(PPh_3)) has been successfully used in RCM and other ruthenium(II)-catalyzed reactions. In all cases, the reactions proceeded in high yields, and the catalyst was recovered quantitatively by simple filtration and reused. Further investigation to apply P,S-$RuCl_2(PPh_3)$ to other ruthenium(II)-catalyzed reactions is now in progress.

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[14] ^{31}P SR-MAS NMR ($CDCl_3$): 50.8 (PCy_3), -144.0 ppm (PF_6^-). Solid PPh_3 ($\delta = -8.4$ ppm) was used as an external standard. ^{31}P NMR of monomeric ruthenium complex was measured in ref. [6c]. ^{31}P NMR ($CDCl_3$): 58.8 (PCy_3), -140.8 ppm (PF_6^-). See also A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, *Chem. Eur. J.* **2001**, *7*, 4811.

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(*E*)-4-Hydroxy-3-methylbut-2-enyl Diphosphate: An Intermediate in the Formation of Terpenoids in Plant Chromoplasts**

Wenyun Gao, Reik Loeser, Maja Raschke, Marco A. Dessoy, Michael Fulhorst, Henriette Alpermann, Ludger A. Wessjohann,* and Meinhart H. Zenk*

Nature's terpenoids, with over 35000 known members, constitute compounds that are either essential for life (namely, cholesterol, vitamins) or represent secondary products, such as chemical attractants, defense compounds, and antibiotics. Until recently, terpenoids were assumed to be formed exclusively by the mevalonate pathway.[1] It has now been shown that an alternative metabolic route exists in plastids of higher plants and in the majority of bacteria. This pathway leads from pyruvate (**1**) and D-glyceraldehyde-3-phosphate (**2**) via 1-deoxy-D-xylulose phosphate (**3**, DXP, Scheme 1) and the intermediates **4**–**7** to the key metabolites isopentenyl diphosphate (**9**, IPP) and dimethylallyl diphosphate (**10**, DMAPP), which are essential to all organisms.[2] The cyclic diphosphate **7** has been proven to be a precursor to **9** and **10** in the alternative pathway and thus to plastidic isoprenoids, mainly phytoene (**11**).[3] This reaction involves a threefold, possibly stepwise, dehydroxylation at carbon atoms C-2, C-3, and C-4 of **7**.

On comparative phytochemical grounds, we postulated that (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate (**8**, Schemes 1 and 2) is a likely intermediate in the deoxyxylulose phosphate pathway between **7** and **9**/**10**.[4] This hydroxylated hemiterpene is seen biogenetically in numerous plant-derived products, such as the plant hormone **13**, the glucoside of (*E*)-2-

