Iterative Construction of Trisubstituted Olefin Units. Short, Stereoselective Synthesis of the Codling Moth Constituent, (2Z,6Z)-7-Methyl-3-propyl-2,6-decadien-1-ol[1]

Anthony Marfat, Paul R. McGuirk, and Paul Helquist*

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

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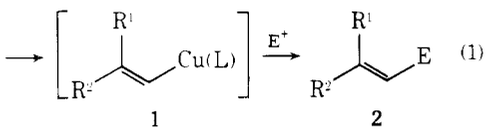
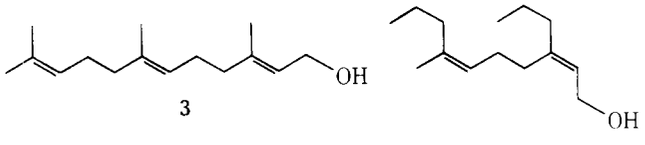
The synthesis of trisubstituted olefins is justifiably a very active area of research in organic chemistry because of the nearly countless numbers of natural products which fall into this broad category of compounds.[2,3] Recently, a very powerful method for the synthesis of these compounds has been developed by Normant,[4] Vermeer,[5] and groups at Stony Brook.[6,7] This method involves the addition of various alkylcopper complexes to acetylenes to give vinylcopper intermediates (1) which then react with various electrophiles to produce the desired olefins (2, eq 1).



1 2 (1)

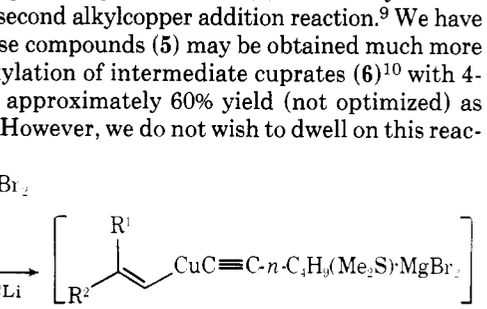
Many naturally occurring compounds contain two or more trisubstituted olefin moieties, most often in a 1,5 relationship to one another. Examples are terpenes such as farnesol (3) and



3 4

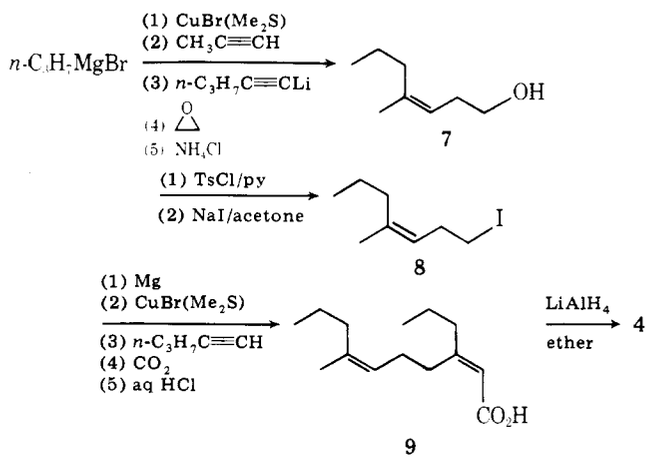
other substances such as the codling moth (*Laspeyresia pomonella* L.) constituent, (2Z,6Z)-7-methyl-3-propyl-2,6-decadien-1-ol (4).[8] The synthesis of these compounds requires methods which permit the iterative introduction of trisubstituted olefin units.

One iterative approach which was employed by Normant involves a multistep chain extension of 1 culminating in the reaction of an allenic Grignard reagent with allylic halides (2, E = CH_2Cl) to give acetylenic olefins (5) which may then be employed in a second alkylcopper addition reaction.[9] We have found that these compounds (5) may be obtained much more directly by alkylation of intermediate cuprates (6)[10] with 4-iodobutyne in approximately 60% yield (not optimized) as shown in eq 2. However, we do not wish to dwell on this reaction because of very closely related results that were recently reported by Vermeer and co-workers.[11] Instead, we wish to report a very short, highly stereoselective synthesis of the codling moth constituent (4) which illustrates an alternative approach to iterative trisubstituted olefin construction.



