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Center-to-propeller and propeller-to-propeller stereocontrol in a series of macrobicyclic tri-λ^5-phosphazenes

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Abstract—Center-to-propeller stereocontrol in a family of macrobicyclic, double-propeller shaped tri-λ^5-triphosphazenes remains constant in the upper tribenzylamine fragment as the size of the pivotal group at the lower tris(phosphane) fragment is gradually increased. In contrast the propeller-to-propeller stereocontrol diminishes as a result of the increasing conformational lability in the lower hemisphere.

The self-assembly of tripodal reactants such as tris(3-azidobenzyl)amines and the commercially available tris(phosphane) $CH_3C(CH_2PPh_2)_3$ gives intermediate triphosphazides[1] which under mild heating in solution yield tri-λ^5-phosphazenes **1**[2] by the well known two-step Staudinger reaction.[3] Macrobicycles **1** so obtained have been shown to possess double-propeller topology and the process occurs with total stereoselectivity in favor of the formation of the species in which both propeller units, the upper tribenzylamine and the lower *tert*-pentane fragments, present the same sense of twist (Fig. 1).

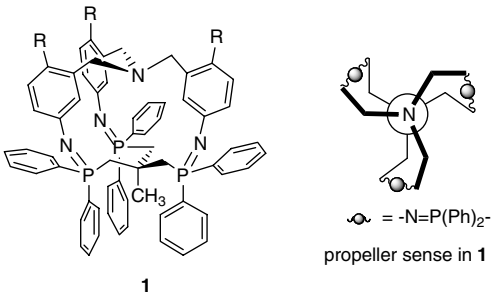

Figure 1. Tri-λ^5-phosphazenes **1** and schematic representation as viewed along their C_3 axis, showing the two propeller units with the same sense of twist.

In the context of these investigations we have demonstrated that the sense of twist of the two propeller units of compounds **1** can be simultaneously controlled by a single chiral benzylic carbon in one of the arms of the upper fragment,[4] just by replacing one of the benzylic protons by a methyl group.

That stereocontrol seems to be determined by the marked preference of the methyl group for occupying a pseudoaxial position (parallel to the pseudo C_3 axis) instead of the alternative pseudoequatorial position closer to the internal cavity, and therefore to the aryl groups. The sense of twist of the arm bearing the α-methyl group in turn determines those of the other two arms (Fig. 2).[5] This was confirmed by an X-ray crystal structure determination that showed the CH_3 pseudoaxial topology of the R^*, M^*, M^* diastereoisomers, the only obtained isomers.[4]

Here we show that while this is valid for several tri-λ^5-phosphazenes in which the lower fragment bears either

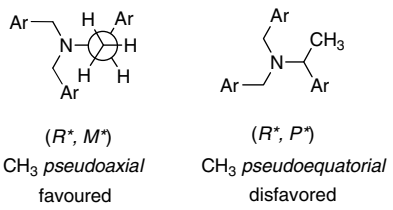

Figure 2. The two possible conformations for the upper fragment of α-methyltribenzylamine of compounds **1**.

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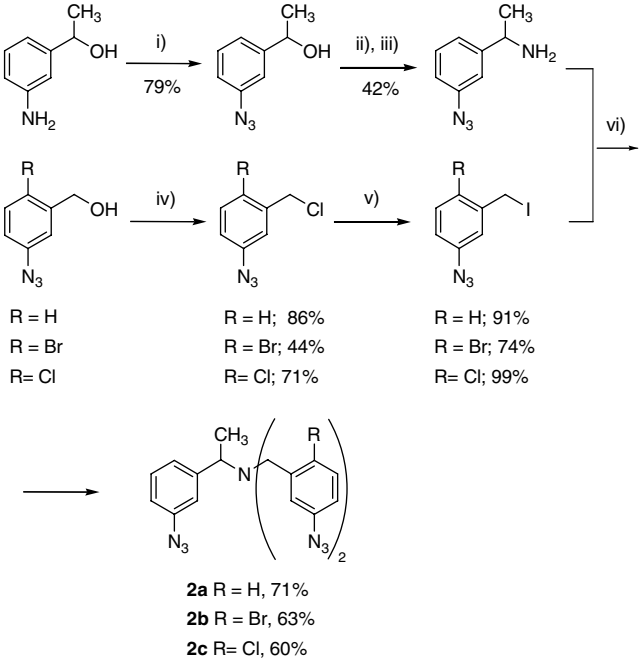
CH_3 at the pivotal carbon atom (as in **1**) or a smaller H atom, the introduction at that position of larger groups, such as Et, ^{i}Pr, and ^{t}Bu, gradually decreases the efficiency of the propeller-to-propeller induction (from the upper to the lower propeller) while retaining the center-to-propeller total induction at the upper hemisphere. This is evidenced by the gradually lower diastereoisomeric excesses measured in the formed macrobicycles (R^*, M^*, M^* and R^*, M^*, P^*, major and minor diastereoisomers, respectively).

