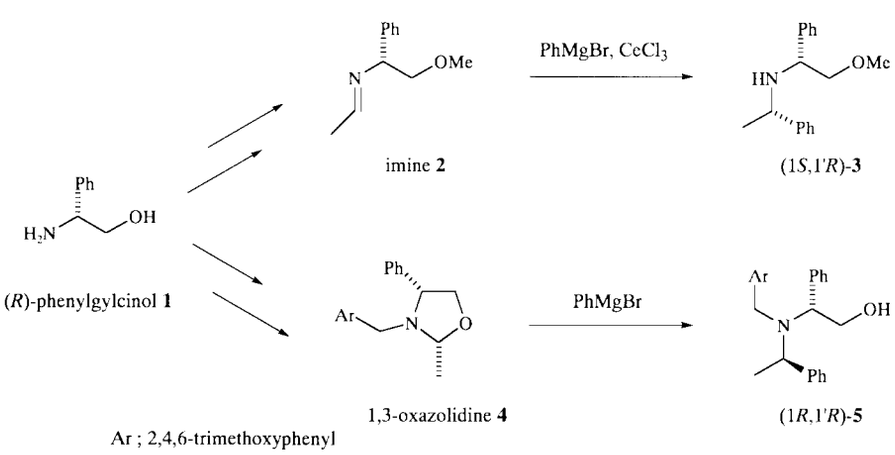
The asymmetric synthesis of the enantiomeric pair of (+)- and (−)-dihydropinidines has been accomplished. Our strategy was based on the enantioselective construction of both enantiomers of the natural products by using a single chiral source, (*R*)-phenylglycinol. Both routes were carried out by similar processes, except for either the presence of an imine or 1,3-oxazolidine intermediate. Excellent diastereoselectivity was observed in the reaction of chiral imines and 1,3-oxazolidines with organometallic reagents, to give the chiral amines in high chemical yields. The absolute configuration of both amines was determined by converting each of them into dihydropinidine. The asymmetric synthesis of the (+)- and (−)-dihydropinidine piperidine alkaloids was realized in four steps each and in 46 and 59% overall yield, respectively, from **6** and **11**.

Introduction

The construction of amines with an α-stereocenter is one of the most important subjects in the enantiospecific synthesis of natural products.[1] We previously described a synthetic method for the stereoselective preparation of both amine enantio- and diastereo-mers starting from a single enantiomeric source, (*R*)-phenylglycinol **1**, using the diastereoselective addition of organometallic reagents to chiral imines and 1,3-oxazolidines.[2] The diastereoselective addition of organocerium reagents to chiral aliphatic imines derived from *O*-alkylated (*R*)-phenylglycinol gave the corresponding chiral amines. In contrast, the addition of Grignard reagents to chiral 1,3-oxazolidines derived from *N*-alkylated (*R*)-phenylglycinol gave the corresponding chiral amines, but with the opposite configuration at the stereogenic center from those obtained using the imine and 1,3-oxazolidine routes (see Scheme 1 for examples). Recently, we suggested that using an *N*-2,4,6-trimethoxybenzyl group as a substituent for the nitrogen of chiral 1,3-oxazolidines would be sure to improve the diastereoselectivity.[2f] We considered that a slight modification of the synthetic strategy might enable both enantiomers of dihydropinidines to be prepared *via* chiral imine and 1,3-oxazolidine intermediates from (*R*)-phenylglycinol as a single chiral auxiliary. Dihydropinidine, a piperidine alkaloid, is widely distributed in *Pinaceae*,[3] and has recently also been isolated from the Mexican bean beetle, *Epilachna varivestis*,[4] as a minor constituent. Several asymmetric syntheses of dihydropinidine have been reported.[2e,5] We previously reported the asymmetric synthesis of (−)-dihydropinidine *via* 1,3-oxazolidine, but the stereoselectivity of the key step was not satisfactory.[6] In this report, we describe the asymmetric synthesis of the (+)- and (−)-dihydropinidine pair from (*R*)-phenylglycinol **1**.

