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On the selective reduction of the distal olefin in geraniol and farnesol derivatives

Alexandre Demotie, Ian J. S. Fairlamb* and Sally K. Radford

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

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Abstract—The selective reduction of the *distal* olefin of many types of terpenoid-based natural products has been commonly approached using gaseous HCl in CH_2Cl_2. We herein present evidence that this method is inefficient and produces many side products, whose formation, in our hands, was difficult to avoid (over several reaction runs). A more efficient procedure for geranyl acetate using 1 equiv. of $TiCl_4$ in CH_2Cl_2 at −78°C is reported.

The polyprenols (isoprenoids) comprise of a vast array of natural products, whose selectivity and activity vary via small changes in structure: (i) by the length of their hydrophobic moiety (acyclic or cyclic); (ii) specific position and stereochemistry of an olefinic bond; (iii) by selective reduction of an olefinic bond. Isoprenoids are known to play a central role in cellular lipid metabolism, e.g. geranyl diphosphate (GDP) and farnesyl diphosphate (FDP) (Fig. 1). Small changes in the structures (i, ii or iii) of GDP and FDP have yielded a plethora of analogues that have been used in enzyme mechanism and inhibition studies. FDP is required, as a substrate, by a number of enzymes, in particular, protein farnesyl transferase (PFTase).[1] Great interest has been attached to the development of protein prenylation inhibitors that specifically inhibit PFTase[2]—a target for chemotherapeutic intervention. We have a specific interest in the design of new PFTase inhibitors.[3] Efficient syntheses for both 6,7-dihydrogeraniol and 10,11-dihydrofarnesol derivatives were sought after to evaluate the effectiveness of our newly proposed cyclic FDP analogues.[4] 6,7-Dihydrogeraniol derivatives have also been employed in mechanistic studies involving the transition metal catalysed (Pd, Pt, and Ru) cycloisomerisation of terpenoid-based 1,6-enynes (**1**→**2**).[5] Indeed this area inadvertently links directly to our efforts to obtain novel cyclopentene FDP analogues.

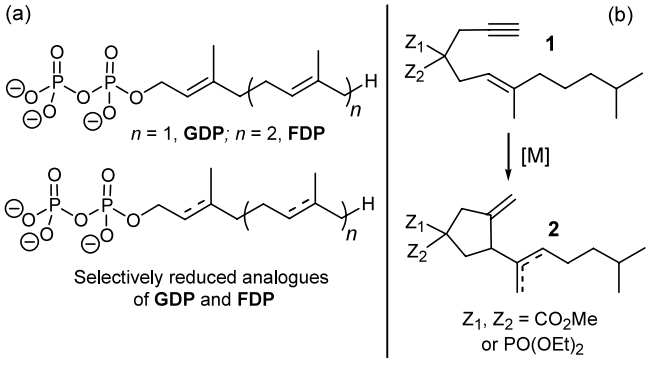

Figure 1. (a) GDP and FDP analogues. (b) Cycloisomerisation of terpenoid 1,6-enynes.

The catalytic hydrogenation of geranyl derivatives occurs preferentially at the *proximal* olefin.[6] Selective hydrogenation of the *distal* olefin in such derivatives is rare.[7] The seemingly most efficient method has been the electrophilic attack of HCl on *distal* trisubstituted double bonds, followed by dehalogenation using either $Zn(BH_4)_2/Et_2O$/cyclohexene/40°C or n-Bu_3SnH/AIBN/benzene/75°C (**3**→**4**→**5**, Scheme 1).

