Table I. Effective Formation of Ligand-Uranyl Complex[a]

ligand	product	eff formation, %
3	$3{\cdot}UO_2^-$	ca. 100
4	$4{\cdot}UO_2^-$	75
Et_2NCS_2	$(Et_2NCS_2)_3{\cdot}UO_2^-$	6×10^{-7}

[a] $[UO_2^{2+}] = 0.1$ mM, $[CO_3^{2-}] = 2.4$ mM, [ligand] = 1.0 mM, $T = 20$ °C, pH 9.5.

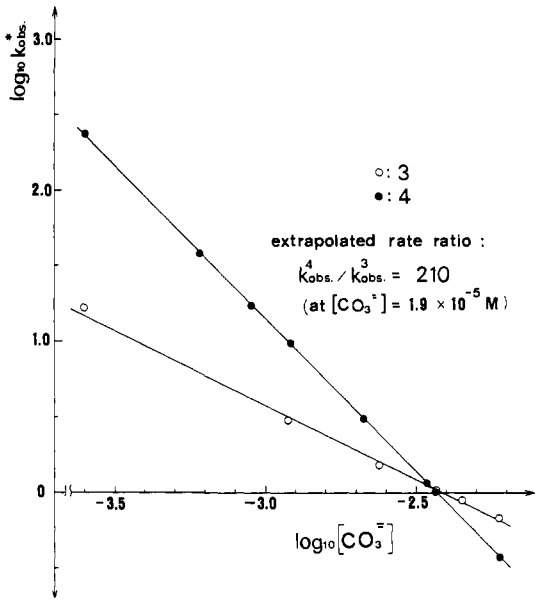

Figure 1. Dependence of $\log_{10} k_{obsd}$ upon $\log_{10} [CO_3^{2-}]$: $T = 20 \pm 0.1$ °C; $[UO_2(CO_3)_3^{4-}] = 1.3 \times 10^{-4}$ M; $[CO_3^{2-}] = (2.5\text{–}63) \times 10^{-4}$ M. k_{obsd}: for 3 from eq 3, $k_{obsd} = k_3/[CO_3^{2-}]$; for 4 from eq 2, $k_{obsd} = k_4/[CO_3^{2-}]^2$.

(VC=S); mp 54–56 °C; MS, *m/e* 355 for triamine, 649 for dithiocarbamate $4{\cdot}Na_3$. Anal. Satisfactory for triamine $3{\cdot}HBr$. Dithiocarbamate 4 forms 1:1 complexes with uranyl ion in aqueous solution. This results in the appearance of new electronic absorption at 265 nm with corresponding disappearance of the free 4 absorptions at 260 and 283 nm.[1d] The molar ratio of 4 to UO_2^{2+} in the complexes, the association equilibrium constants, and the stoichiometry of equilibria (eq 1) were determined by the electronic

$$UO_2(CO_3)_3^{4-} + 4^{3-} \rightleftarrows UO_2{\cdot}4^- + 3CO_3^{2-} \qquad (1)$$

spectroscopy. Equilibrium constant thus obtained is $(1.8 \pm 0.2) \times 10^{17}$ M^{-1} at 20 °C, pH 9.5 ± 0.1, for a concentration range of $(4.5\text{–}430) \times 10^{-4}$ M 4. Compound 4 binds UO_2^{2+} strongly and is more than 10^8 times as effective in uranyl–uranophile complex formation as $Et_2NCS_2^-$ (see Table I).

Rates of carbonate displacement of $UO_2(CO_3)_3^{4-}$ by 4 were measured in an aqueous solution at pH 9.5 ± 0.1 at 20 ± 0.1 °C by the use of stopped-flow-electronic spectroscopy by following the change in absorption at 450 nm[1d]. Observed rates are dependent on concentrations of 4 (or 3) and carbonate:

$$\frac{d[4{\cdot}UO_2^-]}{dt} = k_4 \frac{[4][UO_2(CO_3)_3^{4-}]}{[CO_3^{2-}]^2} \qquad (2)$$

$$\frac{d[3{\cdot}UO_2^-]}{dt} = k_3 \frac{[3][UO_2(CO_3)_3^{4-}]}{[CO_3^{2-}]} \qquad (3)$$