6 5 (2)

Scheme I



Our synthesis is outlined in Scheme I. Thus, through use of our method for the synthesis of homoallylic alcohols,[6c] the alcohol 7 is obtained in 89% yield through addition of a propylcopper complex to propyne followed by alkylation of an intermediate vinyl cuprate with ethylene oxide. The *Z* stereochemistry of 7 follows from our earlier structural studies[6d] and the appearance of the vinyl methyl group at δ 1.67 in the ^1H NMR spectrum.[8b,c] The corresponding homoallylic iodide (8) is prepared in 84% yield by conversion of 7 to the tosylate followed by treatment with sodium iodide under Finkelstein reaction conditions. In order to introduce the second olefin moiety, our approach requires the conversion of 8 into an alkylcopper complex formed from the corresponding homoallylic Grignard reagent, but the formation of this type of Grignard reagent has been reported to be difficult.[12] Consistent with these earlier observations, we find that by slow addition of 8 to magnesium in ether the Grignard reagent is formed in only approximately 65–70% yield as shown by quenching the reaction mixture with aqueous ammonium chloride and analyzing the resulting hydrocarbon by GLC; the remainder of the product is largely the Wurtz-type coupling product. Once formed, though, the Grignard reagent may be converted into an alkylcopper complex which undergoes addition to 1-pentyne. The intermediate vinylcopper complex is carboxylated[13] to afford the α,β-unsaturated acid (9) in 50% overall yield from 8. Reduction with lithium aluminum hydride gives a 98% yield of 4, which is identical with samples provided by Dr. McDonough[8a] and Professor Katzenellenbogen[8c] (comparison by IR, NMR, MS, and GLC). A very careful GLC analysis indicates that our product is 99.5% pure and contains no detectable quantities of the other olefinic isomers according to direct comparison with authentic samples.[8a,c,14] Despite the difficulties with the homoallylic Grignard reagent, our route provides 4 in an overall yield of 37% in only four steps from 1-propyne as compared to the longer routes reported by others.[8c,d]

We wish to emphasize that this synthesis serves to illustrate another method for the iterative construction of trisubstituted olefin units. Also, this method complements the approaches employing allenic Grignard reagents[9] and 4-iodobutyne[11] (vide supra) in that the stereochemistry of the second olefin generated by the new approach is the reverse of that resulting from the former methods. Also, this synthesis of 4 of known configuration serves to confirm the earlier assignment of cis stereochemistry[4a,6d,9] for the addition of alkylcopper complexes to acetylenes.

Further studies are in progress in collaboration with Dr. L. M. McDonough[8a] to determine the biological role of 4 in the various life stages of *L. pomonella*.

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Experimental Section

The ^1H NMR spectra were recorded at 60 MHz with a Varian EM-360 spectrometer or at 80 MHz with a Varian HFT-80 spectrometer, and the ^{13}C NMR spectra were recorded at 20 MHz with a Varian CFT-20 spectrometer. The spectra were obtained using $CDCl_3$ solutions, and the chemical shifts are reported as parts per million downfield (δ) from internal tetramethylsilane. The mass spectra were obtained with Hewlett-Packard Model 5982A and AEI Model MS-20 spectrometers using electron impact ionization at 70 eV. The infrared spectra were obtained with Pye Unicam Model SP-1000 and Perkin-Elmer Model 727 spectrophotometers using neat liquid films and calibrated with a polystyrene standard. Preparative GLC was performed with a Varian Aerograph Model 900 chromatograph equipped with a 6 ft × 0.5 in. 5% SE-30 column, and analytical GLC was performed with a Hewlett-Packard Model 5711A chromatograph equipped with a flame ionization detector, linear temperature programmer, Hewlett-Packard Model 3380A electronic integrator, and a 12 ft × 0.125 in. 5% OV-1 column. Low temperatures were maintained using an acetone bath equipped with a Neslab Model CC-100F Cryo-Cool unit, a Cole-Parmer Model 2158 Versa-Therm temperature controller, and a 500-W immersible heating coil.