Results and discussion

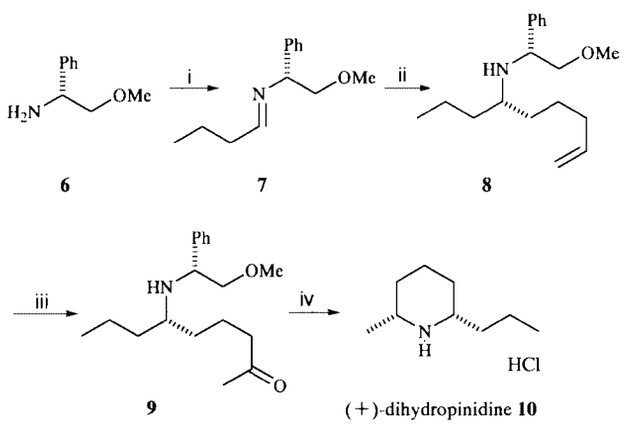
In our prior work, an interesting point in a series of diastereoselective additions was that less bulky *O*-protected substituents of the chiral imine derivatives affected the high diastereoselectivity in the reaction with organocerium reagents. With *O*-TBDMS, *O*-Me, and *O*-methoxyethyl chiral imines, the resulting selectivity varied over a wide range (22–92% de) under the same conditions. The smallest group, the methyl ether



Scheme 1

derivatives, provided superior diastereoselectivity in the reaction with organocerium reagents.

The necessary (*R*)-*O*-Me-phenylglycinol **6** was readily prepared from (*R*)-phenylglycinol **1** by treatment with potassium hydride and methyl iodide.[7] As expected, condensation of **6** with *n*-butanal gave the imine **7** as a single diastereomer in the ^{1}H-NMR spectrum. This configuration was considered to be the *E* form, based on the report by Hine and Yeh.[8] A carbon chain suitable for a piperidine was prepared through the diastereoselective addition of **7** with the appropriate organocerium reagent, which was prepared from the corresponding Grignard reagent and anhydrous $CeCl_3$ *in situ* according to the procedure of Imamoto,[9] to give the diastereomerically pure amine **8** in 85% yield in two steps. Wacker oxidation of the terminal olefin in **8** with $PdCl_2$ gave the corresponding methyl ketone **9** in 74% yield. Finally, six-membered heterocyclization, stereoselective reduction and removal of the chiral auxiliary in **9** were carried out simultaneously by catalytic hydrogenolysis over 10% palladium–carbon, to produce (2*R*,6*S*)-(+)-dihydropinidine hydrochloride **10**, $[a]_D^{23}$ +14.2† (*c* 1.05, EtOH) {lit.,[10] $[a]_D$ +12.8 (*c* 1.07, EtOH)} in 73% yield (Scheme 2). The *cis* configuration was confirmed in the ^{1}H-NMR spectrum.

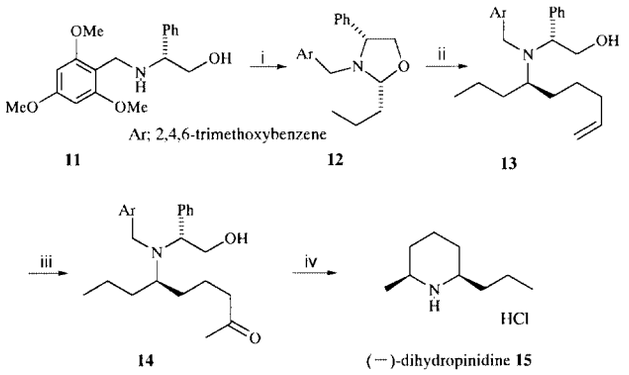


Scheme 2 *Reagents* (*and yields*): i, *n*-butanal, 3 Å MS, CH_2Cl_2; ii, CH_2=$CH(CH_2)_3Br$, Mg, $CeCl_3$, THF (85%); iii, $PdCl_2(MeCN)_2$, $CuCl_2$, O_2, MeOH (74%); iv, H_2/Pd–C, HCl, MeOH (73%).