The relative rate (eq 4) is expected to be a function of carbonate

$$\frac{d[4{\cdot}UO_2^-]}{d[3{\cdot}UO_2^-]} = \frac{k_4[4]}{k_3[3][CO_3^{2-}]} \qquad (4)$$

concentration (eq 4). Observed rate constants are plotted against CO_3^{2-} concentration (Figure 1). Clearly, the rate equations are not the same for 3 and 4. In fact, inverse first- and second-order dependence on CO_3^{2-} was observed for 3 and 4, respectively. Thus, at lower CO_3^{2-} concentrations, 4 displays a much faster rate of exchange than does 3. Compound 4 might be more useful for extracting UO_2^{2+} from natural sea water in a rapid ocean current,[3] since the extrapolated rate ratio is estimated to be ca. 210, in favor of the new linear ligand 4 to macrocycle 3.

Acknowledgment. We are grateful to Prof. Sessler, University of Texas, Austin, for his helpful discussion.

(3) The flow rate of the Black Current near Mikurajima Island, Izu area, reaches to 2 m/s (0.001 s/mm contact time) and any practical adsorbent must show very rapid uranyl uptake rate under the condition of $[CO_3^{2-}] = 1.9 \times 10^{-5}$ M. Tabushi, I.; Kobuke, Y.; Nakayama, N.; Aoki, T.; Yoshizawa, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1984**, *23*, 445.

An Unusual Substituent Effect on a Palladium-Mediated Cyclization: A Total Synthesis of (±)-Sterepolide

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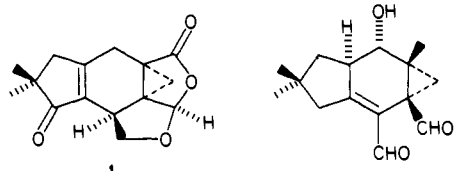
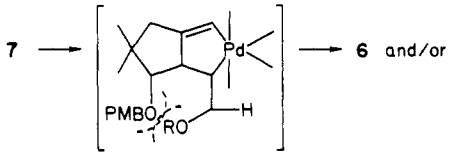
Recently, a new class of sesquiterpenoids, the isolactaranes, have emerged.[1,2] Sterepolide (1), a metabolite of the fungus *Stereum*



1 2

purpureum which is a cause of the silver leaf disease common to a number of fruit trees,[2b] and merulidial (2), a highly active antibiotic,[2c] are two representatives. Scheme I summarizes a retrosynthetic analysis of sterepolide. The key to this analysis is the availability of the reactive diene 6 in permitting the use of a Diels–Alder-based strategy.[3] Our recent discovery of a Pd-based isomerization of acyclic 1,6-enynes[4] suggested the possibility that 7 be considered as a suitable precursor except for the fact that all of the previous examples strongly indicated that the 1,4-diene 11 rather than the 1,3-diene 6 should be the observed product.



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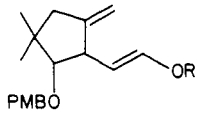

(1)

11

Furthermore, previous work on the Heck reaction[5] demonstrated

(1) For a review, see: Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199.

(2) (a) Isolactarorufin: Daniewski, W. M.; Kocor, M.; Thoren, S. *Pol. J. Chem.* **1978**, *52*, 561. Konitz, A.; Bogucka-Ledochowska, M.; Dautker, Z.; Hempel, A.; Borowski, E. *Tetrahedron Lett.* **1977**, 3401. (b) Sterepolide and dihydrosterepolide: Ayer, W. A.; Saeedi-Ghomi, M. H. *Tetrahedron Lett.* **1981**, *22*, 2071. (c) Merulidial: Steglich, W. *Pure Appl. Chem.* **1981**, *53*, 1233.

(3) Cf. the elegant marasmic acid synthesis: Greenlee, W. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1976**, *98*, 6075. *Tetrahedron.* **1980**, *36*, 3367; Boeckman, R. K. Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.

(4) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.

(5) (a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265. (b) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273. (c) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron* **1979**, *35*, 329.

