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Palladium mediated C–H activation in the field of terpenoids: synthesis of rostratone ☆

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Abstract—We present results, which indicate that Pd-mediated C–H bond activation can be used under mild conditions for the remote functionalization of C-4 methyl groups of molecules with different terpenoid-like skeletons containing six- or seven-membered A rings. This procedure has allowed us to complete a novel strategy for the synthesis of γ-dioxygenated terpenoids in three stages: (i) selective epoxidation of commercial polyenes, (ii) titanium(III)-catalyzed cyclization of epoxypolyprenes, and (iii) Pd-mediated remote functionalization of equatorial methyl groups. This strategy has proved to be useful for the synthesis of the natural labdane rostratone (1).

In nature there are numerous terpenoids bearing a characteristic γ-dioxygenated system on ring A (Fig. 1), as occurs in the labdane diterpenoid (**1**), found in the plant *Nolana rostrata*,[1] in the antibiotic aphidicolin (**2**), excreted by *Cephalosporium aphidicola*,[2] and in the meroterpenoid (+)-pyripyropene A (**3**), isolated from the fungus *Aspergillus fumigatus*.[3] Many of these terpenoids possess interesting pharmacological properties; aphidicolin, for example, shows marked activity against Herpes simplex,[4] whilst pyripyropene A has proved to be a potent inhibitor of acyl-CoA:cholesterol acyltransferase (ACAT),[5] an enzyme related to atherosclerosis.

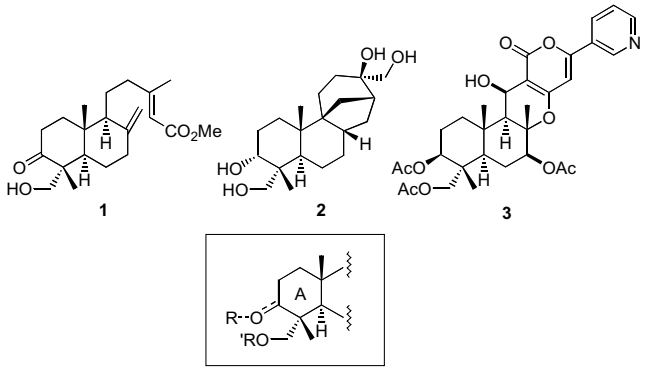

Figure 1. The γ-dioxygenated system of the A ring present in several bioactive terpenoids.

These compounds have consequently attracted the attention of chemists, who have reported some procedures for synthesizing **2**[6] and **3**.[7] These syntheses, however, generally require numerous steps, including tedious protection and deprotection protocols, and eventually provide only low overall yields.

We have recently developed a novel method for the synthesis of complex terpenoids[8] that adheres to the principles of selectivity and atom- and step-economy required in contemporary chemistry.[9] The method is based on the titanium(III)-catalyzed cyclization of epoxypolyprenes (such as **5**), which are easily prepared from commercially available polyenes.[8] Based on biomimetic concepts, this cyclization provides 3β-hydroxy terpenoids (such as **6**) with two 'unactivated' methyl groups at C-4 (Scheme 1). With such derivatives in our hands, we only need to oxidize their equatorial methyl group to achieve the γ-dioxygenated system of compounds such as **7** (including **1**–**3**). To make this transformation by remote functionalization at the end of the synthetic sequence has the advantage that protecting groups would not be required during the

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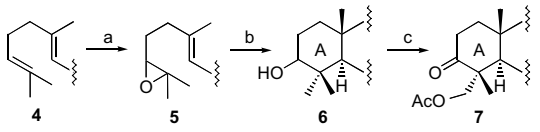


Scheme 1. Synthesis of terpenoids with the γ-dioxygenated system on the A ring: (a) selective epoxidation; (b) titanium(III)-catalyzed cyclization; (c) oxidation and Pd-mediated remote functionalization.

building of the carbocyclic framework. Nevertheless, conventional remote-functionalization methods[10] require thermal or photochemical conditions that are often incompatible with the functional groups present in natural products, and generally give relatively low yields.[11] In this scenario organometallic chemistry may become a valuable alternative, providing milder and more effective procedures to activate C–H bonds.[12] In particular, cyclopalladation reactions have proved to be capable of activating primary C–H bonds for the formation of C–I, C–O, and even C–C bonds.[13] Surprisingly, this kind of chemistry has been largely overlooked in the field of terpenoids.[14]

We have explored the efficiency of palladium-mediated C–H activation reactions over a wide range of terpenoid skeletons to facilitate the completion of the sequence depicted in Scheme 1 and thus devise a novel strategy for the straightforward synthesis of natural products such as **1**–**3**.

