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Cycloisomerisation of modified terpenoid 1,6-enynes—synthesis of conformationally-restricted cyclic farnesyl analogues

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Abstract—The cycloisomerisation of various 1,6-enynes containing a modified terpenoid chain has been investigated to provide cyclopentanes with great potential as novel conformationally-restricted analogues of farnesyl diphosphate. The 4-diethylphosphono-ester substituent is shown to serve as a diastereocontrol element for the 1,6-enyne cycloisomerisation process.

1. Introduction

The synthetic construction of farnesyl diphosphate (FDP) mimetics as enzyme inhibitors has received notable attention, mainly because FDP is used as a substrate by both squalene synthase[1] (SQS) and protein-farnesyl transferase[2] (PFTase). SQS is an enzyme that is membrane-bound and crucial to the cholesterol biosynthetic pathway catalysing the reductive dimerisation of FDP via presqualene diphosphate to squalene. Compounds that inhibit SQS thereby reduce the formation of cholesterol, a substance implicated in the development of atherosclerosis. PFTase catalyses the farnesylation of a thiol group of cysteine located at the fourth-amino acid (CAAX) position from the C-terminus of several small G-proteins. Amongst these proteins is *ras*, a protein involved in the growth regulatory signal transduction pathway. Mutated forms of the *ras* gene are frequently found in human malignancies and play a role in human tumour growth. Selective inhibition of PFTase is therefore highly desirable, as the oncogenic activity of mutated *ras* is dependant on the farnesylation by PFTase.[3] Structural variants of FDP are mimics of both the hydrophobic farnesyl chain (**1**) and hydrophilic diphosphate head (**2** and **3**) (Fig. 1).[4]

Furthermore, Gibbs and co-workers have reported an elegant NMR study into the solution conformation of FDP using ^{13}C-labelled FDP derivatives, and its conformation in the active site of PFTase.[5]

These studies, along with molecular dynamics simulations, demonstrate that the sesquiterpene chain exists primarily in an extended conformation in solution, as in the crystal structure.[6] We suggest that a cyclic structure, in particular a five-membered ring, would lock and conformationally restrict a diphosphate isostere, and serve to position a suitably designed farnesyl mimic. It was envisaged that novel FDP mimetics (**FDP-M**, Fig. 2) could be approached via metal-catalysed cycloisomerisation of 1,6-enynes,[7] allowing the construction of a series of cyclopentanes that incorporate the required hydrophobic and hydrophilic structural architecture (Fig. 2). Indeed our computational molecular modelling studies demonstrate that structures based on **FDP-M** have great potential.[8]

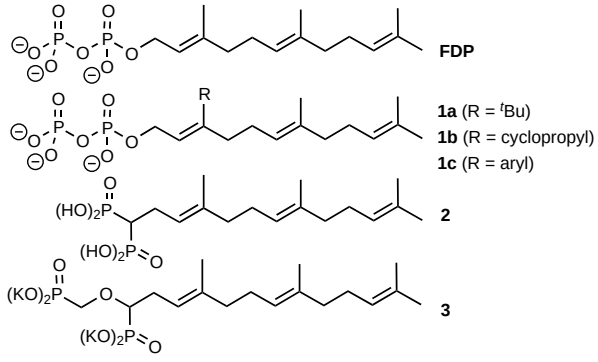

Figure 1. FDP and closely related analogues (**1**, **2** and **3**).

Keywords: palladium; cycloisomerisation; atom economy; Ras protein-farnesyl transferase; squalene synthase.

