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Selective palladium-catalyzed hydrogenolysis of a secondary propargylic alcohol in the synthesis of vitamin D analog Ro 23-7553: substrate and ligand control

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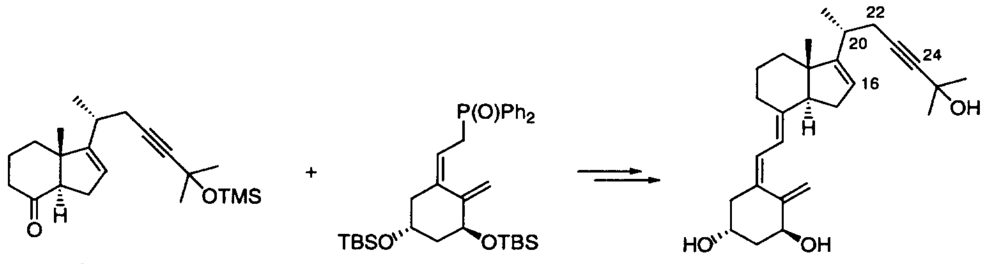
Abstract

Selective palladium-catalyzed hydrogenolysis of propargylic alcohol **9**, via its formate **10** or carbonate **13**, gave up to 98% of alkyne **11**. Alkyne/allene selectivity is controlled by the steric bulk of the phosphine ligand, as well as the propargylic (C-22) and alkyne (C-24) substituents in the substrate. A steric ligand–substrate interaction in the intermediate π-propargyl/allenyl palladium complexes is suggested to explain these effects. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: hydrogenolysis; regiocontrol; alkynes; allenes; palladium catalysis.

Calcitriol, a potent metabolite of vitamin D, is implicated in a host of cellular processes such as calcium homeostasis, immunology, cell differentiation and regulation of gene transcription. Following extensive studies of its molecular mode of action, it and several analogs have been proposed for the treatment of renal osteodystrophy, psoriasis, leukemia, breast cancer, and osteoporosis.[1] Clinical use, however, has been limited by inherent toxicity due to adverse calcium absorption and mobilization effects and low target specificity.[2]



1 **2** **3** (Ro 23-7553)

(1)

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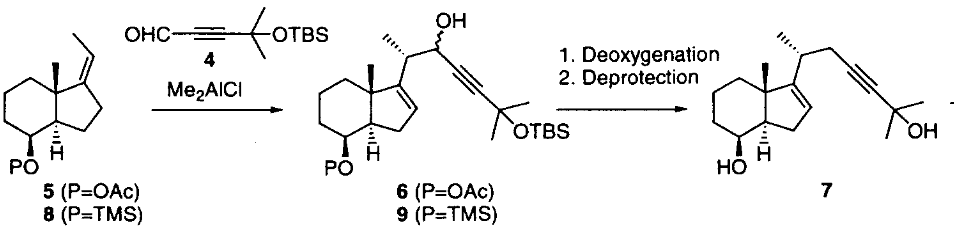
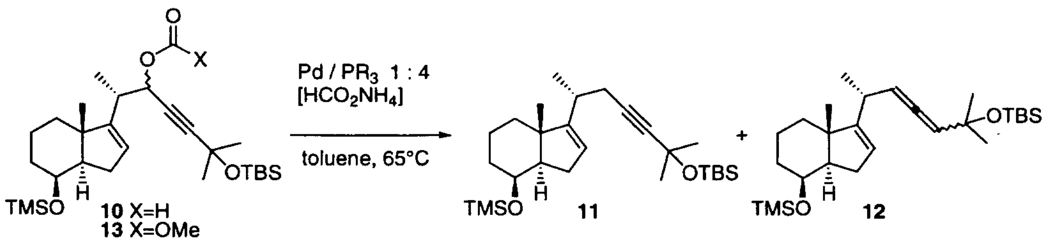
In the search for new analogs, Ro 23-7553 (**3**), a calcitriol analog with a modified D-ring (16-ene) and side chain (23-yne), has been identified as having a more specific action profile, low toxicity and a better therapeutic index than calcitriol.[3] Two syntheses of **3** are available. The first is based on the convergent Lythgoe phosphine oxide approach, in which the CD-ring fragment **1** is coupled with the A-ring fragment **2**, Eq. 1.[4] The second follows the classical Windaus approach starting from a commercially available steroid, dehydroepiandrosterone.[5] In both cases, the new structural elements: the acetylenic side chain and the C-16 double bond, as well as the chiral center at C-20, are incorporated selectively in one economical step by ene-reaction of a Z-alkene with an acetylenic aldehyde **4**, as illustrated for the conversion of alkene **5** to propargylic alcohol **6**, Eq. 2.[6] However, this efficient process is inevitably followed by the removal of the redundant hydroxy group, via a thionocarbonate or thiocarbamate derivative, using a free-radical Barton–McCombie deoxygenation.[7] The latter requires excessive use of expensive and toxic reagents, and is not a clean reaction due to hydrostannylation of the alkyne bond. For instance, deoxygenations using from 3.5 to 45 equivalents of tributyltin hydride have been reported.[4–6] Subsequent purifications then entail tedious HPLC removal of tin-containing byproducts, and after sequential deprotection and an additional HPLC purification diol **7** is obtained in 71% overall yield.[6] Scale-up has been problematic with significantly reduced yields.