In 1986, Julia[8] reported extensive details of this reaction sequence, although the exact procedure given for **3**→**4** was brief (Scheme 2). It became clear after our first two attempts, that the reaction between HCl and **3** in CH_2Cl_2 at −78°C is not facile. Indeed in our hands several side products[9] (**6**–**8**), formed in minor amounts prior to our work, are simultaneously obtained in varying quantities that encumbers the facile purification of **4**. Herein we report details of our attempts at repeating this reaction. A more efficient procedure for the addition of HCl to the *distal* olefin of **3** using $TiCl_4$ in CH_2Cl_2 at −78°C, followed by a H_2O quench, which

* Corresponding author. Tel.: +44(0)1904-434091; fax: +44(0)1904-432516; e-mail: ijsf1@york.ac.uk

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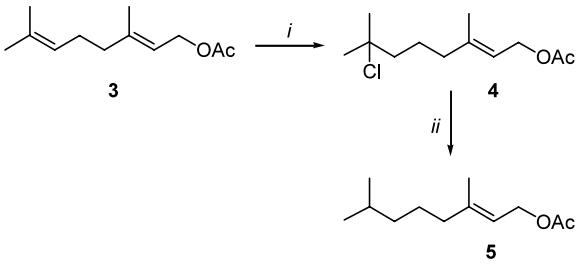
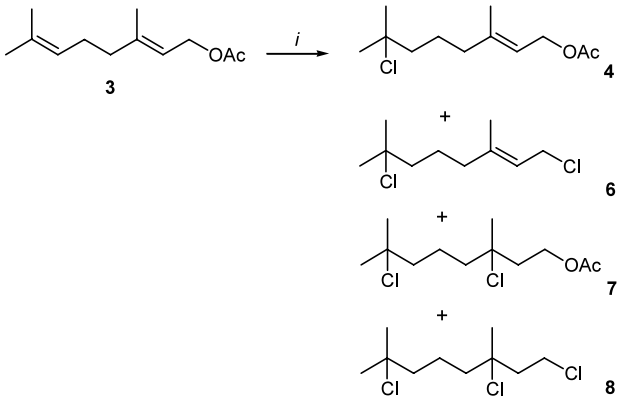
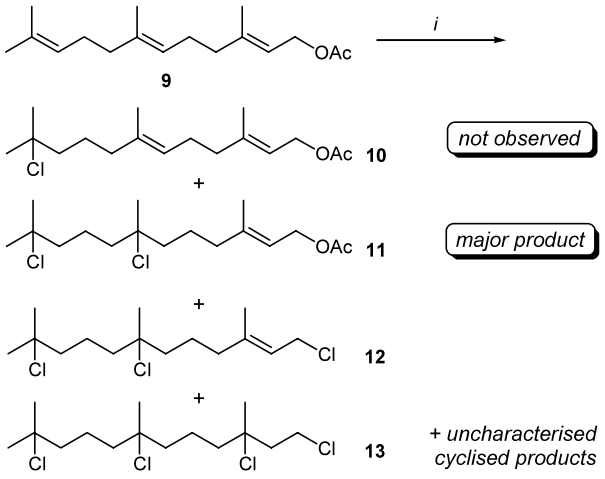


Scheme 1. Selective reduction of the *distal* olefin in geranyl acetate **3**. *i.* HCl (g), dry CH_2Cl_2, −78°C; *ii.* $Zn(BH_4)_2$ or n-Bu_3SnH, AIBN.



Scheme 2. Addition of HCl to geranyl acetate **3**: *i.* HCl (g), CH_2Cl_2, −78°C, 2 h.



Scheme 3. Addition of HCl to farnesyl acetate **9**: *i.* HCl (g), dry CH_2Cl_2, −78°C, 2 h.

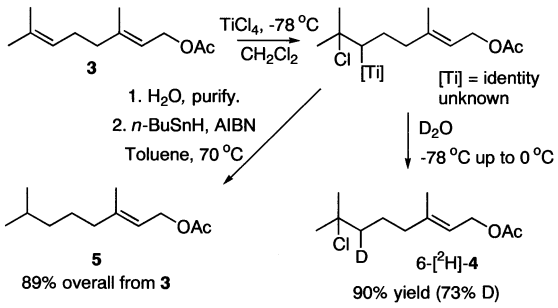
gives **4** reproducibly in >92% yields (after distillation), is reported.