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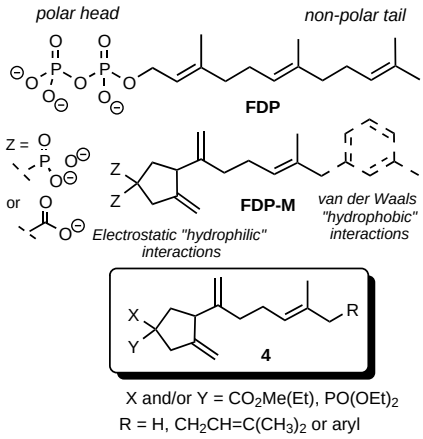
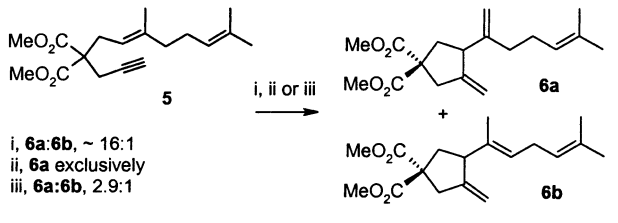


Figure 2. FDP cyclic mimetics as potential competitive inhibitors.

2. 1,6-Enyne cycloisomerisation[9]

We decided to explore the cycloisomerisation via intramolecular carbametalation (Pd, Pt, Ni–Cr and Ru catalytic systems) of 1,6-enynes in order to construct compounds such as **4**, which can be easily transformed into derivatives of the **FDP-M** structure. In pioneering studies Trost et al.[10] have developed a range of catalytic systems for this process and employed them in key steps to synthetic routes of several natural products (Corianin, Picrotoxinin, Picrotin, Cassiol, Chokol C, Sterepolide and Merulidial). Herein we report our chemical synthesis of a range of FDP cyclic analogues and demonstrate how one can exploit the Pd-catalysed cycloisomerisation of 1,6-enynes. We embarked on the synthesis of cyclopentenes using the Trost methodology for the conversion of **5** to **6**, where 'H–Pd–OAc' is considered the active species, generated directly from $Pd(OAc)_2$ in benzene at 60°C (method A)[11] or in situ from a Pd pro-catalyst ($Pd_2dba_3{\cdot}CHCl_3$) and acetic acid in benzene at 25°C (method B)[12] (Scheme 1). The importance of the terminal olefin as a regiochemical control element has been reported.[11]

Palladium-catalysed cycloisomerisation of **5** (method A), produced **6a**, regioselectively (^{1}H NMR) in 74% yield. In our hands, the reaction was facile and proceeded to completion in ca. 2–3 min! This result was quite surprising, in light of the fact that the original reaction time was reported[11] as 1 h at 60°C. Running the reaction under strictly anhydrous conditions slowed the reaction rate appreciably to 2–3 h at 60°C. Trace quantities of water (~1 equiv.) seem to have an effect on the rate of cycloisomerisation of **5** using method A.[13] Saturation of a benzene-d_6 solution of substrate **5** with D_2O followed by addition of 5 mol% $Pd(OAc)_2$ results in no cycloisomerisation of **5**. Running the reactions with 5 mol% catalyst is an efficient process, but the formation of colloidal palladium black is evident and makes isolation of the products, especially on larger scale, more cumbersome. Reducing the catalyst loading serves to attenuate the problem and one can go down to 1 mol% $Pd(OAc)_2$ before conversion and isolated yields begin to suffer. The reaction, which is quenched through a small column of silica and washed with ethyl acetate/hexane (1:10, v/v), gives essentially pure **6a** without the need for further purification. At lower catalyst loadings <0.5 mol% $Pd(OAc)_2$, we see yields of <23%. Changing to method B in the presence of acetic acid[14] enhances the yield of **6a** with the advantage that the reaction can be conducted at ambient temperature over 2–3 h.



Scheme 1. Palladium-catalysed cycloisomerisation of 1,6-enyne **5** to provide 1,4-dienes **6a** and **6b**. *Reagents and conditions*: (i) $Pd(OAc)_2$ (5 mol%), PhH, 60°C (method A); (ii) $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), AcOH (5 mol%), PhH, 25°C (method B); (iii) $(PPh_3)_2Pd(OAc)_2$, benzene, 80°C.

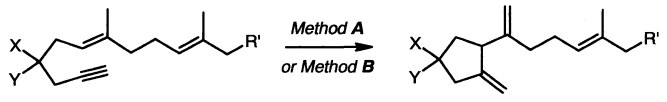
Using both methods A and B, a range of 1,6-enynes were evaluated for their cycloisomerisation to give 1,4-diene cyclopentenes (Table 1).