(2)

We needed a practical deoxygenation procedure that would be suitable for the preparation of kilogram quantities of **3**. An attractive alternative approach is the palladium-catalyzed hydrogenolysis of propargylic alcohols developed by Tsuji.[8] Although the reaction is potentially useful for the preparation of internal alkynes,[9] the regioselectivity of alkyne vs allene formation is generally not well defined.[10] We wish to report here the selective palladium-catalyzed deoxygenation of propargylic alcohol **9** to alkyne **7** (Eq. 2), and some control elements that have emerged from our study which are relevant to the selectivity issue.

To evaluate the catalytic approach (Eq. 3), formate **10** was prepared (98%; 3:1 d.r.) from alcohol **9**, which in turn was obtained quantitatively by ene-reaction of TMS-protected alcohol **8** with **4**.[11] The TMS protecting group is set for a subsequent one-step desilylation to give diol **7**. Furthermore, since the latter is a crystalline compound, a welcome opportunity for purification by crystallization only, instead of chromatography, became possible.



(3)

The standard Pd(acac)$_2$/n-Bu$_3$P (1:1) catalyst system (toluene, 65°C, 16 h)[12] was initially tested, but met with limited success. The reaction was largely incomplete even with 10–20 mol% Pd catalyst and the selectivity was modest. Increasing the n-Bu$_3$P/Pd ratio to 4:1 produced a robust catalyst[13] and solved

Table 1

Entry	Substrate	X	$Pd(acac)_2$ (mol%)	PR_3	Alkyne/Allene[a] **11/12**
1	**10**	H	10	iso-Bu	no reaction
2	**10**	H	10	n-Bu	87 :13
3	**10**	H	10	n-Pr	87 : 13
4	**10**	H	10	Et	91 : 9
5	**10**	H	10	Me	95 : 5
6	**13**	MeO [b]	10	cyclohexyl	no reaction
7	**13**	MeO [b]	10	iso-Bu	18 : 82[c]
8	**13**	MeO [b]	10	n-Bu	90 : 10
9	**13**	MeO [b]	10	Et	95 : 5
10	**13**	MeO [b]	10	Me	98 : 2
11	**10**	H	2	Me	92 : 8
12	**10**	H [b]	2	Me	96 : 4

[a] Determined by HPLC: Nucleosil 5 µm, hexane at 1 mL/min, UV 200 nm; R_t 7.2 and 7.4 min (**12** diastereomers), R_t 10.5 min (**11**), response factor 2.07 (**12/11**).

[b] 2.5 equiv. of HCO_2NH_4 were added to the reaction.

[c] Incomplete conversion.

the reactivity problem: a quantitative conversion of **10** to **11/12** (Eq. 3) was obtained, but the selectivity for alkyne **11** vs allene **12** remained unsatisfactory (87:13). We then evaluated other reaction variables, such as the phosphine ligand, the source of the palladium, the solvent, and the leaving group, in the hope of improving the alkyne/allene ratio (**11/12**).

An interesting trend emerged from the variation of the steric bulk of the phosphine ligand (see Table 1), implying a ligand effect that has not previously been recognized. The selectivity for alkyne formation was found to increase by decreasing the size of the phosphine ligand used (entries 1–5). The highest selectivity 95% was achieved with Me_3P, while the selectivity was only 87% with *n*-Pr_3P and *n*-Bu_3P, and no reaction occurred with (*iso*-Bu)$_3$P.