We began the process by preparing a set of model substrates (**8a**–**14a**) with different terpenoid-related skeletons containing five-, six-, and seven-membered rings (Fig. 2), which we treated with hydroxylamine to form

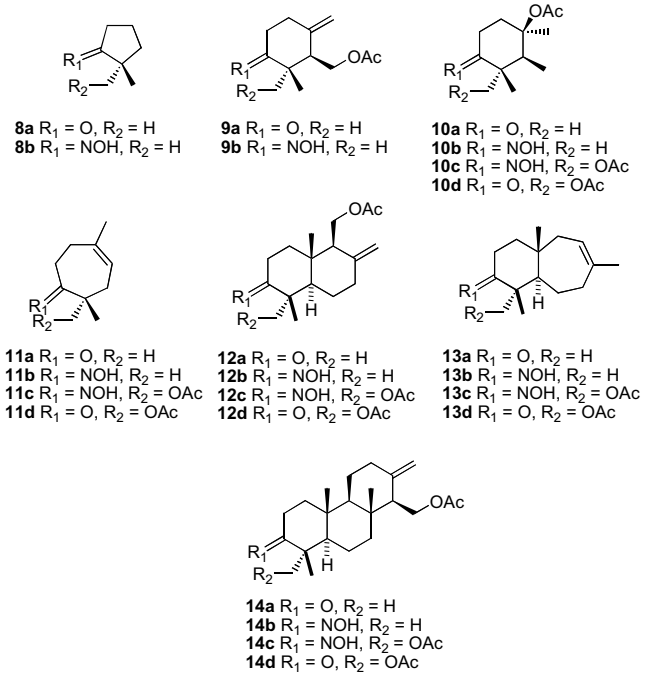
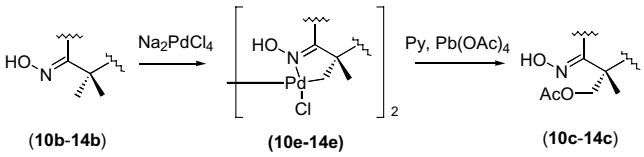


Figure 2. Chemical structure of the model terpenoids **8a**–**14a**, the corresponding oximes and the products derived from Pd-mediated remote functionalization.



Scheme 2. Remote functionalization of terpenoids via dimeric organopalladium complexes.

the corresponding ketoximes (**8b**–**14b**) at yields ranging from 70% (**9b**) to 92% (**13b**).[15]

Remote functionalization processes were then carried out as depicted in Scheme 2. Reactions between ketoximes **10b**–**14b** and sodium tetrachloropalladate(II) gave palladacycle dimers (such as **10e**–**14e**), which were treated with pyridine and lead tetraacetate to obtain acetoxy oximes **10c**–**14c** at yields ranging from 72% to 100% (Table 1).[16] In contrast, **8b** and **9b** decomposed after treatment with Na_2PdCl_4. Apparently, terpenoids with either a five-membered ring or a six-membered one containing an exocyclic double bond cannot be functionalized under these conditions.

Finally, the hydrolysis of oximes **10c**–**14c** with $TiCl_3$/H_2O provided acetoxy ketones **10d**–**14d** (Table 1), thus avoiding any undesirable isomerization of double bonds.[15]

To check the possibility of activating C–H bonds of terpenoid (pseudo)axial methyl groups, reactions with sodium tetrachloropalladate(II) were carried out again, this time using acetoxy oximes **10c**–**14c** as substrates. In this manner, we obtained moderate yields (40%) of acetates **15** and **16** (Fig. 3) deriving from monocyclic oximes **10c** and **11c**, although the polycyclic substrates **12c**–**14c** remained unchanged. Presumably, the stereochemical rigidity of these compounds prevents the adequate conformation to form the required palladacycles.