To our surprise the cycloisomerisation of phosphonate **7**, using either method A or B (entry 2, Table 1), gave one diastereoisomer *trans*-**8** (stereochemistry determined by ^{1}H, 2D NOESY and quantitative nOe experiments), exclusively vide infra. The bisphosphonate **9** gave **10** in slightly lower yield (entry 3, Table 1), although we encountered problems in isolation of these compounds due to their very polar properties. The mono-methylcarboxy ester **11** gave a mixture of diastereoisomers, *trans*-**12** and *cis*-**12** (entry 4, Table 1, 2.9:1 by ^{1}H NMR) (Scheme 2). Note for this particular substrate that the reaction time increased dramatically to 72 h (compare entries 1 and 4, Table 1). Hence, the 4-substituent clearly has an effect on the rate of cyclisation—an effect that has been previously observed in the related Pd-catalysed cycloisomerisation of 1,6-dienes[15] and is proposed to be associated with the Thorpe–Ingold effect and related phenomena.[16] The effect usually results in lower yields (catalyst decomposition), although dba clearly stabilises the active Pd-species, as the isolated yield of **12** (*cis*/*trans* mixture) was 91%.

We found that method B gave both more reliable and better yields than method A; hence we used the former for the cycloisomerisation of the remaining 1,6-enynes (**11**, **13**, **15**, **17** and **19**) (Table 1).

We were able to extend the hydrophobic chain to a farnesyl moiety for 1,6-enynes **13** and **15** to give **14** and *trans*-**16** (one diastereoisomer), respectively, without regioselectivity implications (entries 5 and 6, Table 1). Furthermore, the ω-phenylterpenoid-1,6-enynes **17** and **19** were cycloisomerised to **18** and *trans*-**20** (one diastereomer), respectively, in reasonable reaction times and good yields (entries 7 and 8, Table 1).

Table 1. Cycloisomerisation of 1,6-enynes

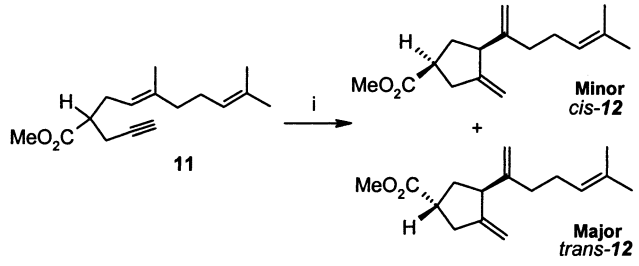


R = H, X, Y = CO_2Me (**5**)
R = H, X = CO_2Et, Y = $PO(OEt)_2$ (**7**)
R = H, X, Y = $PO(OEt)_2$ (**9**)
R = H, X = H, Y = CO_2Me (**11**)
R = $CH_2CH{=}C(CH_3)_2$, X, Y = CO_2Me (**13**)
R = $CH_2CH{=}C(CH_3)_2$, X = CO_2Et, Y = $PO(OEt)_2$ (**15**)
R = Phenyl, X, Y = CO_2Me (**17**)
R = Phenyl, X = CO_2Et, Y = $PO(OEt)_2$ (**19**)

R = H, X, Y = CO_2Me (**6**)
R = H, X = CO_2Et, Y = $PO(OEt)_2$ (**8**)
R = H, X, Y = $PO(OEt)_2$ (**10**)
R = H, X = H, Y = CO_2Me (**12**)
R = $CH_2CH{=}C(CH_3)_2$, X, Y = CO_2Me (**14**)
R = $CH_2CH{=}C(CH_3)_2$, X = CO_2Et, Y = $PO(OEt)_2$ (**16**)
R = Phenyl, X, Y = CO_2Me (**18**)
R = Phenyl, X = CO_2Et, Y = $PO(OEt)_2$ (**20**)

Entry	1,6-Enyne	Method A[a,b]	Reaction time (h)	Method B[a,c]	Reaction time (h)
1	**5**	74 (**6**)	<0.1	92 (**6**)	2
2	**7**	86[d] (**8**)	<0.1	86[d] (**8**)	2
3	**9**	54 (**10**)	4	63 (**10**)	12
4	**11**	–	–	91[e] (**12**)	72
5	**13**	–	–	74 (**14**)	12
6	**15**	–	–	76[d] (**16**)	18[f]
7	**17**	–	–	72 (**18**)	16
8	**19**	–	–	84[d] (**20**)	2

