Pergamon

Tetrahedron Letters, Vol. 35, No. 16, pp. 2509-2512, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0345-X

A Pd(0)-Catalyzed Route to 13-Methylidenefarnesyl Diphosphate

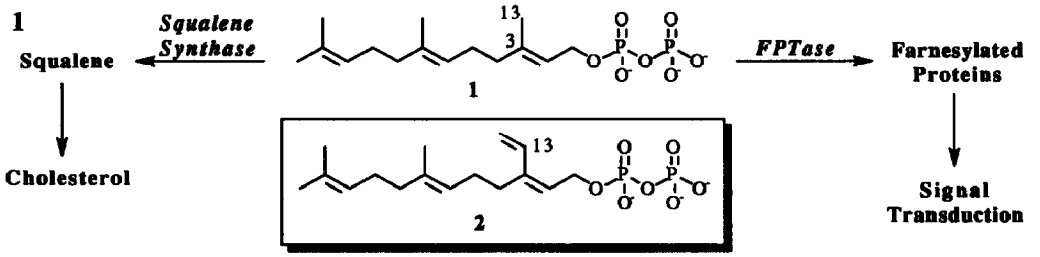
Richard A. Gibbs* and Usha Krishnan

Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202.

Abstract: The synthesis of the novel FPP analog 13-methylidenefarnesyl diphosphate **2** is described. The key step in the synthetic sequence involved the stereoselective coupling of enol triflate **8** with vinyltributyltin using $Pd(AsPh_3)_2$ and CuI as catalysts to afford primarily the desired *cis*-divinylester **7**. It is also demonstrated that other 3-substituted farnesyl analogs can be prepared by this Pd(0)-catalyzed route.

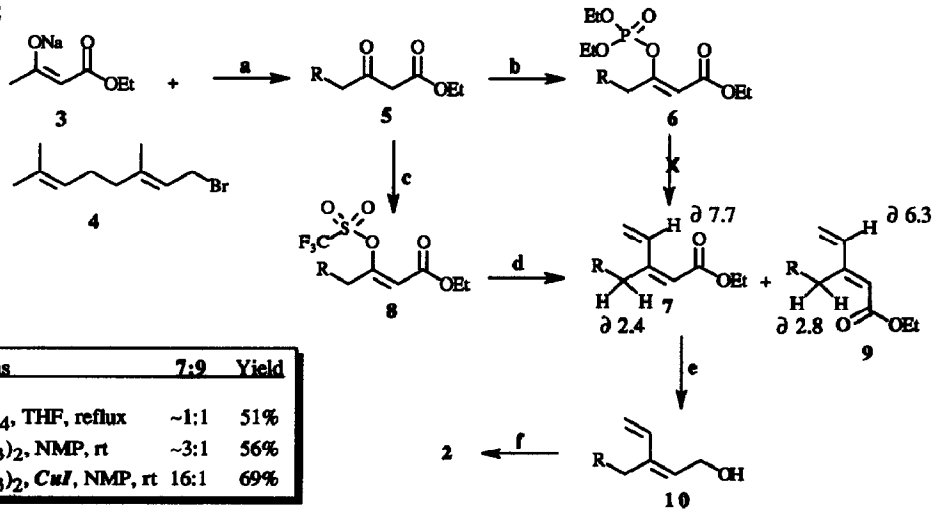
The biosynthetic intermediate farnesyl diphosphate (FPP; **1**) occupies a key position in cellular lipid metabolism. It has long been established that the first committed step in cholesterol biosynthesis involves the reductive head-to-head dimerization of two molecules of FPP to give squalene.[1] More recently, it has been discovered that farnesylation of certain proteins, such as the signal transduction protein (and oncogene product) ras, is absolutely required for their activity.[2,3] There has been a great deal of interest in the development of squalene synthase inhibitors as cholesterol-lowering agents[4-6] and farnesyl-protein transferase (FPTase) inhibitors as potential anti-cancer agents.[7] There has thus been renewed activity directed toward the synthesis of FPP analogs.[8,9] As a part of a program directed toward elucidating the mechanism of FPTase,[10] we targeted 13-methylidenefarnesyl diphosphate **2** for investigation as a possible mechanism-based inhibitor.[11] Herein the synthesis of **2** via a flexible and stereoselective Pd(0)-catalyzed route is described. We have also demonstrated that this route is applicable to the preparation of other farnesyl analogs and farnesyl diphosphate itself. There has also been renewed activity directed toward development of new methods for the stereoselective synthesis of isoprenoids.[12-14]