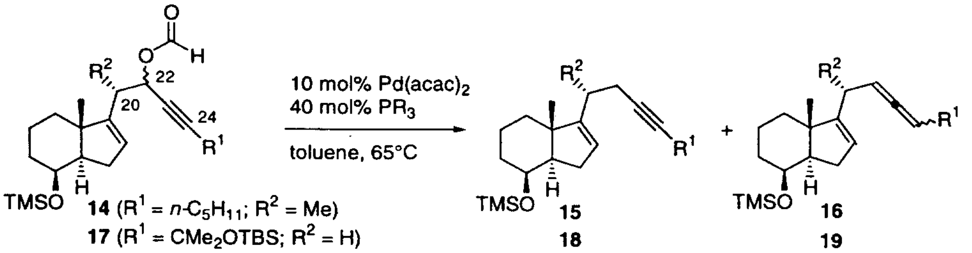
Different leaving groups were also examined using the *n*-Bu_3P/Pd (4:1) catalyst in toluene and ammonium formate as the hydride source, and of these methylcarbonate **13** showed some advantage in terms of selectivity. Thus, the ligand effect was examined with **13** as well, and the results are given in Table 1 (entries 6–10). The trend was similar to that observed with formate **10**, but the selectivities for alkyne **11** were consistently higher. The highest selectivity was again observed with Me_3P (98%).[14] Surprisingly, with the bulky (*iso*-Bu)$_3$P the selectivity was reversed and allene **12** was formed as the major product, but the reaction was incomplete. No reaction occurred with even bulkier tricyclohexylphosphine. Elimination products (4–7%) were observed, however, with the methylcarbonates, whereas the formate reactions were clean.[15]

Solvent effect was also examined with formate **10** and the Me_3P catalyst, and non-polar solvents were found to give higher alkyne/allene ratio. Heptane (94%) and toluene (95%)[16] gave the highest selectivity, THF (92%) and EtOAc (92%) were somewhat inferior, and acetone (84%) and DMF (74%) were clearly inferior. In dichloromethane the reaction was incomplete and the selectivity was modest (90%).

The effect of the palladium source was also evaluated. In agreement with previous reports,[9] ubiquitous $Pd_2dba_3 \cdot CHCl_3$, and $PdCl_2(MeCN)_2$, or $Pd(O_2CCF_3)_2$ did not give an active catalyst. On the other hand $Pd(OAc)_2$ and $[allylPdCl]_2$ were both effective, but the selectivities were lower than with $Pd(acac)_2$.

Finally, the hydrogenolysis of formate **10** was carried out on a larger 90 mmol scale using 2 mol% Pd loading and 8 mol% Me_3P to give a 92:8 mixture of the desired alkyne **11** and the corresponding allene **12** in 96% yield.[17] After desilylation (TBAF, THF, 54°C, 6 h) the allene impurity was removed by crystallization from toluene to yield 78% of pure diol **7**.[6] Interestingly, a slight but reproducible decrease in selectivity was noted with the lower Pd loading (Table 1, entry 11). We have subsequently found that addition of ammonium formate to the reaction of formate **10** with 2 mol% catalyst restored selectivity (entry 12), presumably by improving rate and catalyst turnover.

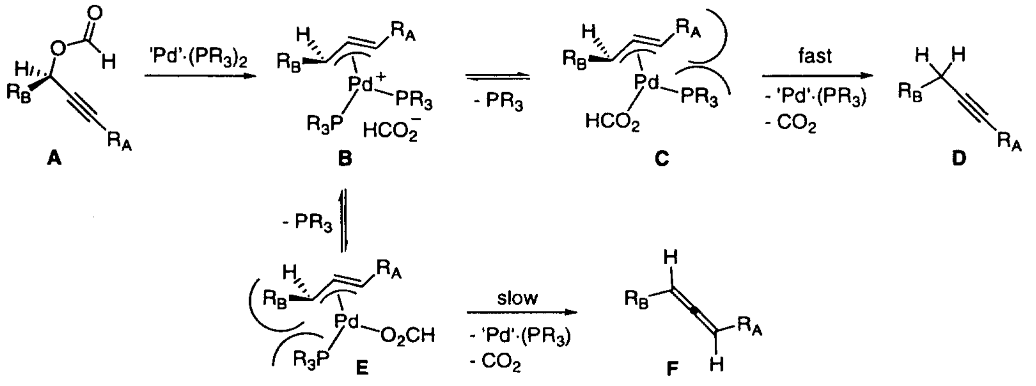
In an attempt to clarify further the interesting ligand effect, which appeared to be of a steric nature, we prepared two additional substrates **14** and **17** (Eq. 4) with different steric requirements for ligand–substrate interaction. Compared with **10**, formate **14** has a less bulky *n*-C_5H_{11} alkyne substituent and therefore a less hindered alkyne carbon C-24. The steric interaction should be reversed in formate **17**, which is lacking the C-20 methyl, and consequently has a less hindered propargylic carbon C-22 compared to **10**. Thus, if steric substrate interaction is involved, these two substrates' opposing steric bias should result in opposite alkyne/allene selectivities.