All reactions involving air- and water-sensitive organometallic compounds were performed under prepurified nitrogen in flame-dried glassware. Air-sensitive solutions were transformed with hypodermic syringes or stainless steel cannulas. Ether was distilled from dark blue or dark purple solutions of sodium benzophenone radical anion or dianion under nitrogen. *n*-Propylmagnesium bromide was prepared[15] and titrated[16] by standard procedures. The dimethyl sulfide complex of cuprous bromide was obtained as a pure, white, crystalline solid by the method of House.[17] Magnesium turnings were washed sequentially with 10% hydrochloric acid, distilled water, 95% ethanol, and dry ether and then stored under nitrogen.[18] The acetylenes, dimethyl sulfide, acetone, and pyridine were distilled under nitrogen, and the *p*-toluenesulfonyl chloride was recrystallized from petroleum ether. Other reagents and solvents were used as obtained commercially.

(*Z*)-4-Methyl-3-hepten-1-ol (7). To a solution of $CuBr(Me_2S)$ (18.4 g, 90 mmol), anhydrous ether (110 mL), and dimethyl sulfide (88 mL) at −45 °C was added a 2.55 M solution (35.3 mL, 90 mmol) of *n*-propylmagnesium bromide in ether over a 10-min period. After 2 h, propyne (5.1 mL, 90 mmol) was added with a dry ice cooled syringe over 5 min to the yellow-orange suspension. The mixture was stirred at −23 °C for 2.5 h, and the resulting dark green solution was cooled to −78 °C. A solution of 1-lithio-1-pentyne (prepared from 90 mmol of *n*-butyllithium and 90 mmol of 1-pentyne) in ether (110 mL) to which $[(CH_3)_2N]_3PO$ (15.7 mL, 90 mmol) had been added was transferred to the green solution. After 1 h, ethylene oxide (4.5 mL, 90 mmol) was added with a dry ice cooled syringe over a 5-min period. The resulting mixture was stirred at −78 °C for 3 h and at −33 °C for 24 h, quenched at 0 °C by addition of a solution (25 mL) of saturated aqueous NH_4Cl (adjusted to pH 8 with aqueous ammonia), and partitioned between water and ether. The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to give 10.30 g (89%) of **7** as a clear colorless oil: bp 45–45.5 °C (77 torr); IR 3300, 2900, 1640, and 824 cm^{-1}; ^1H NMR δ 5.06 (t, J = 7.2 Hz, 1 H), 3.52 (t, J = 6.6 Hz, 2 H), and 0.54–2.44 (several multiplets overlapping a doublet at δ 1.67, J = 1.1 Hz, 11 H overall); ^{13}C NMR δ 138.95, 120.69, 62.69, 34.02, 31.51, 23.49, 21.28, and 14.00; MS *m/e* 128.1221 (M^+; 128.1200 calcd for $C_8H_{16}O$). Careful GLC analysis indicated >99% purity, and TLC on silica gel (methylene chloride) showed only one spot.

(*Z*)-1-Iodo-4-methyl-3-heptene (8). To a mixture of **7** (4.00 g, 31.3 mmol) and *p*-toluenesulfonyl chloride (6.48 g, 34.4 mmol) at −5 °C under nitrogen was added pyridine (9.5 mL, 69 mmol). After 2 h at 0 °C and 0.5 h at 25 °C, the resulting white slurry was quenched with 1 N hydrochloric acid and partitioned between ether and water. From the ether layer was isolated 8.12 g (93%) of crude tosylate as a clear, colorless liquid. A portion (7.80 g, 27.7 mmol) of this material was dissolved in acetone (100 mL), sodium iodide (6.89 g, 46.1 mmol) was added, and the mixture was heated at reflux for 12 h. The mixture was cooled to 25 °C and filtered to remove white solid, the filtrate was concentrated in vacuo, the residue was dissolved in ether, and the solution was washed with aqueous sodium bisulfite, water, and saturated aqueous sodium chloride. From the ether layer was isolated 5.9 g (84% from **7**) of **8** having a purity of >96% (GLC). No increase in purity resulted from a distillation which gave 5.0 g (74% from **7**) of **8** as a clear, colorless oil: bp 45–46 °C (0.77 torr); IR 2950 and 1665 cm^{-1}; ^1H NMR δ 5.10 (t, J = 7 Hz, 1 H), 3.01 (t, J = 7 Hz, 2 H), 2.61 (q, J = 7 Hz, 2 H), 2.0 (t, J = 7.0 Hz, 2 H), 1.68 (d, J = 1.1 Hz, 3 H), 1.38 (m, 2 H), and 0.90 (t, J = 7 Hz, 3 H); MS *m/e* 238.0274 (M^+; 238.0218 calcd for $C_8H_{15}I$).

