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Directed *ortho* Metalation Approach to C-7-Substituted Indoles. Suzuki–Miyaura Cross Coupling and the Synthesis of Pyrrolophenanthridone Alkaloids

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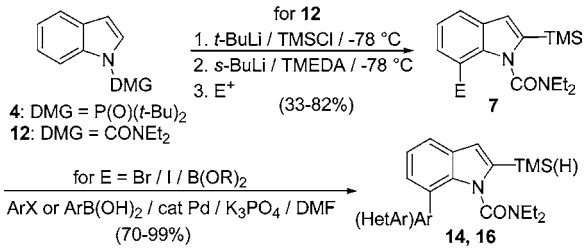
ABSTRACT



Although the indole *N*-phosphinoyl derivative 4 undergoes *n*-BuLi deprotonation/electrophile quench to afford C-7-substituted products, its deprotection requires harsh conditions. On the other hand, the *N*-amide 12, upon sequential or one-pot C-2 metalation, silylation, C-7 metalation, and electrophile treatment, furnishes indoles 7 in good overall yields. In combination with the Suzuki–Miyaura protocol, C-7 aryl (heteroaryl)-substituted indoles 14 and 16 are obtained, including hippadine and pratosine, members of the pyrrolophenanthridone alkaloid family.

We wish to report a new, general, and efficient method for the preparation of C-7 functionalized indoles, **5**, **7**, **13**, **14**, and **16**, by directed *ortho* metalation (DoM) and combined DoM/Suzuki−Miyaura cross-coupling strategies.[1] These findings provide an entry into a difficult indole substitution and bear general consequences on the synthesis of alkaloids[2] and bioactive molecules, which incorporate the key indole moiety.

In addition to traditional methodologies that rely on incorporation of functionality prior to indole ring construction,[2b,3] recent routes to substituted indoles have been dominated by DoM protocols. Although C-2 and C-3 functional group introduction may be thereby readily achieved (**A**, Scheme 1),[4,5] relatively minor effort has been dedicated to benzenoid ring functionalization via metalation tactics.[6]

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(1) For recent reviews, see: (a) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 330.

(2) (a) Lounasmaa, M.; Hanhihen, P. *The Alkaloids* **2001**, *55*, 1−89. (b) Sundberg, R. J. *Indoles*, 2nd ed.; Academic Press: San Diego, CA, 1996.

(3) For a selection of de novo methods of indole ring construction, see: (a) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2757. (c) Soederberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838, and refs cited therein. (d) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045 and refs cited therein. (e) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403. (f) Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819.

(4) (a) Gribble, G. W. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; Jai Press: Greenwich, CT, 1990; Vol. 1, p 43. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Turck, A.; Ple, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. For relevant selected indole metalation chemistry, see: (d) Comins, D. L. *Synlett* **1992**, 615. (e) Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2001**, *42*, 7621. (f) Vasquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

(5) (a) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 172. (b) Ishikura, M.; Matsuzaki, Y.; Agata, I. *Heterocycles* **1997**, *45*, 2309.

(6) (a) Greenhill, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 497. (b) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. For C-4/C-6 DoM chemistry on C-5 *O*-carbamates, see: (c) Griffen, E. J.; Roe, D. G.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484.

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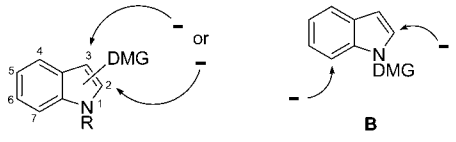
Scheme 1. Indole Functionalization by DoM

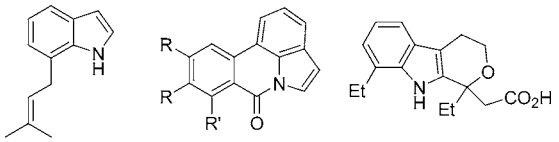


DMG = various [5, 9] (C-2)
DMG = $COCEt_3$ (DEB) [8] (C-2/C-7)
DMG = $CONEt_2$ [this work] (C-7 with C-2-TMS)

Iwao has provided two DoM approaches for C-7-substituted indoles: via *N*-Boc indolines followed by oxidation[7] and, recently, via *N*-(diethylbutanoyl)(DEB)indoles.[8,9] In the excellent latter study, while good yields of C-7 products were achieved, the value of the method was compromised by C-7/C-2 regioselectivity (**B**, Scheme 1).[10]