Figure 1



The synthetic strategy chosen was the homologation sequence originally developed by Weiler and recently employed by Cane for the synthesis of 6,7-dihydrofarnesol.[9,15] Coupling of commercially available sodium salt **3** (Figure 2) with geranyl bromide **4** afforded the β-ketoester **5**. Compound **5** was then converted into the enol phosphate **6** in the manner previously described by Weiler and coworkers.[15] Unfortunately, all attempts to couple **6** with a vinyl cuprate species to afford the desired compound **7** were unsuccessful. Treatment of **6** with vinylmagnesium chloride in the presence of a nickel(II) catalyst[16] also failed to afford **7** (in both instances, only starting material was recovered). It was apparent that a more reactive leaving group was necessary in order to introduce a vinyl moiety into the 3 position of the farnesyl structure.

Figure 2



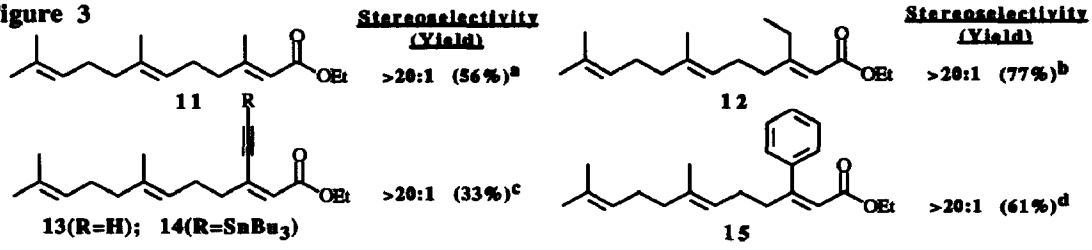
Conditions	7:9	Yield
$Pd(PPh_3)_4$, THF, reflux	~1:1	51%
$Pd(AsPh_3)_2$, NMP, rt	~3:1	56%
$Pd(AsPh_3)_2$, *CuI*, NMP, rt	16:1	69%

Reagents and Conditions: a) 3, nBuLi, THF, 0 °C; 4, 0 °C to rt (71 %); b) NaH, THF, 0 °C; $(EtO)_2P(O)Cl$, 0 °C to rt (66 %); c) $(Me_3Si)_2NK$, THF, -78 °C; $(CF_3SO_2)_2NPh$, THF, -78 °C to rt (52 %); d) $CH_2{=}CHSnBu_3$, $Pd(AsPh_3)_2$, CuI, N-methylpyrrolidone, rt (69 %); e) DIBAL, PhMe, -78 °C (43 %); f) N-Chlorosuccinimide, Me_2S, CH_2Cl_2, -40 to 0 °C; $(Bu_4N)_3HP_2O_7$, CH_3CN 0 °C to rt (20 %)

Numerous studies over the past ten years have established enol triflates as superior intermediates for the stereoselective synthesis of substituted vinyl compounds.[17] Particularly encouraging for our purposes were recent reports that enol triflates derived from β-keto esters couple with vinyltin reagents to give dienyl esters.[18-20] We therefore attempted to prepare the enol triflate **8** from **5**, using a variety of different conditions. Success was only achieved using potassium bis(trimethylsilyl)amide to generate the enolate followed by quenching with N,N-bis(trifluoromethanesulfonyl)-N-phenylimide.[21] Palladium-catalyzed coupling of **8** with vinyltributyltin using the procedure of Scott and Stille[22] afforded the desired ester **7** and its undesired isomer **9** in a ~1:1 ratio. Previously, Houpis had reported the loss of stereochemistry in the Pd(II)-catalyzed coupling of the enol triflate from a β-ketoester and vinyltributyltin.[19] The assignment of stereochemistry was based on the chemical shifts observed for the protons indicated in Figure 2. The ester carbonyl has an anisotropic deshielding effect that results in a downfield shift of protons adjacent to it.[23] A similar, but less pronounced deshielding effect has been observed in other farnesyl ester analogs.[8,15]