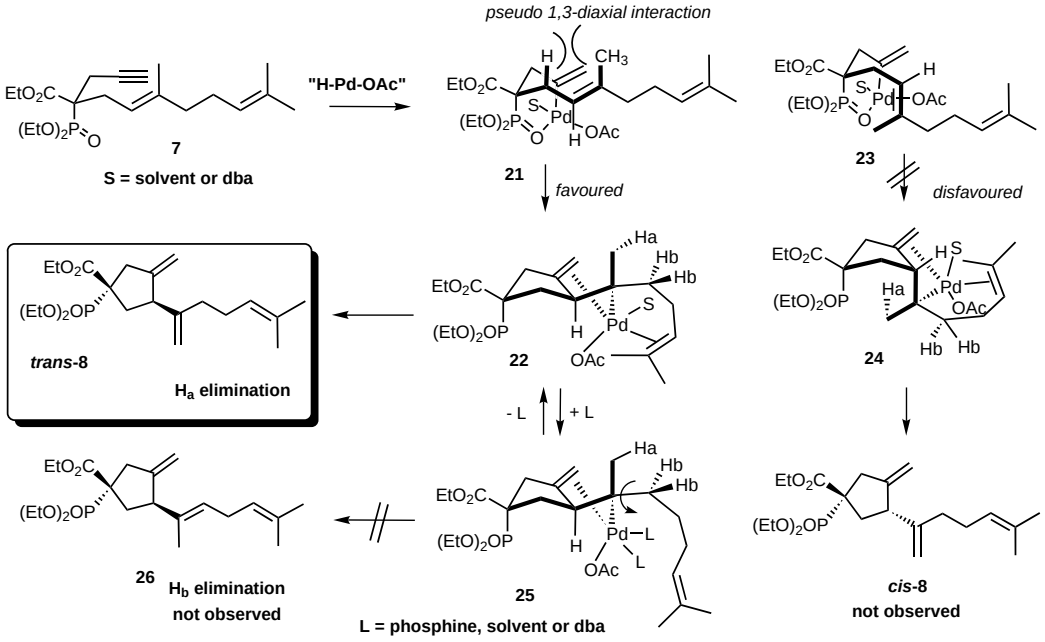
[a] Isolated yields after column chromatography. Compound (products) numbering in parentheses.
[b] Method A: $Pd(OAc)_2$ (5 mol%), benzene, 60°C, N_2. Reaction monitored by ^1H NMR spectroscopy.
[c] Method B: $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), AcOH (5 mol%), benzene, rt. Reaction monitored by ^1H NMR spectroscopy.
[d] Reaction gave the *trans* diastereoisomer, exclusively (stereochemistry confirmed by ^1H NMR spectroscopy and nOe experiments).
[e] As a mixture of diastereoisomers (2.9:1, *trans*:*cis*).
[f] Reaction was not monitored by ^1H NMR and thus left overnight to ensure completion.



Scheme 2. Cycloisomerisation of 1,6-enyne **11**. *Reagents and conditions*: (i) $Pd_2dba_3{\cdot}CHCl_3$, AcOH, benzene, 25°C (method B).

The cycloisomerisation of the mixed phosphonate/ester 1,6-enynes (**7**, **15** and **19**) gave only the *trans*-diastereomer—an intriguing result. We believe that the origin of the diastereoselectivity can be accounted for by examining the transition state **21** of the reaction prior to carbopalladation, where phosphonate chelation to Pd controls the formation of the new stereogenic centre during the carbopalladation process to give **22** (Scheme 3). The existence of a pseudo 1,3-diaxial interaction between the allylic hydrogen and *Z*-substituent in **21** is expected to have an effect. However, the alternative transition state structure **23** would give *cis*-**8** via **23**, and can be discounted as a favoured transition state. The observed diastereoselectivity illustrates the configurational stability of **21** and the presence of the distal olefin moiety may also play an important role in this selectivity. To establish whether the phosphonate was playing a chelating role, rather than just one of increased steric bulk, we added stronger donating phosphine ligands to give a mixture of both diastereo- and regioisomers. Using method A, addition of triphenylphosphine (10 mol%), 1,3-bis(diphenylphosphino)propane (dppp) (5 mol%) or bis(diphenylphosphino)ferrocene (dppf) (5 mol%) has an effect on the turnover rate of **7**, in that reaction times were increased by several hours at 60°C (6–7 h).