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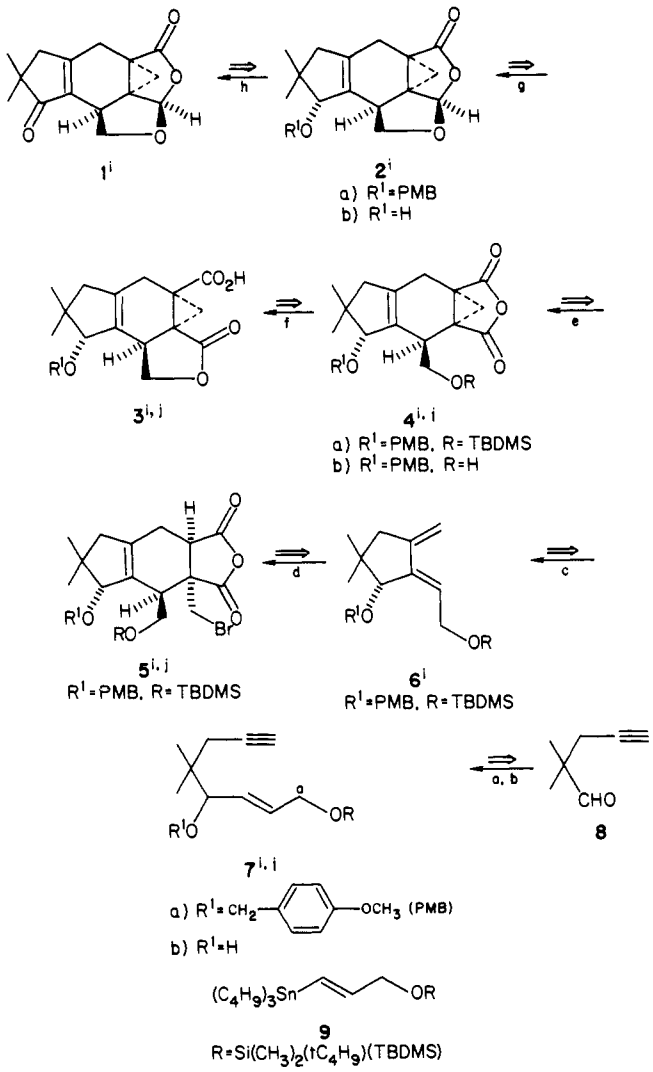
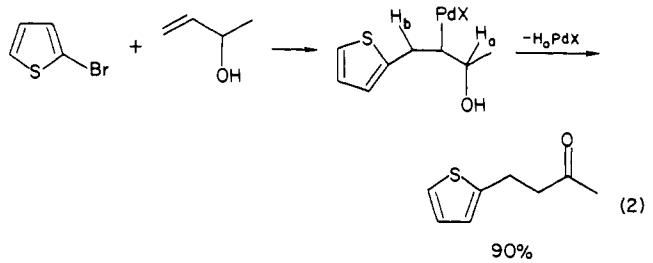
Scheme I.[a] Retrosynthetic Analysis and Synthesis of (±)-Sterepolide



[a] (a) n-C_4H_9Li, THF, −78 °C, 40%; (b) NaH, p-$CH_3OC_6H_4CH_2Br$, THF, 83%; (c) see text, 80%; (d) 2-(bromomethyl)maleic anhydride, PhH, 80 °C, 78%; (e) DBU, PhH, 5 °C, 100%; (f) $PhCH_2N(CH_3)_3F$, THF, room temperature, 72%; (g) Disiamylborane, THF, 0 °C → room temperature, 75%; (h) see text, 83%; (i) complete characterization spectrally; (j) elemental composition determined by combustion analysis.