To this end we prepared a series of α-methyl substituted triazides **2** in racemic form by using standard methods,[4] starting from the commercially available α-methyl-3-aminobenzyl alcohol and 2-substituted 5-azidobenzyl alcohols[2,6] (Scheme 1).

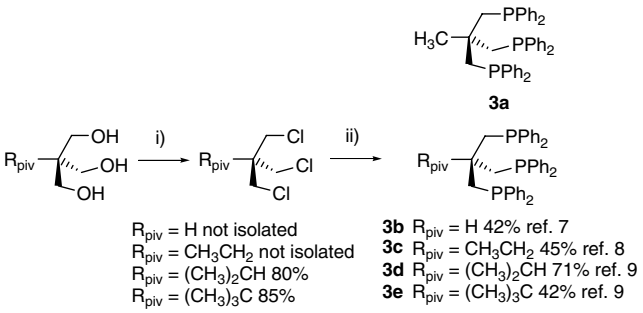
We also synthesized several tris(phosphanes) **3** of general formula $R_{piv}C(CH_2PPh_2)_3$, analogous of the commercially available **3a** ($R_{piv} = CH_3$), in which the pivotal R_{piv} group is H,[7] CH_3CH_2,[8] $(CH_3)_2CH$,[9] and $(CH_3)_3C$[9] (Scheme 2).

Triazides **2** coupled efficiently with triphosphanes **3** to give, after dinitrogen extrusion, macrobicycles **4** in 13–86% yields (based on the starting triazides **2**) (Scheme 3 and Table 1).[10]

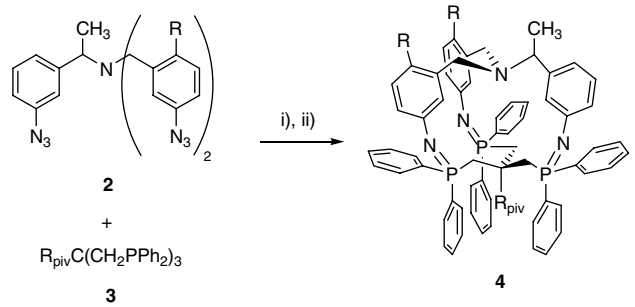
As presumed, macrobicycles **4a** ($R_{piv} = H$) and **4c** ($R_{piv} = CH_3$) were obtained as single diastereoisomers (Table 1, entries 1 and 3) in a similar way to other previously reported by us ($R_{piv} = CH_3$, R = H, Cl, entries 2 and 4)[4] and showing comparable spectroscopic data. In



Scheme 1. Preparation of tribenzylamines **2**. Reagents and conditions: (i) $NaNO_2$, dil HCl, 0 °C, 30 min, then NaN_3, 25 °C, 16 h; (ii) TPP, DEAD, phthalimide, THF, 0–25 °C, 24 h; (iii) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 3 h; (iv) $SOCl_2$, CH_2Cl_2, 0 °C, 3 h; (v) NaI, acetone, 25 °C, 12 h; (vi) CH_3CN, Na_2CO_3, reflux, 16 h.



Scheme 2. Synthesis of tris(phosphanes) **3**. Reagents and conditions: (i) $SOCl_2$, pyridine, 0–115 °C, 6 h; (ii) $HPPh_2$, KO^{t}Bu, THF, reflux, 16 h.