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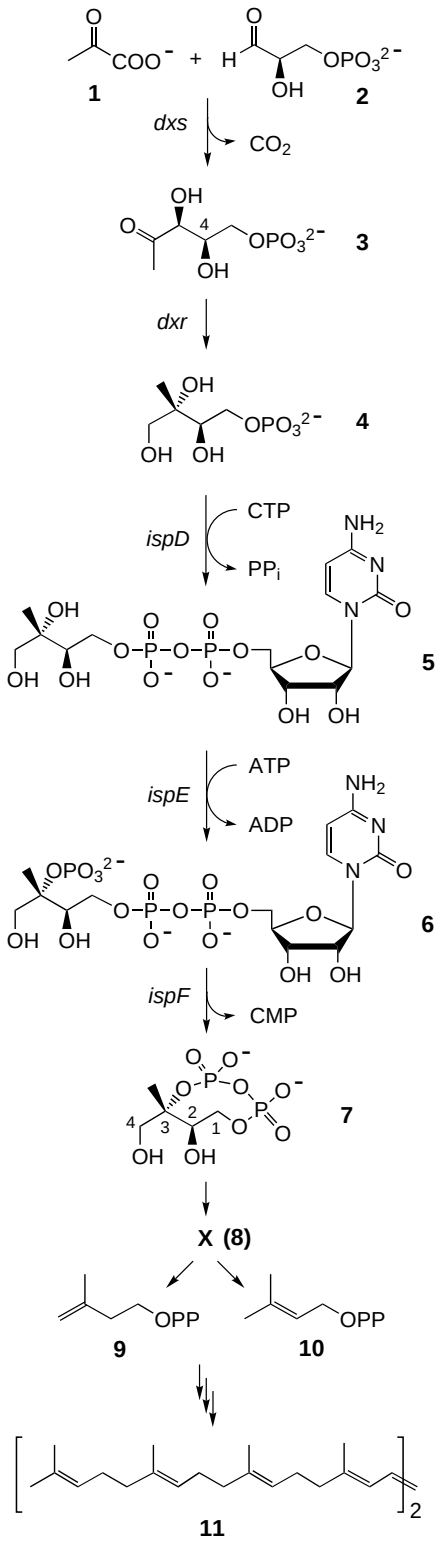
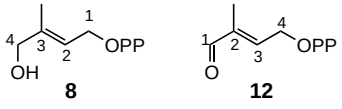
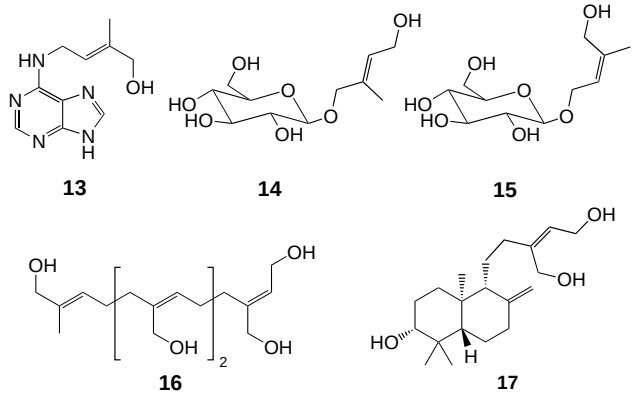


Scheme 1. Deoxyxylulose phosphate (DXP) pathway for the biosynthesis of terpenoids.



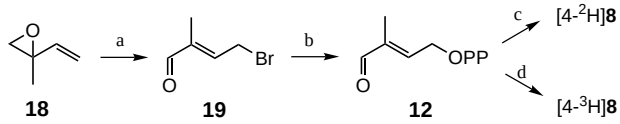
Scheme 2. Proposed late intermediates X (**8**) and **12** of the DXP-isoprenoid pathway.

methylbut-2-ene-1,4-diol(**14**), another glucoside of *Z* isomer **15**, and many other secondary plant products, such as **16** and **17** (Scheme 3).[5]



Scheme 3. Natural products which may be (partially) derived from intermediate **8** or its IPP analogue.

To test the postulated intermediacy, the labeled diphosphates of **8** were synthesized from the new aldehyde **12** (Scheme 4), which itself is a postulated intermediate (see below). This strategy allowed the convenient introduction of



Scheme 4. Synthesis of **12**, [4-^{2}H]**8**, and [4-^{3}H]**8**. Reagents and conditions: a) $CuBr_2$ (2.1 equiv), Li_2CO_3 (1.4 equiv), $CHCl_3$/EtOAc (1:1), 90 °C, 20 min, 87 %; b) $(n\mathrm{Bu}_4\mathrm{N})_2\mathrm{H}_2\mathrm{P}_2\mathrm{O}_7$ (3 equiv), CH_3CN, 0 to 22 °C, 2.5 h, ionic exchange (Na^+), 42 % (the yield of **12**, which is obtained within solid sodium(hydrogen) carbonate buffer, was determined by quantitative ^{31}P NMR spectroscopy in $NaHCO_3$-buffered water using phenylphosphonic acid as the internal standard); c) NaB^2H_4 (2 mol equiv), H_2O/MeOH (2:1), RT, 2 h, 16 %; d) NaB^3H_4 (0.5 mol equiv), H_2O/MeOH (2:1), RT, 2 h, 19 %.

tritium or deuterium as the last step in the synthesis. Aldehyde **12** was obtained in a two-step preparation starting from commercially available 2-methyl-2-vinyloxirane (**18**)[6] following a modification of the method of Davisson et al.[7] It should be noted that the usual counterion exchange of tetra-*n*-butylammonium to ammonium is not advisable in this case because ammonia addition to the enal moiety can occur. The target compound **8** was obtained as the [4-^{2}H]- or [4-^{3}H]-labeled form by reduction of **12** with NaB^2H_4 or NaB^3H_4, respectively.