(2*Z*,6*Z*)-7-Methyl-3-propyl-2,6-decadien-1-oic Acid (9). To a mixture of magnesium turnings (0.516 g, 21.5 mmol) and refluxing ether (10 mL) was added first a drop of ethereal ethylmagnesium bromide as an initiator and then a solution of **8** (2.53 g, 10.7 mmol) and ether (25 mL) from an addition funnel over a 12-h period. The resulting solution was added with a syringe over a 5-min period to a suspension of $CuBr(Me_2S)$ (1.80 g, 8.8 mmol) in ether (5 mL) and dimethyl sulfide (8 mL) at 45 °C. After 2.5 h, 1-pentyne (0.88 mL, 8.8 mmol) was added to the green mixture over 1 min at −45 °C. After the mixture was stirred at −23 °C for 2.5 h, it was cooled to −30 °C and $[(CH_3)_2N]_3PO$ (7.1 mL, 40.8 mmol) and $(EtO)_3P$ (0.18 mL, 0.87 mmol) were added separately. The mixture was stirred for 1 h, and then dry carbon dioxide was bubbled through the mixture[13] at −23 °C for a 6-h period. After being stirred at 0 °C for 2 h, the mixture was quenched with 1 N hydrochloric acid (10 mL). By a standard acid–base workup procedure employing 10% aqueous sodium hydroxide, **9** was obtained as 1.18 g (50%) of clear, colorless oil: IR 2500–3000, 1690, 1630, 1250, and 840 cm^{-1}; ^1H NMR δ 9.2 (br s, 1 H), 5.65 (s, 1 H), 5.16 (t, J = 7 Hz, 1 H), and 0.63–2.86 (several overlapping multiplets and a doublet at δ 1.67, J = 0.9 Hz, 21 H overall); MS *m/e* 224.1813 (M^+; 224.1774 calcd for $C_{14}H_{24}O_2$). Careful GLC analysis revealed only one component (100% pure).

(2*Z*,6*Z*)-7-Methyl-3-propyl-2,6-decadien-1-ol (4). A solution of **9** (0.978 g, 4.37 mmol) in ether (20 mL) was added dropwise over a 5-min period to a suspension of $LiAlH_4$ (0.190 g, 5.01 mmol) in ether (50 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and at 25 °C for 12 h, quenched at 0 °C by sequential addition of water (1 mL), 10% aqueous sodium hydroxide (1 mL), and water (3 mL), and partioned between additional ether and water. From the ether layer was obtained 0.899 g (98%) of **4** as a clear, colorless oil: IR 3350, 2950, 1670, 1010, and 820 cm^{-1}; ^1H NMR δ 5.33 (t, J = 7.0 Hz, 1 H), 5.25 (m, 1 H), 4.04 (d, J = 7.0 Hz, 2 H), 1.18–2.01 (several overlapping multiplets and a singlet at δ 1.67, 16 H overall), and 0.81 (two overlapping triplets, J = 6.6 and 7.4 Hz, 6 H); MS *m/e* 210.2030 (M^+; 210.1983 calcd for $C_{14}H_{26}O$). The product was identical with the samples from Dr. McDonough and Professor Katzenellenbogen according to these data and by direct GLC comparison and was 99.5% pure.

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Registry No.—**4**, 42066-82-0; **7**, 13679-01-1; **8**, 69089-03-8; **9**, 69089-04-9; *n*-propylmagnesium bromide, 927-77-5; propyne, 74-99-7; ethylene oxide, 75-21-8; 1-pentyne, 627-19-0; (*Z*)-4-methyl-3-hepten-1-ol tosylate, 69089-05-0.