Table 1. Yields of products obtained by Pd-mediated remote functionalization of oximes **10b**–**14b**

Substrates	Acetoxy oximes (yield (%))	Acetoxy ketones (yield (%))
10b	**10c** (82)	**10d** (82)
11b	**11c** (88)	**11d** (85)
12b	**12c** (100)	**12d** (85)
13b	**13c** (85)	**13d** (85)
14b	**14c** (72)	**14d** (85)

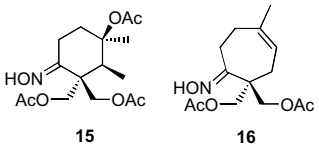
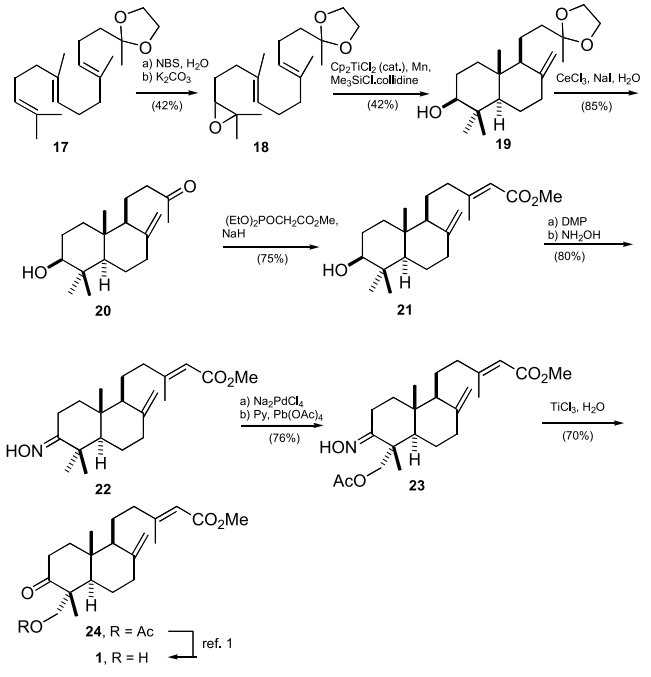


Figure 3. Chemical structure of products **15** and **16**.

Once we were confident about the possibilities of the Pd-based method we attempted to synthesize the target molecule **1** (Scheme 3).

As starting material, we chose ethylene ketal **17**, which is easily prepared from commercially available farnesylacetone.[15] Bromonium-mediated epoxidation of **17**, followed by titanium(III)-catalyzed cyclization of epoxypolyene **18** under anhydrous conditions gave exocyclic alkene **19** (17% yield from farnesylacetone) with high degrees of regio- and stereo-selectivity. Further hydrolysis of ketal **19** with $CeCl_3/H_2O$ avoided undesired double-bond isomerization and provided an 85% yield of ketone **20**. Horner–Emmons olefination of **20**, followed by the oxidation of alcohol **21** with Dess–Martin periodinane (DMP) and treatment of the corresponding ketone with hydroxylamine led to the oxime **22** (60% yield from **20**). Finally, Pd-mediated remote functionalization of **22** and hydrolysis of oxime **23** provided acetoxy ketone **24** (53% yield from **22**). The natural metabolite (**1**) from *N. rostrata* has been isolated and characterized by Garbarino et al. as its acetate (**24**).[1] Spectroscopic data of synthetic **24** matched those of the acetate reported by Garbarino and co-workers,[1] supporting the structure proposed for the natural product **1**. Moreover, these authors described the selective saponification of the acetate group of **24** to give **1**, and therefore the sequence depicted in Scheme 3 may be regarded as the formal synthesis of **1**. To the best of our knowledge this is the first chemical synthesis of this ketone, which we have called rostratone.

In summary, the results described here show that Pd-mediated C–H activation is a suitable procedure for the remote functionalization of C-4 methyl groups of different terpenoid-like skeletons containing six- and seven-membered A rings. This procedure might facilitate the chemical preparation of terpenoids with a γ-dioxygenated system on the A ring and, in fact, it has proved itself useful for the synthesis of the natural diterpenoid rostratone (**1**). At the moment, we are working on the synthesis of both aphidicolin (**2**) and pyripyropene A (**3**) employing this strategy.



Scheme 3. Formal synthesis of rostratone (**1**).

Supplementary material

Supplementary data Synthetic procedures and ^1H and ^{13}C NMR data for some selected compounds.