Farina and Krishnan have recently developed a protocol that provides superior results for a variety of Pd(0)-catalyzed coupling reactions.[24] In our case, use of "$Pd(AsPh_3)_2$" in NMP afforded a higher ratio of the desired isomer **7**. However, the addition of CuI as a co-catalyst *significantly* increased the stereoselectivity of the reaction and increased the yield as well. Johnson[25] and Liebeskind[26] have recently described the beneficial effect of CuI on Pd(0)-catalyzed coupling reactions; however, this is the first report that it can increase the stereoselectivity of this process. Treatment of **7** with $LiAl(OEt)H_3$[9] or Red-Al resulted in reduction of both conjugated double bonds as well as the ester. However, the use of excess DIBAL-H at -78° C successfully produced 13-methylidenefarnesol (**10**; Figure 3).[27,28] The two-step diphosphorylation procedure developed by Poulter et al.[29] was then employed to convert **10** to the desired FPP analog **2**.

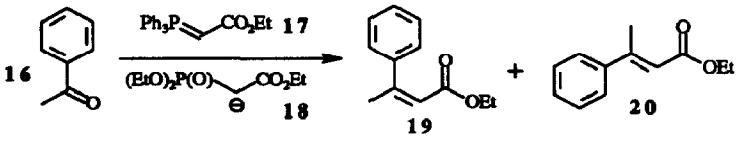
Figure 3



Reagents and Conditions: a) **8**, $SnMe_4$, $Pd(AsPh_3)_2$, CuI, NMP, 100 °C; b) **8**, $SnEt_4$, $Pd(AsPh_3)_2$, CuI, NMP, 100 °C; c) **8**, $HC{\equiv}CSnBu_3$, $Pd(AsPh_3)_2$, CuI, NMP, rt; **14**, Bu_4NF, THF, 0 °C (see text); d) **8**, $PhSnBu_3$, $Pd(AsPh_3)_2$, CuI, NMP, 100 °C.

The Pd(0)-catalyzed coupling of organotin reagents with enol triflate **8** has also been used to synthesize other farnesyl ester derivatives (Figure 3). In all cases, the reaction was highly stereoselective, affording almost exclusively the desired isomer. Compounds **11** and **12** have previously been prepared and converted to the corresponding diphosphates;[8] thus, this provides a highly stereoselective route to **1** and its 13-methyl analog. The ethynyl derivative **13** was also prepared from **8**.[30] Surprisingly, a significant amount of the tributyltin compound **14** was obtained, possibly through generation of $Bu_3SnC{\equiv}CCu$ from ethynyltributyltin followed by its Pd(0)-catalyzed coupling with **8**.[31] Fluoride-induced destannylation of **14** produced additional **13**;[32] however, the combined overall yield of **13** was a modest 33%. Particularly noteworthy is the synthesis of the 3-desmethyl-3-phenyl derivative **15** in a completely stereoselective manner. Figure 4 depicts a prototypical condensation of a hindered ketone with a stabilized phosphorous reagent. Other workers have reported that reaction of acetophenone with Wittig reagent **17** or Horner-Emmons reagent **18** either leads to a ~1:1 ratio of **19** and **20** or primarily the trans isomer **20**.[33] Alternative methods that have been reported for the synthesis of **19/20** also afford primarily **20**.[34] Thus the coupling method described herein could be uniquely useful for the stereoselective preparation of hindered *cis*-β,β-disubstituted α,β-unsaturated esters such as **15** or **19**.[35,36]

Figure 4



Acknowledgments. This research was supported by NSF grant CHE-9213312, the AACP Grant Program for New Investigators, and by a WSU Faculty Research Award. We would also like to thank YongQi Mu for assistance with the conversion of **10** to **2**.