More importantly, we still only observed one diastereomer, *trans*-**8** (identical by ^1H NMR to *trans*-**8** formed in the absence of ligand) in yields that were either improved or unaffected (dppp and dppb ~80–85%, dppf 98%). It should be noted that the ligands reduce the formation of colloidal palladium. The use of 1,2-(diphenylphosphino)ethane (dppe) as a ligand, resulted in no cycloisomerisation (>95% recovered **7** after 96 h), which is consistent with studies performed by the Trost group on other enyne substrates.[17] It is well known that dppp forms Pd(II) catalysts that are more efficient than with dppe.[18] Increasing flexibility in the backbone favours greater dissociability of one of the PPh_2 groups, a strict requirement for bidentate coordination of the enyne starting material. In addition to the improved cycloisomerisation of **7**, it is suggested that the presence of the phosphine ligand serves to displace the coordination of the remote olefin in geranyl(malonate)-1,6-enyne **5**, which is consistent with the formation of the regioisomer **6b** in a 1:2.9 ratio with **6a** (Scheme 1).[10] For phosphonate **7** we did not detect the regioisomer **26** for any of the ligands screened, which would have been expected to pass via transition state **25**. The reason for this selectivity is hard to rationalise,

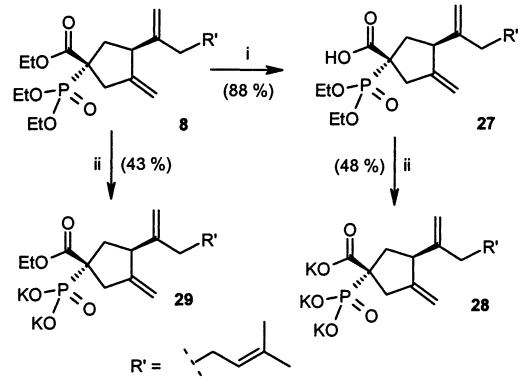


Scheme 3. Proposed diastereoselective discrimination through phosphonate chelation.

as the only difference between **5** and **7** is the phosphonate, and with phosphonate chelation to Pd in **22** unlikely, an alternative explanation is required.

3. Conversion of the cycloisomerisation products into FDP analogues

Compound **8** and its hydrolysis products are designed to allow for variation of negative charge at the head of these terpenoid analogues (Scheme 4). Hydrolysis of the parent triester **8** was accomplished by reaction with ethanolic NaOH at reflux over 4 h followed by acidification to give **27**. Treatment of **27** with excess TMSBr and 2,4,6-collidine in CH_2Cl_2 at reflux for 18 h, cleaved both ethyl groups of the phosphonate, affording the salt **28** after hydrolysis with 0.5 M KOH for 72 h. Furthermore, it is possible to take **8** and selectively hydrolyse the phosphonate esters using the same procedure as for conversion of **27** into **28**, to provide **29** in reasonable yield. In short, the target inhibitors are readily available in 5 steps from commercially available starting materials in essentially diastereomerically pure form.



Scheme 4. Complete synthesis of the new potential inhibitors. *Reagents and conditions*: (i) NaOH, EtOH–H_2O, Δ; (ii) TMSBr (4 equiv.), 2,4,6-collidine, Δ, then KOH.

In summary, we have shown that a phosphonate may be used as a stereocontrol element in the Pd-catalysed cycloisomerisation of 1,6-enynes based on the terpenoid structure. Further mechanistic studies, as well as the biological testing of the new FDP mimetics, will be reported elsewhere.

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