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MECHANISM OF PRESQUALENE PYROPHOSPHATE-SQUALENE BIOSYNTHESIS II. SYNTHESIS OF BIFARNESOL

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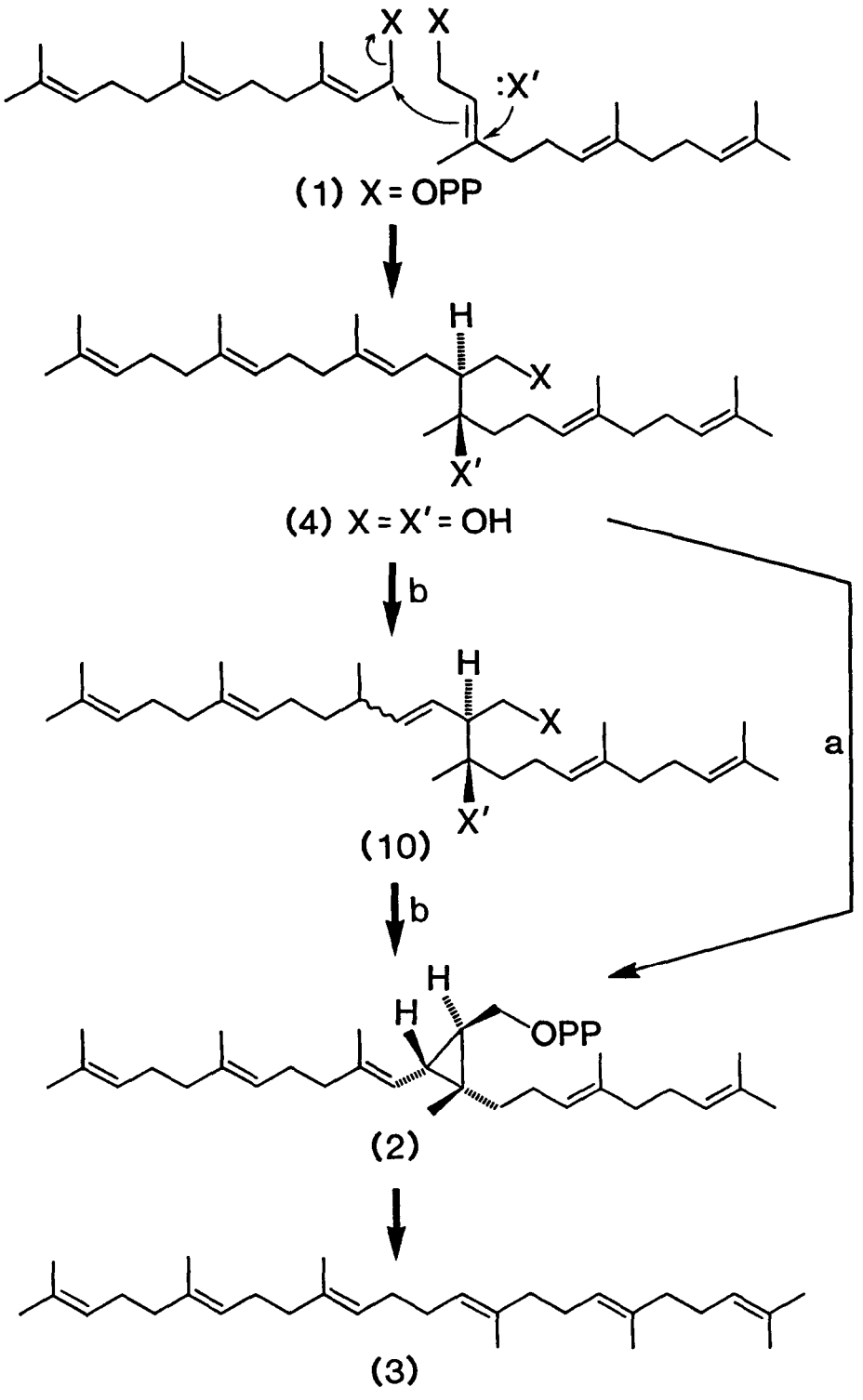
Summary: A convenient synthesis of the racemate of bifarnesol (4), a proposed biochemical precursor of presqualene pyrophosphate and squalene, is described.

In previous bodies of work[1-7] presqualene pyrophosphate (2) has been established as an intermediate in the overall bioconversion of farnesyl pyrophosphate (1) to squalene (3), the precursor of all sterols. The remarkable transformation of the simple sesquiterpenoid (1) to the cyclopropylcarbinol derivative (2) has been the subject of various speculations,[6,8-10] all of which involve the mediation of diol (presumably phosphorylated) 4, a formal dimer of farnesol. Herein we describe a simple, stereoselective laboratory synthesis of this "bifarnesol" in the racemic form.