References and Notes

(1) Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70-77.
(2) Clarke, S. *Ann. Rev. Biochem.* **1992**, *61*, 355-386.
(3) Gibbs, J. B. *Cell* **1991**, *65*, 1-4.
(4) Biller, S. A.; Sofia, M. J.; DeLange, B.; Forster, C.; Gordon, E. M.; Harrity, T.; Rich, L. C.; Ciosek, C. P. *J. Am. Chem. Soc.* **1991**, *113*, 8522-8524.
(5) Oehlschlager, A. C.; Singh, S. M.; Sharma, S. *J. Org. Chem.* **1991**, *56*, 3856-3861.
(6) Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 3734-3739.
(7) For a very recent review of FPTase inhibitors, see: Tamanoi, F. *TIBS* **1993**, *18*, 349-353.
(8) For earlier reports on FPP analogs, see: Ortiz de Montellano, P. R.; Wei, J. S.; Castillo, R.; Hsu, C. K.; Boparai, A. *J. Med. Chem.* **1977**, *20*, 243-249 and references cited therein.
(9) FPP analogs are also of interest due to FPP's role in the biosynthesis of terpenes; see, for example: Cane, D. E.; Pawlak, J. L.; Horak, R. M.; Hohn, T. M. *Biochemistry* **1990**, *29*, 5476-5490.
(10) Gibbs, R. A.; Mu, Y. Q.; Wang, F. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 281-284.
(11) It has recently been reported that a methylidene-substituted epoxysqualene analog acts as a mechanism-based inhibitor of