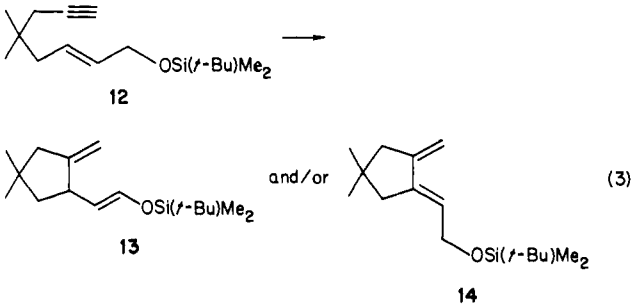
the favorability of β-hydrogen insertion adjacent to oxygen, i.e., H_a (eq 2), even in preference to a benzylic hydrogen—an observation that reinforces the prediction that the 1,4-diene rather than the 1,3-diene should be the product. The use of the trimethylsilyl ether does not alter this bias.[6] While increasing the oxidation level of C_a in **7** (Scheme I) would obviate this problem, the directness of the route outlined in the scheme combined with the ease of access of **7** led us to explore the effect of oxygen on the regioselectivity of the cyclization via isomerization.



(2)

The requisite enyne **7** is readily available by addition of the vinyllithium derived from the stannane **9**[7] to the aldehyde **8**.[8] Surprisingly, exposure of either the free alcohol **7a** or its p-methoxybenzyl ether **7b** to Pd(2+) complexes leads predominantly to exclusively to the 1,3-diene **6**! For example, $(Ph_3P)_2Pd(OAc)_2$[9] (5 mol %, PhH, 80 °C, 1 h) gives a 75% yield of **6** and 3% yield of a compound tentatively identified as **11**; $[(o\text{-}CH_3C_6H_5)_3P]_2Pd(OAc)_2$[9] (2 mol %, PhH, 80 °C, 1 h) increases the yield of **6** to 80% with <2% of **11**. Chromatography provides pure **6** with no detectable contamination with any minor byproducts. The compatability of the free alcohol as in **7a** in this cyclization reaction is noteworthy.

In viewing the proposed intermediate **10**, the possibility exists that the regioselectivity arises from an unfavorable steric interaction (as depicted in **10**) which destabilizes the transition state required for a cis β-hydrogen insertion leading to **11**. Such a proposal is particularly attractive considering the results of the Heck reaction which suggests an activating influence of oxygen.[5,6] Substrate **12** provides a test of such a steric effect. By removing the unfavorable interaction depicted in **10** (eq 1) a return to the normal regioselectivity (i.e., formation of **13**) is expected. Quite the converse happened—again only the 1,3-diene **14** formed [5 mol % $((o\text{-}CH_3C_4H_5)_3P)_2Pd(OAc)_2$, PhH, 80 °C, 1 h, 91% yield].



(3)

Clearly, oxygen is exercising an electronic effect that is strikingly different than its effect in the Heck arylation. One explanation may reside in the notion that in contrast to a Pd(2+) species, which is involved in the Heck reaction, a Pd(4+) species may be involved in the cyclization.[4]

With the fortunate development of the efficiency of the direct cyclization providing the 1,3-diene **6**, the route to sterepolide can now proceed in the synthetic direction (see Scheme I). The Diels–Alder reaction of (bromomethyl)maleic anhydride[3] and **6** gives a 5:1 regioisomeric mixture with **5** as the major regioisomer. That these are regio- not stereoisomers and that generation of a minor amount of the regioisomer is inconsequential is easily shown by the formation of the same cyclopropane **4** from the mixture. Desilylation and lactonization occur simultaneously to give crystalline **3**, mp 108–110 °C, using benzyltrimethylammonium fluoride[10] as the preferred reagent. After a survey of various reduction methods to convert **3** or its methyl ester to lactol–lactone **2**, an excellent solution arises by exposing **3** to disiamylborane.[11] Aqueous sodium bisulfate workup effects lactonization to give **2a** directly. Since removal of the p-methoxybenzyl group proceeds under oxidative conditions,[12] the direct conversion of **2a** to sterepolide (**1**) is possible with excess DDQ (moist CH_2Cl_2, room temperature). The simply deblocked alcohol **2b** is, nevertheless, the major product but is easily converted to (±)-sterepolide, mp 192–193 °C (PDC, CH_2Cl_2, 3-Å molecular sieves) for a combined yield of 83%. Spectral (IR, ^1H and ^{13}C NMR) and chromato-

(6) Hirao, T.; Enda, J.; Ohshiro, Y.: Agawa, T. *Chem. Lett.* **1981**, 403.