The method described herein uses the silicon protection tactic[11] at C-2 for clean C-7 deprotonation leading to indoles **7**, which may be readily N-deprotected and, by cross coupling, converted into compounds **14** and **16**, including pyrrolophenanthridone alkaloids **2a**,**b**. The significance of the new methodology relates to the existence of natural products (e.g., 7-prenylindole **1** as a prototype[12] and pyrrolophenanthridone alkaloids **2a**−**c**,[13] Scheme 2) and to the demand, in today's drug discovery programs, for interesting indole scaffolds (e.g., Etodolac **3**[14]).

Scheme 2. 7-Substituted Indole Alkaloids and Drugs

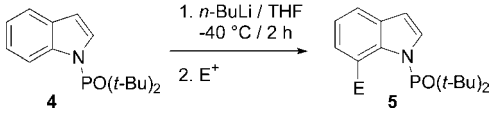


1 **2a-c** **3** (Etodolac)

2a: R = OMe, R´ = H: Pratosine
2b: R = OCH_2O, R´ = H: Hippadine
2c: R = OCH_2O, R´ = OH: Kalbretorine

In an early test, the powerful P(O)(*t*-Bu)$_2$ Directed Metalation Group (DMG)[15] was appended to indole ((1) *n*-BuLi/THF/0 °C and then ClP(*t*-Bu)$_2$; (2) H_2O_2/MeOH) to give **4** in 78% overall yield. Highly regioselective C-2 or C-7 deprotonation of **4** was achieved by choice of conditions. Thus, using 2 equiv of LDA at 0 °C for 15 min provided, after TMSCl quench, *N*-di-*tert*-butylphosphinoyl-2-trimethylsilylindole in 82% yield. In complete regioselective contrast, use of 2.2 equiv of *n*-BuLi at −40 °C for 2 h and TMSCl quench afforded **5a** exclusively (Table 1). Other

Table 1. Metalation and Electrophile Quench of *N*-(Di-*tert*-butylphosphinoyl)indole **4**



E^+	product (E)	yield (%)
Me_3SiCl	**5a** ($SiMe_3$)	72
MeI	**5b** (Me)	93
$BrCH_2CH{=}CMe_2$	**5c** ($CH_2CH{=}CMe_2$)	87
DMF	**5d** (CHO)	53
$ClPPh_2$	**5e** (PPh_2)	44
I_2	**5f** (I)	78

representative electrophiles gave the identical regioselectivity result providing indoles **5b**−**f** in modest to very good yields.[16] In consonance with the proposal by Iwao for the corresponding DEB-indole (**B**, DMG = $COCEt_3$, Scheme 1),[8] the high steric demand of the *tert*-butyl groups may lead to a complex in which the P═O bond orientation favors C-7 hydrogen abstraction rather than the normal higher thermodynamically acidic C-2 site.[17] The proposed phosphinoyl group orientation is evident in the single-crystal X-ray analysis of **5c** (Supporting Information, CCDC 207794). Deprotection of **5c** and other C-7-substituted indoles in this series was unsuccessful using basic or acidic conditions but was achieved by reduction ($LiAlH_4$/toluene/reflux). For example, the natural product **1** (Scheme 2) was thereby obtained in 44% yield from **5c**.[16]

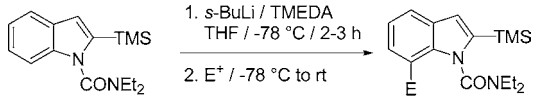
The harsh conditions for cleavage of **5** prompted a search for alternative *N*-DMGs that would promote this direct C-7 deprotonation and yet be cleaved under mild conditions. Considerable experimentation of numerous conditions using *N*-DMG = Boc, SO_2Ph, $CONR_2$ (R = Et, *i*-Pr, Ph, pyrrolidinyl) showed that only C-2 deprotonation was achievable. Furthermore, adapting the silicon protection mode to the above substrates[11] afforded clean results of C-7 lithiation with only the *N*-$CONEt_2$ derivative **6** (preparation from indole: (1) NaH/$ClCONEt_2$/THF/0 °C to room temperature, >98% yield (Kugelrohr distillation); (2) TMSCl/*t*-BuLi/THF/−78 °C, 97%).