On the gaseous HCl procedure. In our first reaction, compound **3** in CH_2Cl_2 was cooled to −78°C and then saturated with a slow passage of dry HCl gas (from a lecture cylinder fitted with a pressure regulator) through a fine pipette over 0.5 h. Analysis by GC (sample quenched with water, neutralised with sat. $NaHCO_3$ and extracted into diethyl ether) showed the presence of several components: **3** (54%), **4** (27%), **6** (14%), **7** (3%) and **8** (2%). Indeed, after 1 h, no further consumption of the starting material **3** was seen by GC, thus HCl gas was again bubbled through at a slow rate over 0.5 h. After a reaction time of 2 h, GC analysis confirmed complete loss of **3**. The proportion of the products **4**, **6**, **7** and **8** were 58, 28, 9 and 5%, respectively.[10] We repeated the reaction several times and observed a similar trend, although the proportions of **4**, **6**, **7** and **8** varied slightly between runs. We obtained **4** in an isolated yield of 42% after high vacuum distillation, which was shown to be 86% pure by ^{1}H NMR; the remaining impurities **6**, **7** and **8** could be separated by careful chromatography. If one changes the solvent to diethyl ether[11] an improvement is seen. Thus reaction of **3** with dry HCl gas at −78°C provides **4** in 68% yield, accompanied by **6** in 5% yield. The dehalogenation of **4** was straight forward using n-Bu_3SnH and AIBN in refluxing benzene, affording **5** in 93% yield.

The HCl procedure is poor for the demanding selectivity required by farnesyl acetate (Scheme 3). Julia reported that the dichlorinated compound **11**[8] is the major product under the standard conditions, accompanied by **12** and **13**, including cyclised derivatives. We can confirm these results, although we have been unable to determine the structures of the cyclised material. It should be noted that we failed to detect compound **10**.

It is quite apparent that the HCl procedure is problematic and as we required large quantities of **5**, we sought a reliable method for the synthesis of **4**.

Selective $TiCl_4$ addition to the distal olefin: Our initial idea for adopting $TiCl_4$ for electrophilic addition on the *distal* olefin came from a recent report by Vidari and co-workers[12] on a $TiCl_4$ promoted reaction of aldehydes with 1,5-dienyl allyl silanes. In two separate reactions, they isolated two products where chlorine had been added to the *distal* olefin (10–14% yields). We were encouraged by this and felt that a direct reaction of **3** with $TiCl_4$ (2 equiv.) in CH_2Cl_2 at −78°C would provide a good yield of **4** (Scheme 4). In this reaction we found that **4** was produced in 45% yield, accompanied by two other products, **6** and **8** in 17 and 5% yields, respectively.[13] We then decided to investigate the effect of adding varying quantities of $TiCl_4$ (Table 1).



Scheme 4.

Table 1. Effect of $TiCl_4$ equiv. on addition to geranyl acetate **3**[a]

$TiCl_4$ (equiv.)	Yields (%)		
	4	**6**	**8**
4	12	42	23
2	45	17	5
1	96	2	0
0.5[b]	47	<1	0
0.25[c]	0	0	0

[a] Conditions: CH_2Cl_2, N_2, −78°C, 0.25 h, 92% purity by ^1H NMR.
[b] Unreacted **3** was recovered (34%).
[c] No products were formed after 0.25 h (98% recovered **3**).

The employment of 4 equiv. of $TiCl_4$ resulted in increased quantities of **6** and **8**. The reaction of **3** with 1 equiv. of $TiCl_4$ gave **4** in essentially quantitiative yield. It should be noted that leaving the reaction for longer than 0.25 h resulted in the production of other side products (cyclisation, dimerisation or polymerisation products). It is our finding that this reaction (1 equiv. of $TiCl_4$) is complete in ca. 2 min. Further reducing the $TiCl_4$ equiv. to 0.5 or 0.25 resulted in incomplete reaction.