Scheme 3. Synthesis of tri-λ^5-phosphazenes **4**. Reagents and conditions: (i) Et_2O, 25 °C, 3 h; (ii) $CDCl_3$, 60 °C, 24 h.

Table 1. α-Methyl substituted tri-λ^5-phosphazene **4**

Entry	Compound	R_{piv}	R	de (%)	Yield (%)
1	**4a**	H	H	>98	61
2	**4b**[a]	CH_3	H	>98	70
3	**4c**	CH_3	Br	>98	89
4	**4d**[a]	CH_3	Cl	>98	63
5	**4e**	CH_3CH_2	Br	90	86
6	**4f**	CH_3CH_2	Cl	86	58
7	**4g**	$(CH_3)_2CH$	Br	52	55
8	**4h**	$(CH_3)_2CH$	Cl	56	42
9	**4i**	$(CH_3)_3C$	Br	4	13

[a] Compounds **4b** and **4d** have been previously described in Ref. 4.

these cases, the sense of twist of their two propeller units is totally controlled by the chiral benzylic carbon atom, and it should be the same for both propellers as in the previously reported examples. That is, **4a** and **4c** are obtained as the R^*, M^*, M^* diastereoisomers exclusively.

The situation changes with the introduction of larger R_{piv} groups. In compounds **4e** and **4f** ($R_{piv} = CH_3CH_2$, entries 5 and 6) minor amounts of a second diastereoisomer were detected in their NMR spectra (de 90 and 86%, respectively). The proportion of the second diastereoisomer increased notably in **4g** and **4h** [$R_{piv} = (CH_3)_2CH$, entries 7 and 8], whereas in **4i** [$R_{piv} = (CH_3)_3C$, entry 9] the two diastereisomers were present in nearly equal amount (Table 1). In all these cases, we could not resolve the diastereoisomeric mixtures into their components by chromatography or fractional crystallization.

In a first approximation we postulated that the minor isomers accompanying the expected, major R^*, M^*, M^* diastereoisomers **4e–i** should be those differing in the sense of twist of the lower propeller, R^*, M^*, P^*, as there is no apparent reason to expect an alteration of the asymmetric control of the center over the upper propeller (R^* leading to M^*), whereas the introduction of large groups at the pivotal carbon of the lower hemisphere could alter considerably the conformational preferences of this moiety.

We have found some support for this assumption. The main spectroscopic differences between the diastereoisomeric macrobicycles in each pair **4e–i** do not lie in the signals attributed to the upper propeller, but in those corresponding to the lower part. For instance,[10] whereas six phosphorus resonances are more or less clearly distinguished in each mixture of two diastereoisomers, the resonances of their α-methyl groups at the benzylic carbon in their ^{1}H NMR spectra appear in a narrow range of chemical shifts. One would expect more significant differences in chemical shifts between pseudoaxial and pseudoequatorial methyl groups, and this seems to be not the case.

Moreover, we have calculated the chemical shift of several nuclei in a model of the upper part of these tri-λ^5-phosphazenes, α-methyltribenzylamine **5** in two conformational minima, those with the Me group in axial and equatorial positions, **5a** and **5b**, respectively (Fig. 3) by means of the GIAO (gauge-independent atomic orbital)[11] computational methodology. The results are summarized in Table 2 and compared with the NMR data of the upper fragment of macrobicycle **4b** measured in $CDCl_3$.

The data in Table 2 clearly reveal the similarity of the shifts measured in **4b** with those calculated for **5a** (α-Me_{ax}) which in turn are considerably far from those of its conformer **5b** (α-Me_{eq}), particularly, but not only, in the ^{13}C NMR shifts of the α-methyl (8.49 vs 26.69) and the methine (54.79 vs 69.19) carbons. These data support the α-Me_{ax} conformation of the tribenzylamine fragment of **4b** and also of the rest of tri-λ^5-phosphazenes here prepared, including the pairs of diastereoisomers **4e–h**. For instance, the α-methyl and methine carbons of diastereoisomeric pair **4h** resonate at 8.28 and 55.21 ppm in the major diastereoisomer, and at 8.00 and 57.77 ppm in the minor component of the mixture.