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Synthesis of 7-Fluorobenz[*a*]anthracene[1]

Melvin S. Newman* and Kenneth C. Lilje[2]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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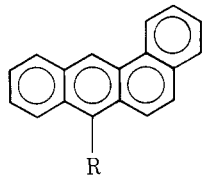
The desirability of testing 7-fluorobenz[*a*]anthracene (**1**) for carcinogenic activity has increased as more was learned about the carcinogenic activity of substituted benz[*a*]anthracenes. The fact that 7-methylbenz[*a*]anthracene (**2**) is the most potent carcinogen of the monomethyl benz[*a*]anthracenes[3] has been explained by two essentially different hypotheses.[4] In one, a metabolic change leading to cancer occurs in the 7-methyl group and in the other, the 7-methyl group confers activity because it blocks a detoxification metabolism which starts at the 7 position.[3] The testing of 7-fluorobenz[*a*]anthracene was deemed important because the 7-fluoro atom could block a detoxification mechanism but would not allow for a carcinogenic metabolism at the fluorine atom.

Attempts at synthesis of **1** have been made[5-7] but insufficient **1** had been made for adequate testing at the time we started the work reported. Our successful route involves the diazotization of 7-aminobenz[*a*]anthracene (**3**) by dry gaseous nitric oxide in dry ether followed by nitrogen dioxide and treatment with HBF_4 (or HPF_6) to give a diazomium salt, **4**, which could be dried and pyrolyzed to yield pure **1** in good yield.[8] This route is essentially that used to convert 9-aminoanthracene into 9-fluoroanthracene.[9] All other diazotization procedures attempted failed to give products which would yield any **1** on pyrolysis. That **1** had the fluorine in the 7 position was supported by the facts that oxidation afforded 7,12-benz[*a*]anthraquinone in high yield and the NMR spectrum had a 1 proton singlet at δ 8.84, characteristic of H_{12} in 7-substituted benz[*a*]anthracenes.[10]



1, R = F
2, R = CH_3
3, R = NH_2
4, R = $N_2^+BF_4^-$
5, R = NO_2
6, R = H

7-Nitrobenz[*a*]anthracene (**50**) was prepared by an improved procedure which affords **5** in 55% yield from benz[*a*]anthracene (**6**). The starting **6** was prepared by condensation of phthalaldehydic acid with naphthalene to yield 3-(1-naphthyl)phthalide[11] which was reduced to 2-(1-naphthylmethyl)benzoic acid[12] followed by ring closure, reduction of benzanthrone, and dehydration to yield **6** in 76% overall yield. Compound **1** is being tested for carcinogenic activity.

Experimental Section[13]

2-(1-Naphthylmethyl)benzoic Acid. 3-(1-Naphthyl)phthalide[11] (76 g, 0.29 mol) was combined with 400 g of Zn dust (activated by washing with dilute HCl) and 2 L of 90% formic acid. After refluxing the vigorously stirred mixture for 72 h the liquid portion was decanted into 1.5 L of ice water. The resulting white solid was collected and the mother liquor as well as the zinc residues were washed with 1 L of ether–benzene. After dissolving the product in ether–benzene, usual treatment of the combined organic phases gave 65.5 g (85%) of white solid, mp 144.0–146.0 °C (lit.[12] mp 148–148.5 °C), suitable for use in the next step.

Benz[*a*]anthracene (6) 2-(1-Naphthylmethyl)benzoic acid (20 g, 76.5 mmol) was added to 250 mL of anhydrous HF. After 20 min the red solution was poured onto 1 kg of ice. The pale yellow solid was collected, washed with water, and added to a flask containing 75 g of Zn dust (activated with $CuSO_4$), 800 mL of 2 N NaOH, and 200 mL of toluene.[14] After refluxing the solution for 18 h, an additional 25-g portion of activated Zn was added. After a total reflux time of 48 h, the reaction mixture was cooled to 80 °C and 200 mL of benzene added. The liquid portion was decanted and the solids washed with an additional 200 mL of benzene. The organic phase was separated and treated as usual to give 16.63 g (94%) of colorless **6**, mp 155.0–156.5 °C. Recrystallization from ethanol–benzene gave 15.59 g (89.5%), mp 157.0–158.0 °C (lit.[15] mp 160.5–161 °C).