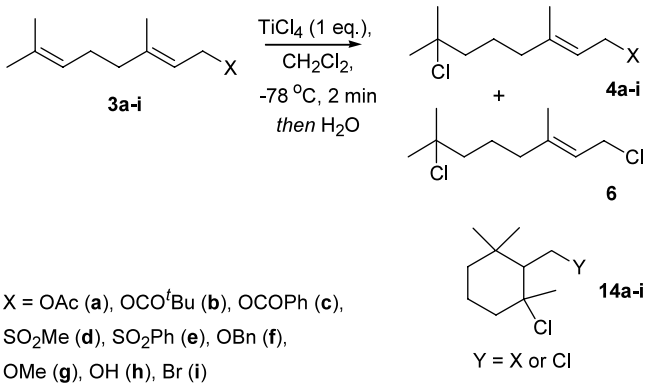
The identity of the intermediate titanium species is unknown. However, we observed an intense red colour, produced after complete addition of $TiCl_4$ (1 equiv.). Addition of 0.5 equiv. of $TiCl_4$ gives only a yellow colour.

We have established that quenching the reaction with deuterium oxide results in deuterium incorporation at the C-6 position to give 6-[^{2}H]-**4** in 90% yield ({^{1}H}^{2}H NMR, 76 MHz, δ 1.67, 73% ^{2}H incorporation).[14]

In order to investigate the scope of this reaction we decided to change the C1-substituent (Table 2) to see if the standard procedure[15] was general. Previous results have shown that the C1-substituent can have a marked effect on the yields obtained in SeO_2/^{t}BuO$_2$H *E*-selective oxidations of the terminal methyl group at the *distal* olefin in a variety of geranyl derivatives.[16]

We encountered no problems changing the substituent to pivaloate (**3b**→**4b**, entry 2, Table 2). However on shifting to the benzyloxycarbonyl substituent (**3c**→**4c**, entry 3, Table 2) **4c** was isolated in 41% yield, accompanied by **6** in 39% and the cyclised material **14c** in 17% yield. It was subsequently found that an excess of $TiCl_4$ (2 equiv.) provides **14c** as the major identifiable product in 34%, accompanied by polymerisation and decomposition. The ^{1}H NMR spectra of the mixture of products obtained from this reaction was complex, but it did demonstrate that both the *distal* and *proximal* olefins had been lost. The sulphone substituents facilitate some selective addition although the yields of the desired products are low with dramatic decomposition observed for the SO_2Ph substituent (entries 4 and 5, Table 2).

Table 2. Effect of protecting group[a]



Entry	X	Yield[b] (%)		
		4	**6**	**14**
1	OAc	96	2	0
2	OCO^{t}Bu	94	3	0
3	OCOPh	41	39	17
4	SO_2Me	25	12	19
5	SO_2Ph[c]	12	18	–
6	OBn[d]	0	0	54
7	OMe[d]	0	0	48
8	OH[e]	0	0	>45
9	Br[e]	0	0	64

[a] Conditions: dry CH_2Cl_2, N_2, −78°C, 0.25 h.
[b] Isolated yields after distillation and/or flash chromatography.
[c] Extensive decomposition.
[d] Polymerisation.
[e] Decomposition and polymerisation.

For those geranyl derivatives containing OBn, OMe, OH and Br substituents (**3f–i**) only cyclised material could be detected (entries 6–9, Table 2). The ^{1}H NMR spectra of the products from these reactions again showed the disappearance of both *proximal* and *distal* olefins, however the ^{1}H integrals suggest that extensive polymerisation had taken place, particularly where X = OH (**3h**) and Br (**3i**) (entries 8 and 9, Table 2).

In a recent report, Jones et al. have shown that $TiCl_4$ catalyses phosphoryl transfer to a variety of alcohols.[17] It was noted that geraniol **3h**, a particularly activated alcohol, decomposes under the reaction conditions (2 mol% $TiCl_4$, 1.5 equiv. $(PhO)_3P(O)Cl$ and 1.5 equiv. Et_3N in THF). Indeed it is our finding that the reaction of 0.25 equiv. $TiCl_4$ with **3h** results in rapid cyclisation/polymerisation/decomposition. It is clear that certain types of C1-substituents trigger this process, although the exact mechanism remains unknown at the current time.