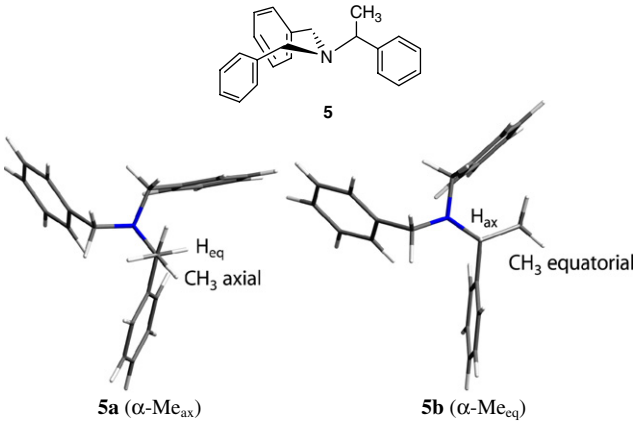


Figure 3. Two conformations of α-methyltribenzylamine **5**.

Table 2. Calculated chemical shifts of **5a**[a] and **5b**[a] and experimental chemical shifts of **4b**[b]

Compound	^{1}H NMR		^{13}C NMR			
	C*H*MeN	α-Me	*C*HMeN	α-Me	$(CH_2)_A$	$(CH_2)_B$
5a (α-Me_{ax})	3.64	1.35	54.79	8.49	52.47	54.14
5b (α-Me_{eq})	3.28	0.94	69.19	26.69	56.29	69.37
4b	3.66	1.22	55.24	7.35	51.94	53.76

[a] The data for **5a** and **5b** were obtained by GIAO calculations at the RHF/6-31G* level.
[b] Measured in $CDCl_3$ at 300 (^{1}H NMR) and 75 (^{13}C NMR) MHz.

Thus, the experimental and calculated data of compounds **4** are in accord with the assignation of the R^*, M^*, M^* and R^*, M^*, P^* relative configurations to the major and minor components of the mixtures of diastereoisomers **4e–h** respectively, which differ only in the sense of twist of the lower tris(phosphane) propeller (Fig. 4).

The results of molecular mechanics calculations[12] of the two diastereoisomers in each pair **4e–h** are summarized in Table 3. In all the cases the R^*, M^*, M^* isomer is the most stable and the differences in energy with respect to the R^*, M^*, P^* isomer ΔE are gradually lower when the size of the pivotal group R_{piv} increases. The same tendency was observed as far as the experimental diastereoisomeric excesses were concerned.

In summary, in macrobicyclic tri-λ^5-phosphazenes **4a–e** (R_{piv} = H, CH_3) the chiral center at the benzylic carbon controls the sense of twist of the upper tribenzylamine fragment, which in turn determines that of the lower tris(phosphane) propeller. The propeller-to-propeller

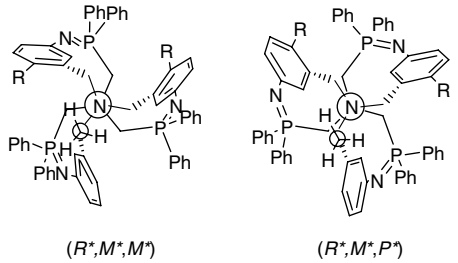


Figure 4. Major and minor diastereoisomers of compounds **4e–h**.

Table 3. Calculated difference of energy for the components of the pairs (R^*, M^*, M^*)/(R^*, M^*, P^*) of some tri-λ^5-phosphazenes **4**

Tri-λ^5-phosphazene	R	R_{piv}	ΔE (kcal mol^{-1})
4c	Br	CH_3	25.86
4e	Br	CH_3CH_2	19.45
4g	Br	$(CH_3)_2CH$	11.04
4i	Br	$(CH_3)C$	1.95

stereocontrol is gradually less effective as the size of the pivotal group increases (Et, ^{i}Pr, ^{t}Bu), whereas the center-to-propeller stereocontrol remains equally effective. Large pivotal groups in the lower hemisphere increase the conformational lability of this moiety.