14 (R^1 = *n*-C_5H_{11}; R^2 = Me)
17 (R^1 = CMe_2OTBS; R^2 = H)
15 **18**
16 **19**

(4)

Indeed, while the selectivity for alkyne formation from **14** (Table 2, entries 13 and 14) increased with Me_3P ligand (97%) and even more significantly with *n*-Bu_3P (93%) to **10** (95% and 87%, respectively), the selectivity for alkyne formation from **17** (entries 16 and 17) sharply decreased to 75% with Me_3P, and its hydrogenolysis was unselective (50%) with *n*-Bu_3P. A bidentate ligand, 1,2-bis(dimethylphosphino)ethane (entry 15), behaved similarly to *n*-Bu_3P rather than Me_3P in this reaction, indicating that a single phosphine may be coordinated to palladium in the intermediate Pd complexes.



(5)

Based on these results we speculate that a steric substrate–ligand interaction, as illustrated (Eq. 5),[18] should be at the origin of the substrate and ligand effects on selectivity. Thus, the requisite propargylic ester, formate **A**, reacts with the palladium catalyst to give the ionic π-propargyl/allenyl palladium complex **B**, in equilibrium with neutral formate complexes **C** and **E**. The latter would then yield alkyne **D** and allene **F**, respectively, by regiospecific reductive elimination. The planar geometry of such complexes is well established,[19,20] and would secure configurational stability. Note that, due to different configurations, the steric relationship of the phosphine ligand and the π-propargyl/allenyl ligand is different in **C** than in **E**: the out-of-plane interaction with propargylic substituent R_B in **E** is less severe

Table 2

Entry	Substrate	R^1	R^2	PR_3	Alkyne/Allene	Ratio[a]
13	**14**	n-C_5H_{11}	Me	Me	**15/16**	97 : 3
14	**14**	n-C_5H_{11}	Me	n-Bu	**15/16**	93 : 7
15	**14**	n-C_5H_{11}	Me	$Me_2PCH_2CH_2PMe_2$[b]	**15/16**	93 : 7
16	**17**	CMe_2OTBS	H	Me	**18/19**	75 : 25
17	**17**	CMe_2OTBS	H	n-Bu	**18/19**	50 : 50

[a] Determined by HPLC (see Table 1).

[b] In contrast, 1,2-Bis(diethylphosphino)ethane gave only elimination products.

than the in-plane interaction with alkyne substituent R_A in **C**. Consequently, complex **E** is more stable and its conversion to allene **F** is slow, while complex **C** is less stable and its conversion to alkyne **D** is fast, as the alkyne is usually the major product.[21]

Thus, as the size of the phosphine is increased, steric interaction in **C** should increase the equilibrium concentration of complex **E** and more allene is competitively formed. The substrate effect on selectivity is similarly explained. When the size of substituent R_A is decreased (compare **10**, entries 2 and 5, to **14**, entries 13 and 14), the equilibrium concentration of complex **C** would increase favoring the alkyne product **D**. On the other hand, when the size of substituent R_B is decreased (compare **10**, entries 2 and 5, to **17**, entries 16 and 17), reduced steric interaction in complex **E** would result in competitive formation of more allene **F**. Furthermore, the extent of this effect is more significant with **17** rather than **14**, which verifies that the steric control of R_A is indeed more prominent than that of R_B.

In summary, we have improved the synthesis of the promising vitamin D analog Ro 23-7553 by using a selective palladium-catalyzed hydrogenolysis of propargylic alcohol **9** for the preparation of alkyne diol **7**. In this reaction model we have established that reduced steric bulk of the phosphine ligand favors alkyne formation, and the selectivity is increased with substrates having a smaller alkyne substituent (R_A), and a larger propargylic substituent (R_B). We suggest a steric ligand–substrate interaction as the key control element for this regioselectivity.

Acknowledgements

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14. Benzylcarbonate gave a similar 97% selectivity with the Me_3P catalyst.
15. Elimination products were formed exclusively from methylcarbonate **13** in the absence of HCO_2NH_4.
16. Better catalyst turnover was achieved in toluene, than in heptane, as a result of better catalyst solubility.
17. Pd(acac)$_2$ (544 mg, 1.79 mmol) was dissolved in toluene (7.2 mL) under nitrogen and Me_3P, 1 M solution in toluene (7.2 mL, 7.2 mmol) was added. The suspension was stirred for 35 min at rt. Then, a solution of **10** (45.8 g, 90.4 mmol) in toluene (130 mL) was cannulated under nitrogen and the solution was heated for 6 h at 70°C. The solvent was evaporated in vacuum, and the residue was dissolved in hexane (100 mL) and filtered through flash (230–400 mesh) silica gel (45 g) to remove the catalyst. The products were washed out with hexane (1.5 L), and the combined filtrates and washes were concentrated to dryness under reduced pressure to give 40.2 g (96%) of a colorless oil. HPLC: **12** (8%, 1:3.4 d.r.); **11** (92%); purity >99%.
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