In a previous paper, we outlined a highly diastereoselective method for addition to chiral oxazolidines with an *N*-2,4,6-trimethoxybenzyl group using various Grignard reagents.[2f] This was supported by the experimental finding that an increase in the bulkiness of the *N*-functional group on the oxazolidine enhanced the diastereoselectivity in the reaction with the Grignard reagent. The auxiliary **11** was easily accessible by a synthesis involving condensation of 2,4,6-trimethoxybenzaldehyde with (*R*)-phenylglycinol **1** followed by reduction with $NaBH_4$. The initial oxazolidine **12** was built up by the condensation of (*R*)-*N*-(2,4,6-trimethoxybenzyl)phenylglycinol **11** with *n*-butanal in CH_2Cl_2 by the addition of 3 Å molecular sieves. The oxazolidine **12** was treated with the Grignard reagent derived from 5-bromopent-1-ene in THF at an appropriate temperature to give the diastereomerically pure amine **13** in 92% yield. Wacker oxidation of **13** gave **14** in 76% yield. After reductive cleavage of the chiral auxiliary over 10% palladium on carbon under hydrogen, followed by ethanolic hydrochloric acidification, (−)-dihydropinidine hydrochloride **15** was obtained as colorless needles, $[a]_D^{23}$ −12.7 (*c* 1.14, EtOH) {lit.,[10] (+)-**15**; $[a]_D$ +12.8 (*c* 1.07, EtOH)} in 84% yield (Scheme 3).

Conclusions

A dramatic reversal in diastereoselectivity was attained in the synthesis of both (+)- and (−)-dihydropinidine by changing the pivotal intermediates, *i.e.*, the imine **7** or the oxazolidine **12** from a single enantiomeric source **1**. The different configurations in these diastereoselective additions may originate in the transition-state energy by steric repulsion due to a chiral auxiliary, but the details are not clear. Highly diastereofacial addition with organometallic reagents was successfully applied to chiral amines **8** and **13**. The enantioselective synthesis of (+)-dihydropinidine was achieved in 46% overall yield in four steps, while (−)- dihydropinidine was obtained in 56% overall yield in four steps. We are confident that this methodology may be applicable to the enantioselective synthesis of other nitrogen-containing compounds.



Scheme 3 *Reagents* (*and yields*): i, *n*-butanal, 3 Å MS, CH_2Cl_2 (96%); ii, CH_2=$CH(CH_2)_3Br$, Mg, $CeCl_3$, THF (92%); iii, $PdCl_2(MeCN)_2$, $CuCl_2$, O_2, MeOH (76%); iv, H_2/Pd–C, HCl, MeOH (84%).

Experimental

Mps were measured with a Yanagimoto Micro melting Point apparatus without correction. IR spectra were recorded on a 215 Hitachi Grating IR spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL GSX 270 instrument, and chemical shifts are reported in ppm on the δ-scale from internal Me_4Si. *J*-values are in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer using the chemical ionization (CI) (isobutane) and the electron impact (EI) methods. Optical rotations were taken with a JASCO-DIP-370 polarimeter. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. A Sibata Glass Tube Oven GTO-350RD was used as distillation apparatus. Column chromatography was performed on silica gel (45–75 μm, Wakogel C-300). Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel F_{254} (Merck). Spot detection was performed with UV 254 nm, iodine vapor, or with a solution mixture of *p*-anisaldehyde, sulfuric acid, acetic acid and ethanol (2.5:3.5:1:93). Tetrahydrofuran was distilled over potassium metal; methylene dichloride and methanol were used as obtained commercially without further purification.

(*R*)-(*E*)-*N*-Butylidene-2-methoxy-1-phenylethylamine 7

To a solution of (*R*)-**6** (3.2 g, 20 mmol) in CH_2Cl_2 (100 cm^3) was added *n*-butanal (1.6 g, 22 mmol) and 3 Å molecular sieves at 0 °C. The reaction mixture was stirred at room temperature for 2 h, filtered through Celite, and evaporated under reduced pressure to give the *imine* **7**. This compound was not stable enough to give a satisfactory microanalysis and was used without further purification: $\delta_H(CDCl_3)$ 0.93 (3 H, t, *J* 7.3, 4′-H_3), 1.43–1.68 (2 H, m, 3′-H_2), 2.19–2.44 (2 H, m, 2′-H_2), 3.35 (3 H, s, OMe), 3.61 (1 H, dd, *J* 4.3 and 9.8, 2-H), 3.66 (1 H, dd, *J* 8.6 and 9.8, 2-H), 4.30 (1 H, dd, *J* 4.3 and 8.6, 1-H), 7.22–7.40 (5 H, m, Ph).