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(10) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257.

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(12) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

graphic comparison to the natural product establishes their identity. This synthesis provides further confirmation of the structural assignment which was based primarily upon spectral analysis.[2b]

The dramatic effect of an oxygen substituent on the regioselectivity of this Pd(2+)-catalyzed cyclization via isomerization indicates the complexity of the mechanism of this unusual reaction. What the role of oxygen may be can only be speculated upon until more definitive mechanistic work is available. Nevertheless, it appears that by use of proper substituents, either 1,3- or 1,4-dienes may be selectively available—a major broadening of the synthetic potential. This first short (eight steps from **8**) synthesis of an isolactarane, sterepolide, illustrates the potential that such a broadening can have. The applicability of this reaction toward developing effective approaches to a broad array of polyhydrindanes such as the illudanes, sterpuranes, and marasmanes[1] is a goal of future work.

Acknowledgment. We thank the National Institutes of Health, General Medicinal Sciences, and the National Science Foundation for their generous support of our programs. We are particularly grateful to Prof. W. Ayer for spectra and an authentic sample of natural sterepolide.

Supplementary Material Available: Characterization of **2**, **3**, **4a**, **5**, **6**, and **7** (3 pages). Ordering information is given on any current masthead page.

Stereochemistry of the Carbon to Carbon Bond Formation in the Biosynthesis of Polyprenyl Chains with *Z* Double Bonds. Studies with Undecaprenyl-Pyrophosphate Synthetase

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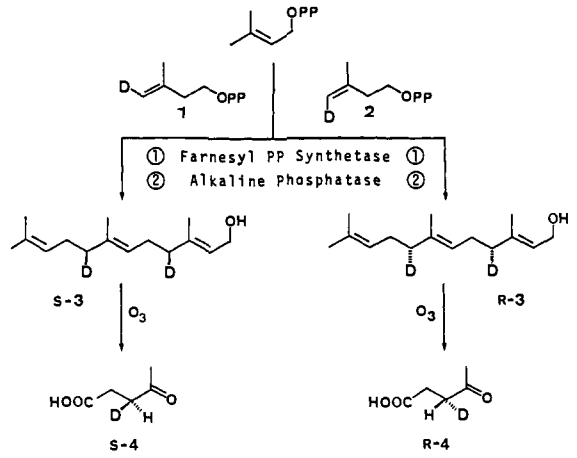
Received September 4, 1984

Since Cornforth, Popjāk, and their co-workers[1,2] established the stereochemistry of fundamental chain elongation processes involved in isoprenoid biosynthesis, the stereochemistry of the proton elimination from isopentenyl pyrophosphate (IPP) during the condensation with allylic pyrophosphates has been well documented with enzymes from various organisms.[3] However, nothing other than pig liver prenyltransferase catalyzing the synthesis of (*E*,*E*)-farnesyl pyrophosphate[2] has been studied in terms of stereochemical direction of the C–C bond formation with respect to the face of the double bond of IPP. Therefore, the stereochemistry of enzymatic C–C bond formation leading to a (*Z*)-prenyl chain has been a problem of particular interest to be solved. We here report evidence to show that allylic pyrophosphates add to the *si* face of IPP during the *Z* chain elongation catalyzed by undecaprenyl-pyrophosphate synthetase.

Cornforth et al.[2] have determined the steric course of farnesyl-pyrophosphate synthetase reaction by identifying the absolute configuration of [2-^{2}H]succinic acid derived from [4,8,12-$^2H_3$]-farnesol biosynthesized from mevalonic acid labeled chirally with deuterium at C-2. On the basis of their work, we examined a direct and feasible method of analysis for the stereochemistry of prenyltransferase reactions. The strategy was as follows: A prenyltransferase reaction with an allylic pyrophosphate and (*E*)-(**1**) or (*Z*)-[4-^{2}H]IPP (**2**) would give a product labeled chirally with deuterium in the prenyl moiety derived from **1** or **2**. Ozonolysis of this product would give (*S*)- or (*R*)-[3-^{2}H]levulinic acid, which could be correlated with a specimen derived from the chiral [4,8-$^2H_2$]farnesol [(*S*)-**3** or (*R*)-**3**] synthesized from dimethylallyl pyrophosphate (DMAPP) and **1** or **2** by the pig liver farnesyl-pyrophosphate synthetase reaction.[2]