To test the postulated role of **8** as a biosynthetic intermediate between **7** and **9**/**10**, chromoplasts from *Narcissus pseudonarcissus* and *Capsicum annuum* were supplied with [4-^{3}H]**8** in the presence of a phosphatase inhibitor (NaF), an energy source (adenosine-5′-triphosphate (ATP)/Mg^{2+}), and a reductant (the reduced form of nicotinamide adenine dinucleotide (NADPH)). The incubations were performed as previously published and terpenoids were isolated from the incubation mixture by extraction with ethyl acetate.[3]

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In the presence of chromoplasts, [4-^{3}H]**8** is rapidly converted in the incubation mixture and radioactivity accumulates in the ethyl acetate phase (Table 1). 50% of the

Table 1. Conversion of [4-^{3}H]**8** [nmol, from radioactivity] into ethyl acetate soluble material ("lipids") containing phytoene (**11**) by *N. pseudonarcissus* and *C. annuum* chromoplasts.[a]

t [min]	*N. pseudonarcissus*		*C. annuum*	
	lipids	**11**	lipids	**11**
0	0	0	0	0
10	0.4	0.2	0.2	0.1
30	0.6	0.3	0.4	0.2
60	0.8	0.4	0.6	0.3
120	1.1	0.6	0.7	0.4
240	1.3	0.7	0.8	0.4

[a] Incubation mixture (total volume: 500 μL): 2.6 μM [4-^{3}H]**8**, 100 mM tris(hydroxymethyl)aminomethane·HCl (Tris·HCl) buffer (pH 7.6), 2 mM $MnCl_2$, 10 mM $MgCl_2$, 5 mM NaF, 2 mM $NADP^+$, 1 mM NADPH, 6 mM ATP, 2 mg chromoplast protein, 30 °C.

radioactivity in the ethyl acetate fraction was located in phytoene (**11**), which is the main metabolite synthesized from the more distant precursor **7**.[3] The remaining 50% of the radioactivity from [4-^{3}H]**8** in that fraction was found in various carotenoids. Phosphorylated intermediates other than **8**, **9**, and **10** were barely detected after HPLC analysis of the aqueous phase (for the HPLC conditions, see ref. [3]). The almost quantitative transformation of labeled **8** into plastidic terpenoids in these taxonomically separate plant species demonstrates for the first time the intermediacy of **8** in the terpenoid pathway in higher plants.

Short term (5–20 min) application of [$^{14}C_2$]**7** to both chromoplast preparations resulted in the incorporation of this cyclic diphosphate into terpenoids,[3] but upon HPLC analysis of the aqueous phase, radioactivity was clearly seen to transiently accumulate in an intermediate (up to 25% of the total supplied [$^{14}C_2$]**7**) in both the *Narcissus* and *Capsicum* chromoplasts (Figure 1). Phosphatase or chemical hydrolysis[8] of this labeled compound yielded an allylic alcohol, which corresponded to synthetic (*E*)-2-methyl-2-butene-1,4-diol (various chromatographic analyses).[4b] This observation is consistent with the intermediacy of **8** in the conversion of **7** into **9**/**10** in plants. The methylerythritol found in the *Capsicum* system (Figure 1a) is a result of the action of NaF-insensitive phosphatases on **7**.