7-Nitrobenz[*a*]anthracene (5). A solution of 10 g (44 mmol) of **6** and 600 mL of CH_2Cl_2 was cooled to −15 °C and 3.2 g of 90% HNO_3 (46 mmol) was added over 15 min. The temperature was raised to 0 °C and 2.5 g of additional HNO_3 was added over 1.5 h. Addition of 100 mL of water followed by the usual workup gave 12 g of orange solid. Recrystallization from ethanol–benzene (4:1) gave 6.61 g (55%) of yellow **5**, mp 159.0–161.0 °C (lit.[5] mp 163–164 °C), suitable for reduction to **3** as described.[16]

7-Diazoniumbenz[*a*]anthracene Tetrafluoroborate (4). A yellow solution of 1.0 g (4.28 mmol) of **3**[16] in 150 mL of anhydrous ether was flushed with N_2 and cooled in an ice bath. Nitric oxide (supplied by Matheson and passed through a concentrated H_2SO_4 scrubber) was bubbled slowly through the solution for 1 h to produce a cinnamon-colored, nonhomogeneous mixture. Dry air was then combined with the NO flow to generate NO_2, which was passed through the mixture for 1 h. During this period an orange precipitate formed. The addition of 4 mL of 48% HBF_4 caused no observable color change. After 0.5 h the bright orange solid was collected, washed with ether, and dried in a vacuum desiccator to give 1.22 g (90%) of **4**, mp 118.0–120.0 °C dec. A similar result was obtained using HPF_6 instead of HBF_4 but the mp was not sharp and not reproducible.

7-Fluorobenz[*a*]anthracene (1). A mixture of 0.5 g (1.57 mmol) of **4** and 0.5 g of powdered dry KF was added over 0.5 h to 50 mL of refluxing xylenes. The resulting dark solution was filtered and evaporated to dryness. The residue was dry column chromatographed[17] on 90 g of silica gel[18] in a 0.75 in. × 20 in. Nylon column using hexane as the eluant. Under these conditions the product band moves most rapidly (R_f 0.5) and separates from impurities (short wave UV light used to visualize bands). The band was cut out and extracted with ether to yield 350 mg (91%) of pure **1**, mp 93.5–94.3 °C. A similar pyrolysis on three times the scale resulted in a 72% yield of pure **1**. Neat pyrolysis on a 3 mmol scale afforded only 60% of pure **1**. The following spectral data were obtained: mass spectra; parent ion *m/e* 246 (rel intensity 100); NMR ($CDCl_3$, Me_4Si) δ 8.84 (s), 8.84–8.60 (m, 2 H, H_{12}, and H_1 respectively), 8.35–7.4 (complex multiplet, 9, H, all remaining protons).[10] Repeated recrystallization from ethanol to obtain an analytical sample did not raise the mp over 93.8–94.3 °C. Anal. Calcd for $C_{18}H_{11}F$: C, 87.8; H, 4.5; F, 7.7. Found: C, 87.8; H, 4.6; F, 7.6.

Benz[*a*]anthracene-7,12-dione. A solution of 100 mg of **1**, 7 mL of glacial acetic acid, and 130 mg of sodium dichromate was refluxed for 0.5 h. The resulting green solution was added to 10 mL of water. The yellow solid was collected, washed with water, and oven dried to yield 100 mg of quinone, mp 166.0–168.5 °C. Recrystallization from benzene–ethanol afforded yellow quinone mp and mmp with authentic quinone (supplied by Eastman) 167.0–168.5 °C (lit.[19] mp 168 °C). Mass spectrum showed a parent ion of *m/e* 258.

Registry No.—**1**, 23683-26-3; **3**, 2381-18-2; **4**, 69238-66-0; **5**, 20268-51-3; **6**, 56-55-3; benz[*a*]anthracene-7,12-dione, 2498-66-0; 2-(1-naphthylmethyl)benzoic acid, 69238-67-1; 3-(1-naphthyl)-phthalide, 56282-14-5.

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(4) For a discussion of many hypotheses concerning cancer induction see J.

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