Scheme I



Substrates **1** and **2** were synthesized by pyrophosphorylation of the corresponding alcohols obtained as follows: 3,4-Dibromo-3-methyl-1-butanol obtained by bromination of 3-methyl-3-buten-1-ol was dehydrobrominated with KOH to give (*E*)- and (*Z*)-4-bromo-3-methyl-3-buten-1-ol, which were separated from each other by silica gel chromatography. The bromo derivatives were converted into the corresponding lithium compounds, which were then quenched with ^2H_2O to give (*E*)- and (*Z*)-[4-^{2}H]-3-methyl-3-buten-1-ol. The NMR spectra of the *E* and *Z* isomer showed absorptions for the olefinic protons at δ 4.70 (s) and 4.74 (s), respectively. The deuterium contents of these alcohols were both 93% as determined by mass spectrometry.

In order to clarify the relation between the configuration of [3-^{2}H]levulinic acid and its optical rotation, (*R*)- and (*S*)-[3-^{2}H]levulinic acids were synthesized as shown in Scheme I by large-scale incubations as follows: Two flasks, each containing, in a final volume of 1 L, 20 mmol of Tris-HCl buffer, pH 7.7, 10 mmol of $MgCl_2$, 7 mmol of 1,4-dithiothreitol, 300 μmol of DMAPP, 300 μmol of **1**, and 100-mg protein of pig liver farnesyl-pyrophosphate synthetase[4] were incubated at 37° C for 24 h and then treated with alkaline phosphatase as usual. The reaction mixtures were extracted with pentane, and the extracts were purified by silica gel chromatography to give 17.8 mg of (4*S*,8*S*)-[4,8-$^2H_2$]farnesol [(*S*)-**3**, $[\alpha]_{320}$ + 3.0 ± 1.3°, ^{2}H content 92%], yield 26.0% based on **1**. (4*R*,8*R*)-[4,8-$^2H_2$]Farnesol [(*R*)-**3**, $[\alpha]_{320}$ −3.8 ± 0.5°, ^{2}H content 92%] was also obtained by similar incubations using **2** in place of **1**, yield 15.6 mg, 48% based on **2**. The ozonolysis of (*S*)-**3** and (*R*)-**3** under conditions similar to those reported[2] gave (*S*)-[3-^{2}H]levulinic acid [(*S*)-**4**, ^{2}H content 92%, $[\alpha]_{320}$ +63 ± 17°], and the *R* isomer [(*R*)-**4**, ^{2}H content 92%, $[\alpha]_{320}$ −82 ± 6°], respectively. Thus, the former and the latter were found distinguishable from each other, showing positive and negative Cotton effects, respectively.

Then this method was applied to the stereochemical analysis of undecaprenyl-pyrophosphate synthetase reaction. Five flasks, each containing in 1 L, 100 mmol of Tris-HCl buffer (pH 8.5), 500 μmol of $MgCl_2$, 50 mmol of NH_4Cl, 5 g of Triton X-100, 25 μmol of (*E*,*E*)-farnesyl pyrophosphate, 100 μmol of **1**, and partially purified undecaprenyl-pyrophosphate synthetase obtained from 25 g of *Bacillus subtilis*,[5] were incubated at 37 °C for 24 h. The products were treated with acid phosphatase by the method of Fujii et al.,[6] and the hexane extracts were purified on TLC and

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(3) Poulter, C. D.; Rilling, H. C. In "Biosynthesis of Isoprenoid Compounds"; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; p 165.
(4) Holloway, P. W.; Popjāk, G. *Biochem. J.* **1967**, *104*, 57–70.
(5) Takahashi, I.; Ogura, K. *J. Biochem.* (*Tokyo*) **1982**, *92*, 1527–1537.
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