During the course of this investigation, three research groups reported that **8** accumulates in *Escherichia coli* mutants overexpressing the *GcpE* (*IspG*) gene,[9, 10] and in bacterial mutants that are deficient in the *LytB* (*IspH*) gene.[11] Most probably **8** represents a novel intermediate in the deoxyxylulose phosphate pathway, and is likely the missing link **X**[12] in the formation of **9**/**10** from **7** (Scheme 1 and Scheme 2). Compound **8** was synthesized previously in unlabeled form by different, more lengthy, routes.[13]

Aldehyde **12** has been postulated in the hypothetical mechanism of the conversion of **7** into **8** mediated by the *IspG* gene product.[9] It was also reported that the in vivo conversion of [U-$^{13}C_5$]1-deoxy-D-xylulose resulted in a 5:1 mixture of [U-$^{13}C_5$]**9** and [U-$^{13}C_5$]**10**.[14] This ratio was not

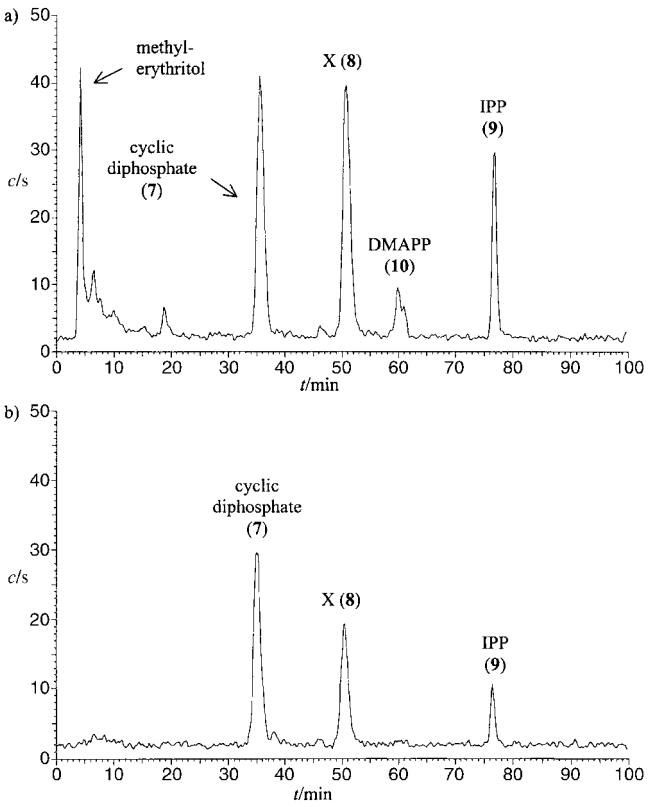

Figure 1. HPLC radiogramm of an aliquot of an assay mixture containing the [$^{14}C_2$]**7** and chromoplasts from either a) *C. annuum* or b) *N. pseudonarcissus*. The incubation conditions were as described in ref. [3]. Retention times: methylerythritol: 4.5 min, cyclic diphosphate **7**: 35 min, diphosphate **8**: 50 min, DMAPP **10**: 60 min, IPP **9**: 77 min.

observed by us during the time course of the conversion of **8** into **9** and **10** by chromoplast and bacterial preparations. One discrepancy between the bacterial and the plant systems, however, still needs clarification. While it has been shown that the label from [4-^{2}H]**3** is retained exclusively in the dimethylallyl diphosphate starter unit in the bacterial system,[15, 16] the dimethylallyl diphosphate starter unit in the plant system (*Catharanthus roseus*) is completely devoid of the deuterium label.[17] However, feeding experiments using a different plant system, *Eucalyptus globulus*, show that the deuterium label is retained in the dimethylallyl diphosphate starter unit.[12] No plausible explanation can yet be given for this discrepancy that may reflect different metabolic routes within the plant kingdom.

The demonstration of the rapid and unequivocal transformation of synthetic **8** into isoprenes of the phytoene type and with transition from **7** through **8** to **9**/**10** in plant chromoplasts provides evidence that **8** is indeed the biologically active intermediate in this pathway present in plastids of higher plants.[20]

Experimental Section

Isolation of chromoplasts from *C. annuum* and *N. pseudonarcissus*, incorporation experiments with isotope-labeled substrates, and isolation of phytoene and HPLC analyses of phosphorylated metabolites were conducted exactly as previously published.[3] [3-^{14}C, Me-^{14}C]**7** was prepared as described[18] from [U-$^{14}C_3$]**1** and unlabeled **2**. The specific activity

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achieved was 103 μCi μmol^{-1}. The genes *dxs*, *ispC*, *ispD*, *ispE*, and *ispF* were amplified by the polymerase chain reaction from *Escherichia coli* DNA and were functionally expressed as His-tag fusion proteins to facilitate purification.