Acknowledgments

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9. Tris(phosphanes) **3d** and **3e** were prepared following the same experimental procedure used for **3c**, as reported in Ref. 8.
10. *Tri-λ^5-phosphazene* **4c**: Yield: 89%; mp 259–261 °C (yellow prisms from chloroform/*n*-pentane); ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.76 (s, 3H; CH_3), 1.42 (d, J(H,H) = 6.8 Hz, 3H; α-CH_3), 3.20 (m, 5H; 2 CH_AH$_B$N + 3 CH_AH$_B$P), 3.56 (d, J(H,H) = 12.1 Hz, 1H; CH$_A$H$_B$N), 3.69 (q, J(H,H) = 6.8 Hz, 1H; CH), 3.85 (d, J(H,H) = 12.9 Hz, 1H; CH$_A$H$_B$N), 3.90 (m, 3H; CH$_A$H$_B$P), 6.32 (d, J(H,H) = 2.8 Hz, 1H; H$_{arom}$), 6.35 (br s, 1H; H$_{arom}$), 6.41 (d, J(H,H) = 2.8 Hz, 1H; H$_{arom}$), 6.66 (d, J(H,H) = 6.6 Hz, 1H; H$_{arom}$), 6.95 (dd, J(H,H) = 5.8, 2.9 Hz, 1H; H$_{arom}$), 6.98 (dd, J(H,H) = 5.8, 2.9 Hz, 2H; H$_{arom}$), 7.10–7.13 (m, 5H; H$_{arom}$), 7.26–7.45 (m, 22H; H$_{arom}$), 7.79–7.91 (m, 6H; H$_{arom}$); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 8.68 (α-CH_3), 27.50 (*C*H$_3$C), 36.73–37.26 (m, 3CH$_2$P), 38.98 (q, ^2J(C,P) = 3.8 Hz; CH$_3$*C*), 50.09 (CH$_2$N), 52.57 (CH$_2$N), 55.84 (CH), 112.49 (*q*), 112.59 (*q*), 115.32, 123.16 (d, ^3J(C,P) = 12.7 Hz; *s-cis*-*C*H=C–N=P), 123.99 (d, ^3J(C,P) = 12.2 Hz; *s-cis*-*C*H=C–N=P), 124.45 (d, ^3J(C,P) = 12.7 Hz; *s-cis*-*C*H=C–N=P), 125.43 (d, ^3J(C,P) = 28.3 Hz; *s-trans*-*C*H=C–N=P), 127.19 (d, ^3J(C,P) = 28.6 Hz; *s-trans*-*C*H=C–N=P), 127.29 (d, ^3J(C,P) = 28.7 Hz; *s-trans*-*C*H=C–N=P), 128.34–132.80, 140.24 (*q*), 140.37 (*q*), 145.06 (*q*), 150.73 (3 *q*); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ 0.44 (s, 1P), 1.36 (s, 1P), 1.54 (s, 1P); IR (Nujol): ν = 1453 (CP), 1118 (NP) cm^{-1}; MS (FAB+): m/z (%) = 1124 (13) [M$^+$+4], 1122 (13) [M$^+$+2], 1121 (11) [M$^+$+1], 1120 (6) [M$^+$], 133 (100); $C_{63}H_{57}Br_2N_4P_3$ (1122.88): Calcd C, 67.39, H, 5.12, N, 4.99. Found: C, 67.50, H, 5.07, N, 5.13.