In the key, α-alkylation step,[11] methyl farnesate (5) (2 mmol in 0.5 ml THF) was first subjected to the action of lithium diisopropylamide (0.97 equiv) in 385 μl HMPA-1.5 ml THF at -78°C for 1.5 hr, after which 1.04 equiv farnesyl bromide (6) in 32 μl HMPA-0.5 ml THF was added. After being warmed to room temperature overnight, the reactants yielded (54%) the deconjugated ester (±) 7, an oil purified by vacuum dry chromatography (silica gel/toluene).[12,13] ^{1}H NMR (100 MHz, $CDCl_3$) δ: 5.11 (multiplet, 5 H), 4.97 (s, 1 H), 4.92 (s, 1 H), 3.65 (s, 3 H), 3.02 (t, J = 7 Hz, 1 H), 2.04 (multiplet, 18 H), 1.64 (d, J = 7 Hz, 21 H); IR (film) inter alia 1740 cm^{-1}; M + 454.3804; VPC (SE-54 capillary, 15 M, T = 260°C) peak at 4.52 min. The hexatriene methyl ester (7) was reduced with $LiAlH_4$ (THF, room temperature overnight) to give (93%) the oily (±) alcohol (8). NMR (100 MHz, $CDCl_3$) δ: 5.10 (multiplet, 5 H), 4.96 (s, 1 H), 4.87 (s, 1 H), 3.55 (d, J = 3 Hz, 2 H), 2.01 (s, 19 H), 1.64 (d, J = 8 Hz, 21 H); IR (film) inter alia 3340 cm^{-1}; M + 426.3869; VPC (SE-54 capillary, 15 M, T = 260°C) 4.80 min. The $VO(acac)_2$-catalyzed oxidation (100%) of the unsaturated alcohol (0.187 mmol) to non-crystalline (±) glycidol (9) was carried out by means of 0.280 mmol t-butylhydroperoxide[14] in 3 ml refluxing benzene for 45 min. NMR (100 MHz, $CDCl_3$) δ: 5.09 (multiplet, 5 H), 3.54 (d, J = 3 Hz, 2 H), 2.86 (d, J = 4 Hz, 1 H), 2.67 (d, J = 4 Hz, 1 H), 2.00 (s, 18 H), 1.63 (d, J = 8 Hz, 21 H); M + 442.3804. Further reduction with 100 mg $LiAlH_4$ in 6 ml THF (room temperature overnight) converted (78%) the epoxide 9 (0.074 mmol) to the 1,3-diol (4) (±), impervious to the action of periodic acid. NMR (100 MHz, $CDCl_3$) δ: 5.12 (d, J = 5 Hz, 5 H), 3.74 (d, J = 5 Hz, 2 H), 2.01 (s, 18 H), 1.64 (d, J = 8 Hz, 21 H), 1.19 (s, 3 H); M + 444.3970; TLC (R_f 0.31, 20% EtOAc/hexane). The stereochemical assignments follow from the established pattern of t-butylhydroperoxide/$VO(acac)_2$ oxidation of homoallylalcohols.[14,15]


X X
:X'
(1) X = OPP
H
X
X'
(4) X = X' = OH
b
H
X
X'
(10)
a
b
H
H
OPP
(2)
(3)

One group of proposals[6,8] for the conversion of farnesyl pyrophosphate to presqualene pyrophosphate incorporates (a) a type of 1,3 elimination involving an allylic hydrogen and an appropriate leaving group X', while a second suggestion[9,10] features (b) preliminary double bond migration to yield (10), which subsequently undergoes a well-precedented homoallyl ring closure to the cyclopropylcarbinyl system (2). The availability of diol (4) now permits biological testing of phosphorylated, radiolabeled versions as presqualene pyrophosphate, precursor candidates, while the recently disclosed synthesis of isomer (10)[16] offers the possibility for distinguishing between the biopathways a and b.

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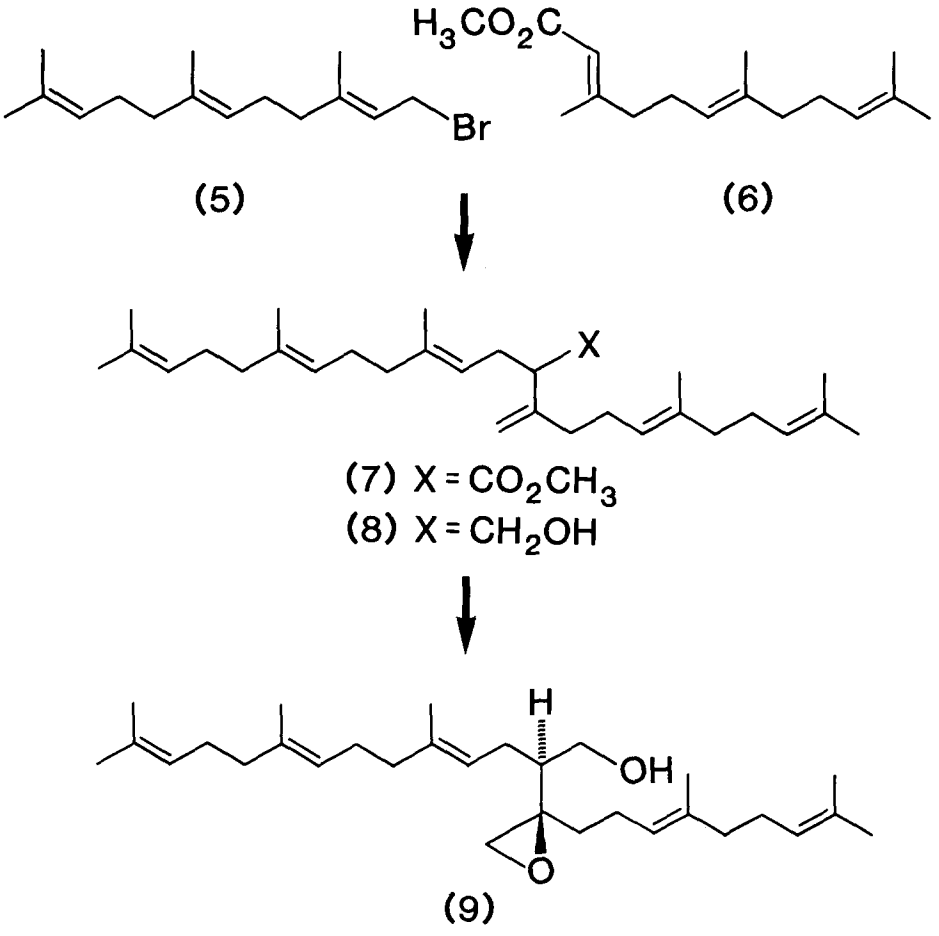

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