In order to see whether we could improve on the selectivity observed for the addition of HCl to farnesyl acetate, we attempted to mono-chlorinate **9** using our $TiCl_4$ mediated procedure. However, competing cyclisation reactions thwarted our attempts. This is not surprising given the propensity for isoprenoids to undergo rapid cyclisation reactions in cellular biosynthesis.

In conclusion we have illustrated that the direct HCl addition to **3** is problematic and the production of chlorinated side products hampers the yield and purification of the desired product **4**. Our $TiCl_4$ mediated procedure overcomes this limitation. It was shown that the use of 1 equiv. of $TiCl_4$ and a reaction time of <0.25 h is crucial for obtaining a high yield of **4**. It was however somewhat disappointing to discover that the generality of the reaction could not be extended to include a range of C1 substituents. On the other hand it is clear that this could be exploited in the future.

Overall we believe that researchers in two very different fields: (1) design of terpenoid mimetics for enzyme inhibition/mechanistic studies; (2) identification of new selective transition metal catalysts for 1,6-enyne cycloisomerisation, will benefit from an efficient synthesis of 6,7-dihydrogeranyl acetate **5** and associated derivatives.

Acknowledgements

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9. A 72% isolated yield of **4** after distillation was reported in Ref. 8. Several products were isolated in very minor quantities when the crude product was purified via flash chromatography: 3,7-dichloro-3,7-dimethyl-1-octyl acetate **7**, 1,7-dichloro-3,7-dimethyl-2*E*-octene **6** and 1,3,7-trichloro-3,7-dimethyloctane **8**.
10. The characterisation data (^1H, ^{13}C NMR and CI-MS) for products **4**–**8** agreed with that given in Ref. 8.
11. The selective addition of HCl to the distal olefin of several geranyl derivatives in diethyl ether was reported some 13 years prior to the publication by Julia (Ref. 8). See: (a) Kahovcova, J. *Collect. Czech. Chem. Commun.* **1973**, *38*, 765. Use of acetic acid as a solvent represents the first report of selective addition of HCl to **3** to give **4** in 46% yield. See: (b) Brieger, G. *J. Am. Chem. Soc.* **1963**, *85*, 3783. No side products were reported in this reaction. Our attempts at this reaction and careful analysis of the ^1H NMR of the crude material show that chloride **6** is a side-product in this reaction (23% yield). Protonation of the acetate is expected where HCl or acetic acid is present in excess, thus creating a better leaving group for displacement by chloride. Selected data for compound **4**: δ_H (270 MHz, $CDCl_3$) 5.29 (1H, tq, $^3J_{HH}=7.02$, $^4J_{HH}=1.2$, C2-*H*), 4.57 (2H, d, $^3J_{HH}=7.02$, C1-H_2), 2.05 (3H, s, OCOCH_3), 1.99 (2H, br m, C4-H_2), 1.67 (2H, br s, C6-H_2), 1.56–1.63 (11H, br m, C5-H_2, 3×CH_3). MS (CI) m/z 252 (MH+NH_3, ^{37}Cl, 23%), 250 (MH+NH_3, ^{35}Cl, 69%), 214 (22%), 154 (36%), 137 (100%), 121 (12%), 81 (22%).
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13. Side-product **7** was not observed using this procedure.
14. The ^2H incorporation was calculated from the CI-MS of deuterated-**4** and non-deuterated-**4**.
15. *Typical $TiCl_4$ procedure*: Geranyl acetate (1 equiv.) in dry CH_2Cl_2 was stirred at −78°C for 2 min under an atmosphere of argon. $TiCl_4$ (1 equiv.) was added directly via syringe over 1 min. The mixture was stirred for 2 min and then quenched by careful addition of water and allowed to warm to 0–5°C (slowly turns to a white colour). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (×2). The combined organic extracts were washed with water (×1) and then brine (×1), dried ($MgSO_4$) and concentrated in vacuo to give a crude oil which was subjected to flash chromatography (elution with diethyl ether/hexane (19:1, v/v) to give a clear oil.
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