(6*S*,1′*R*)-6-(2′-Methoxy-1′-phenylethylamino)non-1-ene 8

Anhydrous cerium(III) chloride (9.8 g, 40 mmol) was placed in a

† Specific optical rotations ($[a]_D$-values) are given in units of 10^{-1} deg cm^2 g^{-1}.

500 cm³ two-necked flask and was heated at 140 °C under 0.1 mmHg for 2 h. While the flask was still hot, nitrogen gas was introduced and the flask was cooled in an ice-bath. Dry THF (150 cm³) was then added with stirring, and stirring was continued for 2 h at room temperature. The resulting suspension was again cooled to 0 °C and Grignard reagent [freshly prepared with 5-bromopent-1-ene (6.0 g, 40 mmol) and magnesium turnings (0.97 g, 40 mmol)] was added. After this mixture had been stirred for 1.5 h at 0 °C, a solution of crude imine (*R*)-**7** (20 mmol) in dry THF (50 cm³) was added dropwise over a 10 min period and the mixture was warmed to room temperature. After the reaction mixture had been stirred for 20 h, it was quenched with a small amount of saturated aq. K_2CO_3. The resulting white precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The crude product was purified by bulb-to-bulb distillation (bp 120 °C, 2 mmHg) to give the *amine* **8** (85%) as a colorless oil (Found: C, 78.35; H, 10.71; N, 4.98. Calc. for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09%); $[\alpha]_D^{24}$ −78.6 (*c* 1.62 in EtOH); ν_{max}(film)/cm^{-1} 3360 (NH), 2940 (CH); δ_H($CDCl_3$) 0.77 (3 H, t, *J* 6.7, 9-H_3), 1.17–1.48 (8 H, m, 4-, 5-, 7- and 8-H_2), 1.69 (1 H, br, NH), 1.98–2.06 (2 H, m, 3-H_2), 2.29–2.37 (1 H, m, 6-H), 3.35 (3 H, s, OMe), 3.38–3.43 (2 H, m, 2′-H_2), 4.00 (1 H, dd, *J* 5.5 and 7.3, 1′-H), 4.92–5.03 (2 H, m, 1-H_2), 5.80 (1 H, ddt, *J* 6.7, 10.4 and 17.1, 2-H), 7.22–7.38 (5 H, m, Ph); *m*/*z* (CI, isobutane) 276 (M^+ + 1).

(6*S*,1′*R*)-6-(2′-Methoxy-1′-phenylethylamino)nonan-2-one 9

Oxygen was bubbled into a solution of (6*S*,1′*R*)-**8** (3.8 g, 14 mmol), palladium(II) chloride bisacetonitrile complex (0.6 g, 2.0 mmol) and cupric [copper(II)] chloride (1.8 g, 20 mmol) in MeOH (100 cm³) at room temperature. After being stirred for 2 h, the reaction mixture was filtered, and evaporated under reduced pressure. The residue was treated with benzene (100 cm³), water (100 cm³) and 28% aq. ammonia (20 cm³). The organic layer was separated, dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 98 : 2) to give ketone **9** (2.9 g, 74%) (Found: C, 74.04; H, 10.11; N, 4.68. Calc. for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81%); $[\alpha]_D^{24}$ −49.0 (*c* 1.17 in EtOH); ν_{max}(film)/cm^{-1} 3450 (NH), 2930 (CH), 1720 (CO); δ_H($CDCl_3$) 0.78 (3 H, t, *J* 6.7, 9-H_3), 1.20–1.63 (8 H, m, 4-, 5-, 7- and 8-H_2), 1.84 (1 H, br, NH), 2.12 (3 H, s, 1-H_3), 2.32–2.39 (1 H, m, 6-H), 2.39 (2 H, t, *J* 6.7, 3-H_2), 3.35 (3 H, s, OMe), 3.38–3.43 (2 H, m, 2′-H_2), 3.99 (1 H, dd, *J* 4.9 and 7.9, 1′-H), 7.22–7.38 (5 H, m, Ph); *m*/*z* (CI, isobutane) 292 (M^+ + 1).