oxidosqualene cyclase: Xiao, X.-y.; Prestwich, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 9673-9674.
(12) For a review of earlier methods for isoprenoid synthesis, see: Cainelli, G.; Cardillo, G. *Acc. Chem. Res.* **1981**, *14*, 89-94.
(13) Corey, E. J.; Shieh, W.-C. *Tetrahedron Lett.* **1992**, *33*, 6435-6438.
(14) Kocienski, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215-1217.
(15) Sum, F-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431-1441.
(16) Armstrong, R. J.; Harris, F. L.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 1002-1006.
(17) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47-54.
(18) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833-5847.
(19) Houpis, I. N. *Tetrahedron Lett.* **1991**, *32*, 6675-6678.
(20) Lipshutz, B. H.; Alami, M. *Tetrahedron Lett.* **1993**, *34*, 1433-1436.
(21) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972-6975.
(22) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040.
(23) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds;* 4th ed.; John Wiley & Sons: New York, 1981, pp 442.
(24) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.
(25) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. *Tetrahedron Lett.* **1992**, *33*, 919-923.
(26) Liebskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408-413.
(27) The procedure used was that employed in the synthesis of a vitamin D A-ring synthon: Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098-3108.
(28) The stereochemistry of **10** was further verified by the similarity of the vinyl portion of its NMR spectrum to that of (Z)-7-methyl-3-vinyl-2,6-octadien-1-ol: Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411-2424. ^{1}H-NMR of **10**: (300 MHz, C_6D_6): ∂ 1.56 (s, 6H, two vinylic CH_3), 1.67 (s, 3H, vinylic CH_3), 2.0-2.2 (m, 8H, C_5, C_6, C_8 and C_9 CH_2), 4.05 (d, J~6.7Hz, 2H, C_2 CH_2), 5.01 (d, J~11.3Hz, 1H, CH_2=CH-(cis H)), 5.20 (m, 3H, H_6, H_{10}, and CH_2=CH-(trans H)), 5.50 (t, J~6.7Hz, 1H, H_2), 6.52 (dd, J~17.4Hz, 11.3Hz, 1H, CH_2=CH-).
(29) Davisson, V. J.; Woodside, A. B.; Neal, T. R.; Stremler, K. E.; Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1986**, *51*, 4768-4779.
(30) The stereochemistry of **13** was confirmed by the similarity of the vinyl portion of its NMR spectrum to that of methyl (Z)-3-methyl-2-penten-4-ynoate: Constantino, M. G.; Donate, P. M.; Petragnani, N. *J. Org. Chem.* **1986**, *51*, 253-254.
(31) Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320-322.
(32) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072-4083 & ref. 20 therein.
(33) a) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1979**, 884-885. b) Isaacs, N. S.; El-Din, G. N.; *Tetrahedron Lett.* **1987**, *28*, 2191-2192. c) Rathke, M. W.; Bouhlel, E. *Synth. Commun.* **1990**, *20*, 869-875. d) Eguchi, T.; Aoyama, T.; Kakinuma, K. *Tetrahedron Lett.* **1992**, *33*, 5545-5546.
(34) a) Jalander, L.; Broms, M. *Acta Chemica Scand. B* **1983**, *37*, 173-178. b) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 607-610. c) Olah, G. A.; Wu, A.; Farooq, O.; Prakash, G. K. S. *Synthesis* **1988**, 537-538.
(35) The stereochemistry of **15** was confirmed by the similarity of its NMR spectrum to that of **19** (and its dissimilarity to **20**).[33,34]
(36) Synthesis of **7** and **9**: In an argon flushed flask were placed *bis*(benzonitrile)palladium(II) chloride (0.025mmol; 9.5mg), triphenylarsine (0.05mmol; 15.5mg), copper (I) iodide (0.05mmol; 9.5mg) and triflate **8** (0.5mmol; 199.5mg) to which was added N-methylpyrrolidone (0.5ml). To this solution vinyltributyltin (0.6mmol; 190mg; 0.18ml) was then added. The reaction was stirred under argon for ~15 hours at rt. The mixture was dissolved in EtOAc (100mL) and treated with aqueous KF (3x30ml). The aqueous layers were then combined, back-extracted with EtOAc (60mL) and the combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo to give an oily residue. Purification by flash chromatography (98:2 hexane/EtOAc) afforded the vinyl ester as a mixture of cis (**7**) and trans (**9**) isomers in the ratio of 94:6 (determined by integration of the NMR peaks at ∂7.74 and 6.32; yield: 95mg, 69%). HPLC purification afforded analytical samples of each isomer. **7**: ^{1}H-NMR (300 MHz, $CDCl_3$): ∂ 1.28 (t, J~7.1Hz, 3H, OCH_2CH_3), 1.6 (two s, 6H, two vinylic CH_3), 1.69 (s, 3H, vinylic CH_3), 2.1-1.9 (m, 4H, C_8 and C_9 CH_2), 2.20 (q, J~7Hz, 2H, C_5 CH_2), 2.37 (t, J~7Hz, 2H, C_4 CH_2), 4.21 (q, J~7.1Hz, 2H, OCH_2CH_3), 5.12 (m, 2H, H_6 and H_{10}), 5.48 (d, J~11.0Hz, 1H, CH_2=CH-(cis H)), 5.61 (d, J~17.9Hz, 1H, CH_2=CH-(trans H)), 5.68 (s, 1H, H_2), 7.74 (dd, J~17.9Hz, 11.0Hz, 1H, CH_2=CH-). ^{13}C-NMR (75.4 MHz, $CDCl_3$): ∂ 14.29, 16.04, 17.66, 25.64, 26.70, 27.45, 33.60, 39.64, 59.80, 117.47, 119.76, 123.07, 124.26, 131.38, 133.19, 136.26, 154.31, 166.3. UV: (hexanes) λ_{max} 252 nm (ε 13,400). MS-EI: m/e-276(M+), 233, 161, 133, 109, 93, 81, 69, 55. HRMS: calculated for $C_{18}H_{28}O_2$-276.2089, found-276.2093. **9**: ^{1}H-NMR (300 MHz, $CDCl_3$): ∂ 1.28 (t, J~7.1Hz, 3H, OCH_2CH_3), 1.60 (s, 6H, two vinylic CH_3), 1.68 (s, 3H, vinylic CH_3), 2.1-1.9 (m, 4H, C_8 and C_9 CH_2), 2.18 (q, J~7.8Hz, 2H, C_5 CH_2), 2.80 (t, J~7.9Hz, 2H, C_4 CH_2), 4.18 (q, J~7.1Hz, 2H, OCH_2CH_3), 5.10 (m, 1H, H_{10}), 5.22 (t, J~7.3Hz, 1H, H_6), 5.39 (d, J~10.8Hz, 1H, CH_2=CH-(cis H)), 5.64 (d, J~17.4Hz, 1H, CH_2=CH-(trans H)), 5.76 (s, 1H, H_2), 6.32 (dd, J~17.4Hz, 10.8Hz, 1H, CH_2=CH-). ^{13}C-NMR (75.4 MHz, $CDCl_3$): ∂ 14.30, 15.98, 17.65, 25.65, 26.75, 27.23, 28.01, 39.71, 59.74, 118.96, 119.60, 123.59, 124.40, 131.28, 135.72, 139.09, 156.19, 166.51. UV: (hexanes) λ_{max} 255 nm (ε 31,000).

(*Received in USA* 23 *September* 1993; *revised* 26 *January* 1994; *accepted* 14 *February* 1994)