Acknowledgements

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References and notes

1. Garbarino, J. A.; Chamy, M. C.; Gambaro, V. *Phytochemistry* **1986**, *25*, 2833–2836.
2. (a) Brundret, K. M.; Dalziel, W.; Hesp, B.; Jarvis, J. A. J.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 1027–1028; (b) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841–2851.
3. Omura, S.; Tomoda, H.; Kim, Y. K.; Nishida, H. *J. Antibiot.* **1993**, *46*, 1168–1169.
4. Bucknall, R. A.; Moores, H.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.* **1973**, *4*, 294–298.
5. (a) Kim, Y. K.; Tomoda, H.; Nishida, H.; Sunazuka, T.; Oba, R.; Omura, S. *J. Antibiot.* **1994**, *47*, 154–162; (b) Tomoda, H.; Kim, Y. K.; Nishida, H.; Masuma, R.; Omura, S. *J. Antibiot.* **1994**, *47*, 148–153; (c) Tomoda, H.; Tabata, N.; Yang, D. J.; Takayanagi, H.; Nishida, H.; Omura, S.; Kaneko, T. *J. Antibiot.* **1995**, *48*, 495–503.
6. For a review concerning the total synthesis of aphidicolin, see: Toyota, M.; Ihara, M. *Tetrahedron* **1999**, *55*, 5641–5679.
7. (a) Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Omura, S.; Smith, A. B., III. *J. Org. Chem.* **1995**, *60*, 8126–8127; (b) Aggarwal, V. K.; Bethel, P. A.; Giles, R. *J. Chem Soc., Perkin Trans. 1* **1999**, 3315–3321.
8. Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778–1788, and references cited therein.
9. (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281; (c) Fürstner, A. *Synlett* **1999**, 1523–1533; (d) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308–311.
10. For a review, see: Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095–7129.

11. For classic examples in the field of steroids, see: (a) Jones, A. J.; Alewood, P. F.; Benn, M.; Wong, J. *Tetrahedron Lett.* **1976**, *20*, 1655–1658; (b) Desai, M. C.; Singh, C.; Chawla, H. P. S.; Dev, S. *Tetrahedron Lett.* **1979**, *22*, 5047–5050; For more recent results obtained in our laboratory with terpenoids, see: (c) Barrero, A. F.; Oltra, J. E.; Álvarez, M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 5461–5469.
12. For an excellent overview of the use of organometallic chemistry in contemporary organic synthesis, see: (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, CA, 1999; For a recent review into the potentials of organometallic chemistry for useful C–H bond activation strategies, see: (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.
13. (a) Carr, K.; Sutherland, J. K. *J. Chem. Soc. Chem. Commun.* **1984**, 1227–1228; (b) Baldwin, J. E.; Nájera, C.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 126–127; (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856–11857; (d) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372–13373.
14. We have only found two reports, both dealing with Pd-mediated primary C–H activation of pentacyclic triterpenoids, see: (a) Peakman, T. M.; Lo ten Haven, H.; Rullkotter, J.; Curiale, J. A. *Tetrahedron* **1991**, *47*, 3779–3786; (b) Bore, L.; Honda, T.; Gribble, G. W. *J. Org. Chem.* **2000**, *65*, 6278–6282.
15. All products were fully characterized by spectroscopic techniques, including HRMS and NMR spectra. For experimental details see Supplementary Material.
16. Model experimental procedure: A mixture of oxime (1 mmol), NaOAc (1.2 mmol) and Na_2PdCl_4 (1.2 mmol) in AcOH or MeOH (2–5 mL)[15] was stirred at rt for 48 h. The solvent was removed and the resulting residue was diluted with CH_2Cl_2, filtered through a Celite® pad and concentrated. The new residue and Py (3.2 mmol) in THF (10 mL) were stirred at rt for 15 min. The reaction was then cooled to −78 °C, AcOH (66 mmol) and $Pb(OAc)_4$ (1.1 mmol) were added and the resulting mixture warmed to rt and stirred for 24 h. Subsequently *t*-BuOMe was added and the mixture was washed with sat. $NaHCO_3$, dried (anhyd Na_2SO_4) and the solvent removed. The residue was submitted to flash chromatography (hexane: *t*-BuOMe) giving the corresponding functionalized oximes.