Tri-λ^5-phosphazenes **4h** + **4h′** (diastereoisomers ratio 3.5:1): Yield: 42%; ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.41 [d, J(H,H) = 6.9 Hz, 3H; (CH$_3$)$_A$ (h)], −0.29 [d, J(H,H) = 6.9 Hz, 3H; (CH$_3$)$_A$ (h′)], −0.23 [d, J(H,H) = 6.9 Hz, 3H; (CH$_3$)$_B$ (h)], −0.03 [d, J(H,H) = 6.9 Hz, 3H; (CH$_3$)$_B$ (h′)], 0.93 [m, 2H; C*H*(CH$_3$)$_2$ (h + h′)], 1.13 [d, J(H,H) = 6.7 Hz, 3H; α-CH$_3$ (h′)], 1.26 [d, J(H,H) = 6.9 Hz, 3H; α-CH$_3$ (h)], 2.90 [d, J(H,H) = 12.6 Hz, 1H; CH_AH$_B$N (h)], 2.94 [d, J(H,H) = 12.2 Hz, 1H; CH_AH$_B$N (h)], 3.03 [d, J(H,H) = 16.5 Hz, 1H; CH_AH$_B$N (h′)], 3.24 [d, J(H,H) = 16.5 Hz, 1H; CH_AH$_B$N (h′)], 3.45–4.31 [m, 18H; 4 CH$_A$H$_B$N (h + h′) + 12 CH$_2$P (h + h′) + 2 C*H*CH$_3$ (h + h′)], 6.25 (br s, 1H; H$_{arom}$), 6.30 (br s, 2H; H$_{arom}$), 6.52 (d, J(H,H) = 7.2 Hz, 1H; H$_{arom}$), 6.97–7.53 [m, 64H; H$_{arom}$ (h + h′)], 7.96–8.00 [m, 12H; H$_{arom}$ (h + h′)]; ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 8.00 [α-CH$_3$ (h′)], 8.28 [α-CH$_3$ (h)], 19.30 [(CH$_3$)$_A$ (h)], 19.72 [(CH$_3$)$_A$ (h′)], 20.01 [(CH$_3$)$_B$ (h)], 20.08 [(CH$_3$)$_B$ (h′)], 35.34 [(CH$_3$)$_2$*C*H (h)], 35.39 [(CH$_3$)$_2$*C*H (h′)], 36.60–37.40 [m, 3CH$_2$P (h + h′)], 47.07 [q, ^2J(C,P) = 3.1 Hz; (CH$_3$)$_2$CH*C* (h)], 49.48 [q, ^2J(C,P) = 3.6 Hz; (CH$_3$)$_2$CH*C* (h′)], 49.77 [CH$_2$N (h)], 49.98 [CH$_2$N (h)], 50.38 [CH$_2$N (h′)], 52.51 [CH$_2$N (h′)], 55.21 [*C*HCH$_3$ (h)], 57.77 [*C*HCH$_3$ (h′)], 115.02 (h), 115.83 (h′), 122.46 [2 *q*; (h/h′)], 122.57 [2 *q*;(h/h′)], 123.27 [d, ^3J(C,P) = 12.8 Hz; *s-cis*-*C*H=C–N=P (h)], 123.97 [d, ^3J(C,P) = 12.2 Hz; *s-cis*-*C*H=C–N=P (h)], 124.44 [d, ^3J(C,P) = 12.2 Hz; *s-cis*-*C*H=C–N=P (h)], 125.54 [d, ^3J(C,P) = 27.8 Hz; *s-trans*-*C*H=C–N=P (h)], 126.70 [d, ^3J(C,P) = 27.3 Hz; *s-trans*-*C*H=C–N=P (h)], 126.81 [d, ^3J(C,P) = 27.3 Hz; *s-trans*-*C*H=C–N=P (h)], 127.84–133.55 (h + h′), 136.42 [*q*; (h′)], 136.66 [*q*; (h′)], 138.05 [*q*; (h)], 144.70 [*q*; (h)], 144.82 [*q*; (h′)], 149.71 [*q*; (h′)], 149.93 [2 *q*; (h)], 150.47 [2 *q*; (h′)], 150.59 [*q*; (h)]. Only signals clearly observed for the minor diastereoisomer are detailed; ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ −0.90 [s, 1P; (h′)], −0.07 [s, 1P; (h′)], 0.55 [s, 1P; (h′)], 2.75 [s, 1P; (h)], 4.07 [s, 2P; (h)]; IR (Nujol): ν = 1444 (CP), 1114 (NP) cm^{-1}; MS (FAB+): m/z (%) = 1064 (76) [M$^+$+4], 1062 (100) [M$^+$+2], 1060 (37) [M$^+$]; $C_{65}H_{61}Cl_2N_4P_3$ (1062.03): Calcd C, 73.51, H, 5.79, N, 5.28. Found: C, 73.64, H, 5.82, N, 5.19.
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