12: Bromoaldehyde **19** was prepared in 87% yield from **18** (4.20 g, 50.0 mmol) according to the method of Gray.[6] Freshly prepared pyrophosphoric acid[7] was immediately titrated to pH 5.3 with approximately 20% (w/w) aqueous tetra-*n*-butylammonium hydroxide. After lyophilization, bis(tetra-*n*-butylammonium) dihydrogen pyrophosphate was quantitatively obtained as a white, highly hygroscopic solid. This product (9.91 g, 15.0 mmol) was dissolved in dry acetonitrile (20 mL) under a nitrogen atmosphere. The resulting clear solution was then cooled to 0 °C and neat **19** (0.815 g, 5.0 mmol) added. While stirring, the reaction was allowed to warm up to room temperature over 2.5 h. The reaction mixture was poured into a cold, aqueous solution (50 mL) of sodium hydroxide (0.60 g, 15.0 mmol) and the acetonitrile partially evaporated under vacuum. The remaining aqueous solution was passed through a column of approximately 30 exchange equivalents of Lewatit SP 112 WS cation exchange resin (Na^+ form). The column was eluted with three column volumes of a 1:49 mixture (v/v) of isopropyl alcohol and 1.8 mM sodium bicarbonate. The eluent was lyophilized to dryness to yield a fluffy solid. The crude material was purified by means of HPLC[19] (YMC-Pack R& 250 × 20 mm, ODS 120A, 5 μm, 1.8 mM sodium bicarbonate eluent). The eluent was lyophilized to dryness to yield a white fluffy solid. Negative mode ESI MS-MS: *m*/*z*: 259 $[M-H]^-$, 241 $[M-H-H_2O]^-$, 177 $[H_3P_2O_7]^-$, 159 $[HP_2O_6]^-$, 79 $[PO_3]^-$, ^{1}H NMR (400 MHz, D_2O): $\delta = 9.34$ (s, 1H; H-1), 6.85 (t, $J = 5.3$ Hz, 1H; H-3), (4.7–4.9, 1H and HDO overlap from solvent), 1.72 ppm (s, 3H; CH_3); ^{31}P NMR (162 MHz, H_2O): $\delta = -5.75$ (d, $J = 22$ Hz), −10.89 ppm (dt, $J_{P,P} = 22$ Hz, $J_{H,P} = 7.7$ Hz).

[4-^{2}H]**8**: Aldehyde **12** (20 mg, 77 μmol) was reduced in a 2:1 mixture of water and methanol (0.21 mL) at pH 9 with NaB^2H_4 (6.4 mg,154 μmol) at room temperature (2 h) and the reaction product was purified by ion-exchange chromatography on DEAE Sephadex (3.2 mg, 16%). Negative mode ESI MS-MS data: *m*/*z*: 262 $[M-H]^-$, 244 $[M-H-H_2O]^-$, 177 $[H_3P_2O_7]^-$, 164 $[M-H-H_3PO_4]^-$, 159 $[HP_2O_6]^-$, 97 $[H_2PO_4]^-$, 79 $[PO_3]^-$; ^{1}H NMR data (400 MHz, D_2O): $\delta = 5.66$ (t, $J = 7$ Hz, 1H; H-2), 4.55 (dd appearing as pseudo-triplet, $J_{H,H} = J_{H,P} = 7$ Hz, 2H; H-1), 4.01 (s, 1H; H-4), 1.72 ppm (s, 3H; CH_3).

[4-^{3}H]**8**: This was prepared by reduction of **12** with NaB^3H_4 and purified in the same way as 4-deuterated **8** (19% yield). The specific activity achieved was 1.56 μCi nmol^{-1}.

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