Using the optimized metalation conditions (1.5−2.5 equiv of *s*-BuLi/TMEDA/THF/−78 °C/2−3 h)[18] on **6** followed by electrophile quench gave products **7a**−**k** and **8** in moderate

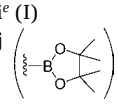
(7) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031.
(8) Fukuda, T.; Maeda, R.; Iwao, M. *Tetrahedron* **1999**, *55*, 9151.
(9) For C-7 functionalization via $Cr(CO)_3$ derivatives, see: (a) Masters, N. F.; Mathews, N.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1989**, *45*, 5955. Via C−H activation, see: (b) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557.
(10) For use of DEB−indole for C-2 and C-3 functionalization by metalation reactions, see: Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron* **2001**, *57*, 975.
(11) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.
(12) Achenbach, H.; Renner, C. *Heterocycles* **1985**, *23*, 2075.
(13) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 79.
(14) Jones, R. A. *Inflammopharmacology* **2001**, *9*, 63.
(15) Gray, M.; Chapell, B. J.; Felding, J.; Taylor, N. J.; Snieckus, V. *Synlett* **1998**, 422.
(16) For the complete study, see: Chapell, B. J., Ph.D. Thesis, University of Waterloo, Waterloo, ON, Canada, 2001.
(17) This may be reasonably rationalized by a complex induced proximity effect (CIPE): Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(18) Success of this reaction is highly dependent on the quality and quantity of the *s*-BuLi; see also footnote 23 in ref 8.

to high yields (Table 2). Although deuteration is not quantitative (entry 1), a variety of carbon (entries 2−6),

Table 2. Metalation and Electrophile Quench of 1-(*N*,*N*-Diethylcarbamoyl)-2-trimethylsilylindole **6**[a]



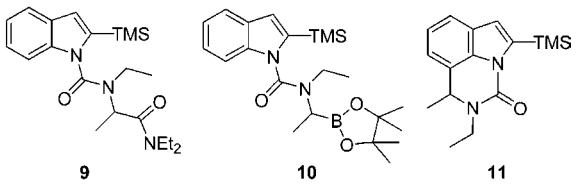
6 **7a-k**

entry	E^+	product (E)	yield (%)
1	MeOD	**7a** (D)	>99[b]
2	MeI	**7b** (Me)	81
3	EtI	**7c** (Et)	70
4[c]	$BrCH_2CH{=}CMe_2$	**7d** ($CH_2CH{=}CMe_2$)	66
5	DMF	**8**[d] (CHO)	40
6[c]	$ClCONEt_2$	**7e**[e] ($CONEt_2$)	72
7	Me_3SiCl	**7f**[e] ($SiMe_3$)	82
8	Bu_3SnCl	**7g** ($SnBu_3$)	33
9[c]	$BrCH_2CH_2Br$	**7h** (Br)	69
10[c]	I_2	**7i**[e] (I)	75
11[c]	(1) $B(O^iPr)_3$, (2) pinacol	**7j** 	60
12[c]	(1) $B(O^iPr)_3$, (2) H_2O_2	**7k**[e] (OH)	58

[a] Typical procedure: (1) 2.5 equiv of *s*-BuLi/TMEDA/THF/−78 °C/2−3 h/0.5 M; (2) E^+/−78 °C to room temperature/8−12 h. [b] D:H = 5:1. [c] *s*-BuLi (1.5 equiv)/TMEDA. [d] Product: 7-formyl-indole-1-carboxylic acid diethylamide. [e] **7e**, **7f**, **7i**, and **7k** can be obtained without chromatography by direct recrystallization of the crude product.

silicon (entry 7), tin (entry 8), halogen (entries 9 and 10), boron (entry 11), and oxygen (entry 12) electrophiles are introduced.[19] To improve operational efficacy, on the basis of the observation that C-2 TMS introduction proceeds in quantitative yield (GC analysis), a one-pot procedure was developed (Scheme 3) that provided the 7-functionalized indole derivatives in yields within experimental error to those obtained by stepwise reactions. Further walk-around-the-ring metalation was demonstrated by the conversion of **7e** into the 6-TMS derivative **13** in high yield. *N*-$CONEt_2$ (and simultaneous 2-TMS) cleavage was effected using (i) 25% KOH or 25% aqueous NaOH (EtOH/reflux/1−16 h),[20] (ii) 5 equiv of KO*t*Bu (THF/rt/1.5−12 h), or (iii) 1 equiv of TBAF (THF, 1 h) and then 2.2 equiv of KO*t*Bu (THF/rt/2