(2*R*,6*S*)-Dihydropinidine hydrochloride 10

To a solution of **9** (2.2 g, 7.6 mmol) in MeOH (40 cm³) were added a catalytic amount of 10% palladium on carbon and 3% HCl (15 cm³). The reaction mixture was stirred under hydrogen (1 atm) at room temperature for 40 h. Then it was filtered through Celite and evaporated under reduced pressure. The residue was treated with distilled HCl and washed with diethyl ether. The aqueous layer was evaporated under reduced pressure to give the title compound **10** as colorless needles (0.97 g, 73%), mp 245 °C (from EtOH–EtOAc) (lit.,[5a] 245–246 °C); $[\alpha]_D^{23}$ +14.2 (*c* 1.05 in EtOH) {lit.,[10] $[\alpha]_D^{20}$ +12.8 (*c* 1.07 in EtOH)}; ν_{max}(KBr)/cm^{-1} 2940, 2840, 2800, 2750, 1460; δ_H($CDCl_3$) 0.93 (3 H, t, *J* 7.3, Me), 1.24–1.98 (9 H, m), 1.58 (3 H, d, *J* 6.7, Me), 2.08–2.21 (1 H, m), 2.86–2.99 (1 H, m, 2-H), 3.03–3.15 (1 H, m, 6-H), 9.01 (1 H, br, NH), 9.34 (1 H, br, NH); *m*/*z* (EI) 141 (M^+), 140 (M^+ − 1), 126.

(2*R*,4*R*)-4-Phenyl-2-propyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidine 12

To a solution of (*R*)-**11** (5.0 g, 15.75 mmol) in CH_2Cl_2 (60 cm³) were added *n*-butanal (1.36 g, 18.90 mmol) and 3 Å molecular sieves at 0 °C. The reaction mixture was stirred at room temperature for 40 h, filtered through Celite, and evaporated under reduced pressure to afford the crude product, which was purified by distillation with a tube oven to give the *oxazolidine* **12** (5.6 g, 96%), bp 245 °C/4 mmHg (Found: C, 71.21; H, 7.99; N, 3.75. Calc. for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77%); $[\alpha]_D^{22}$ −59.33 (*c* 1.07 in EtOH); ν_{max}(film)/cm^{-1} 2830 (CH); δ_H($CDCl_3$) 0.93 (3 H, t, *J* 7.3, Me), 1.38–1.70 (4 H, m), 3.51 (1 H, dd, *J* 7.3 and 7.9, 5-H), 3.66 (6 H, s, OMe), 3.76 (2 H, s), 3.78 (3 H, s, OMe) 3.92 (1 H, dd, *J* 6.7 and 7.9, 5-H), 4.01 (1 H, dd, *J* 6.7 and 7.3, 4-H), 4.38 (1 H, dd, *J* 2.4 and 6.1, 2-H), 6.01 (2 H, s, ArH), 7.16–7.41 (5 H, m, Ph); *m*/*z* (CI, isobutane) 372 (M^+ + 1).