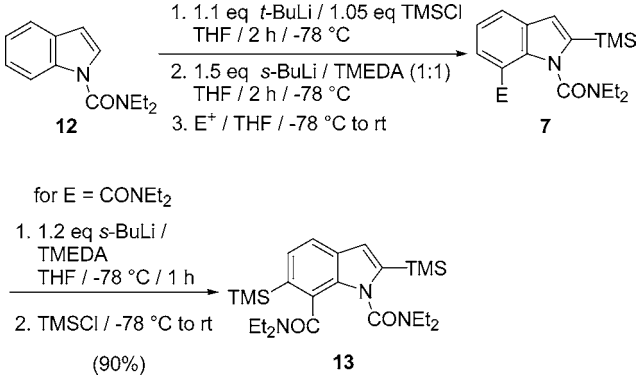
(19) For entries 6 and 11, products **9** (10%) and **10** (16%) were isolated; for entries 9 and 10, **11** (10−20%) was obtained. Product **11**, presumably the result of benzyne formation of the normal product (**7h**, **7i**) followed by carbamoyl α-deprotonation−cyclization, is formed in 50% yield under the following conditions: (1) 3 equiv of *s*-BuLi/TMEDA/THF/−78 °C/2 h; (2) 3 equiv of Br_2 or I_2/−78 °C → rt (Supporting Information).



9 **10** **11**

(20) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869. (b) Castells, J.; Troin, Y.; Diez, A.; Rubiralta, M.; Grierson, D. S.; Husson, H. P. *Tetrahedron* **1991**, *47*, 7911.

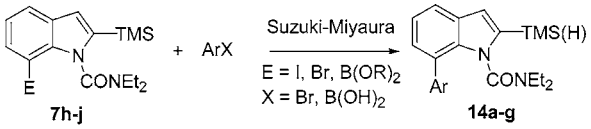
Scheme 3. One-Pot Conversion of **12** into 2,7-Substituted Indole Derivatives **7** and Further C-6 Functionalization to **13**



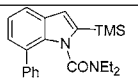
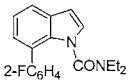
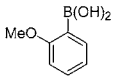
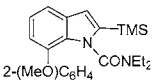
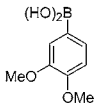
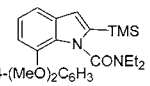
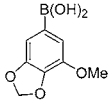
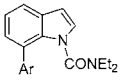
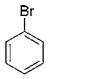
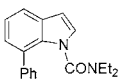
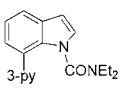
12 **7** **13**

h). Corresponding C-7-substituted indoles were thus obtained: indole from **6** (i, 85%; ii, 94%; iii, 92%), 7-methyl indole from **7b** (i, 75%), 7-TMS indole from **7f** (i, 94%), 7-bromo indole from **7h** (ii, 88%), 7-diethylcarboxamide indole from **7e** (ii, 82%), and 7-phenylindole from **14f** (ii but reflux, 15 h, 71%).

Table 3. Suzuki−Miyaura Cross-Coupling Reactions of the 7-Iodo, 7-Bromo, and 7-Pinacolboronate Indole Derivatives[a]



7h-j **14a-g**

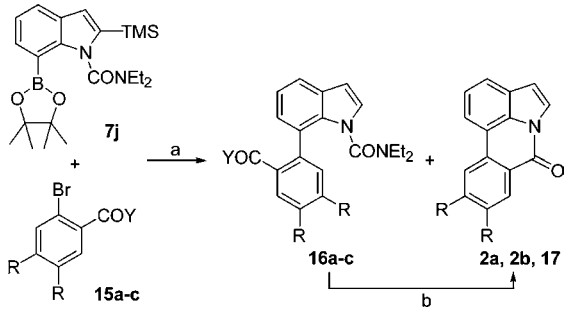
entry	E	ArX	product		yield (%)
1[b]	I (**7i**)			**14a**	90
2	I (**7i**)			**14b**	82
3	I (**7i**)			**14c**	70
4	I (**7i**)			**14d**	99
5[c]	I (**7i**)			**14e**	91
6	Br (**7h**)				83
7	$B(OR)_2$ (**7j**)			**14f**	94
8	$B(OR)_2$ (**7j**)			**14g**	89

[a] Typical procedure: 1.2 equiv of ArX/5 mol % $Pd(PPh_3)_4$/DMF/3 equiv of K_3PO_4/80 °C/15−20 h. [b] $Pd(PPh_3)_4$(2 mol %)/DME/H_2O/1.5 equiv of Na_2CO_3/80 °C/16 h. [c] After 20 h: addition of 1.1 equiv TBAF in THF/2 h/rt.

To explore combined D*o*M/Suzuki−Miyaura cross-coupling methodology, a general theme pursued in our laboratories,[1a] the haloindoles **7h** and **7i** along with indole boronate **7j** were tested with representative aryl boronic acids and halides (Table 3), respectively.[21] Thus, coupling of iodide **7i** and bromide **7h** with phenyl boronic acid (entry 1) and substituted phenylboronic acids (entries 2−6) afforded products **14a**−**e** in generally high yields even in *ortho*-substituted cases. Inversion of the coupling partners (entries 7 and 8) also efficiently furnished products **14f** and **14g**. In some cases of the Suzuki−Miyaura processes, concurrent C-2 desilylation was observed (entries 2 and 5−8).

As an application of the overall method, the synthesis of representative members of the pyrrolophenanthridone alkaloids (*Amaryllidaceae*), exhibiting antitumor and other biological activities,[13] was targeted.[22] Thus, Suzuki−Miyaura reaction of the boron pinacolate **7j** with aryl bromides **15a**−**c** provided products **16a**−**c** (Scheme 4) accompanied by **2a**

Scheme 4. Synthesis of Pyrrolophenanthridone Alkaloids[a]



[a] Key: (a) 1.2 equiv of ArX **15**/ 5−7.5 mol % $Pd(PPh_3)_4$/DMF/3 equiv of K_3PO_4/80 °C/20−24 h. **a**: R = OMe, Y = NEt_2, **16a** 40%, **2a** 18% (Pratosine). **b**: R = $-OCH_2O-$, Y = OEt, **16b** 90%, **2b** 7% (Hippadine). **c**: R = H, Y = OEt, **16c** 76%, **17** 13%. (b) LiOH (2.5 M) in MeOH/THF or 25% aqueous NaOH in EtOH/reflux/6−60 h/66−88%.

(pratosine) (18%), **2b** (hippadine) (7%), and **17** (13%) as side products. Prolonged cross-coupling reaction times or hydrolysis of the isolated compounds **16a**−**c** (LiOH/MeOH/THF/reflux or aqueous NaOH/EtOH/reflux) afforded **2a**, **2b**, and **17** in good yields (up to 80% for the hydrolysis of **16a**−**c** with LiOH or NaOH).

In summary, while the indole *N*-P(O)(*t*-Bu)$_2$ is a powerful DMG for selective C-2 or C-7 indole deprotonation (Table 1), its synthetic value is compromised by severe cleavage conditions. On the other hand, the *N*-CONEt$_2$ derivative **12** with prior C-2 TMS protection is very effective for the synthesis of C-7-substituted indoles (**7a**−**k**) and, via subsequent Suzuki−Miyaura cross-coupling reactions, for 7-aryl indoles (**14a**−**g** and **16a**−**c**), including pyrrolophenanthridone alkaloids (**2a**, **2b**, and **17**). The dependence on indole as a starting point (rather than de novo construction[3] from intermediate anilines or nitrobenzenes), the formulation of a one-pot procedure by metalation of **12**, and the demonstration of further D*o*M chemistry (**13**) allow anticipation of further application of this methodology for the construction of natural products and bioactive molecules.

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Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0344772

(21) Considering the explosion of cross-coupling chemistry, it is fair to say that indole C-7 derivatives have been infrequently described: see, e.g.: (a) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523. (b) Sakamoto, T.; Yasukura, A.; Kondo, Y.; Yakamaka, H. *Heterocycles* **1993**, *36*, 2597. (c) Black, D. S. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1993**, *49*, 151. (d) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockeless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551. (e) Hutchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004. (f) Carbonnelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Rossi, G. *Tetrahedron Lett.* **1998**, *39*, 4467 and refs cited therein. (g) Tsuge, O.; Hatta, T.; Tsuchiyama, H. *Chem. Lett.* **1998**, 155.

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