(6*R*,1′*R*)-6-[*N*-(2′-Hydroxy-1′-phenylethyl)-2,4,6-trimethoxybenzylamino]non-1-ene 13

To a solution of (2*R*,4*R*)-**12** (5.0 g, 13.5 mmol) in dry THF (20 cm³) was added dropwise Grignard reagent [freshly prepared with 5-bromopent-1-ene (6.0 g, 40 mmol) and magnesium turnings (0.97 g, 40 mmol)] at 0 °C. After the reaction mixture had been stirred for 20 h at room temperature, it was quenched with a small amount of saturated aq. K_2CO_3. The resulting white precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 99 : 1) to give enol **13** (5.47 g, 92%) (Found: C, 73.48; H, 9.20; N, 3.04. Calc. for $C_{27}H_{39}NO_4$: C, 73.43; H, 8.90; N, 3.17%); $[\alpha]_D^{24}$ −133.43 (*c* 1.05 in EtOH); ν_{max}(film)/cm^{-1} 3440 (OH), 2920 (CH); δ_H($CDCl_3$) 0.54 (3 H, t, *J* 6.7, 9-H_3), 0.66–1.67 (8 H, m, 4-, 5-, 7- and 8-H_2), 1.92 (2 H, dt, *J* 6.7 and 7.7, 3-H_2), 2.46 (1 H, m, 6-H), 3.36 (1 H, br, OH), 3.75–3.99 (5 H, m), 3.82 (3 H, s, OMe), 3.83 (6 H, s, OMe), 4.90 (1 H, dd, *J* 1.8 and 10.4, 1-H), 4.93 (1 H, dd, *J* 1.8 and 17.1, 1-H), 5.77 (1 H, ddt, *J* 6.7, 10.4, and 17.1, 2-H), 6.13 (2 H, s, ArH), 7.26–7.42 (5 H, m, Ph); *m*/*z* (CI, isobutane) 442 (M^+ + 1).

(6*R*,1′*R*)-6-[*N*-(2′-Hydroxy-1′-phenylethyl)-2,4,6-trimethoxybenzylamino]nonan-2-one 14

Oxygen was bubbled into a solution of (6*R*,1′*R*)-**13** (5.0 g, 11.32 mmol), palladium chloride bisacetonitrile complex (0.3 g, 1.13 mmol) and cupric chloride (2.0 g, 14.71 mmol) in MeOH (100 cm³) at room temperature. After being stirred for 3 h, the reaction mixture was filtered, and evaporated under reduced pressure. The residue was treated with benzene (50 cm³), water (50 cm³) and ammonia water (10 cm³). The organic layer was separated, dried over anhydrous Na_2SO_4, evaporated under reduced pressure and purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 98 : 2) to give ketone **14** (3.94 g, 76%) (Found: C, 70.94; H, 8.76; N, 3.05. Calc. for $C_{27}H_{39}NO_5$: C, 70.86; H, 8.59; N, 3.06%); $[\alpha]_D^{24}$ −122.52 (*c* 1.04 in EtOH); ν_{max}(film)/cm^{-1} 3460 (OH), 2920 (CH), 1700 (CO); δ_H($CDCl_3$) 0.57 (3 H, t, *J* 6.7, 9-H_3), 0.67–1.74 (8 H, m, 4-, 5-, 7- and 8-H_2), 2.06 (3 H, s, 1-H_3), 2.19 (2 H, m, 3-H_2), 2.43 (1 H, m, 6-H), 3.38 (1 H, m, OH), 3.79–3.99 (5 H, m), 3.82 (3 H, s, OMe), 3.83 (6 H, s, OMe), 6.15 (2 H, s, ArH), 7.27–7.41 (5 H, m, Ph); *m*/*z* (CI, isobutane) 458 (M^+ + 1).

(2*S*,6*R*)-Dihydropinidine hydrochloride 15

To a solution of (6*R*,1′*R*)-**14** (2.0 g, 4.37 mmol) in MeOH (20 cm³) were added a catalytic amount of 10% palladium on carbon and 3% HCl (7 cm³). The reaction mixture was stirred under hydrogen (1 atm) at room temperature for 40 h. Then it was filtered through Celite and evaporated under reduced pressure. The residue was treated with distilled HCl and washed with diethyl ether. The aqueous layer was evaporated under reduced pressure to give the *title compound* **15** as colorless needles (0.63 g, 84%); $[\alpha]_D^{24}$ −12.71 (*c* 1.14 in EtOH) {lit.,[10] $[\alpha]_D^{20}$ +12.8 (*c* 1.07 in EtOH)}.

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