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Preparation of bioactive podolactones via a new Pd-catalysed bislactonisation reaction. Synthesis of oidiolactone C

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Abstract

A new route towards podolactone skeleton compounds, including the recently discovered Oidiolactone C, is described, using Pd-catalysed elimination of allylic trifluoroacetates and Pd-catalysed bislactonisation as key steps.

Keywords: palladium; bislactonisation; elimination reactions; dienes; natural products; herbicides.

Podolactones are norditerpenic metabolites isolated chiefly from different plant species of the genus *Podocarpus* and filamentous fungi, displaying some interesting biological activity (antifeedant, antitumoral, herbicide, etc).[1] The literature has described, to date, several methods for the preparation of podolactones.[2] Recent research carried out by our group led to the synthesis of nagilactone F and antibiotic LL-Z1271α,[3] as well as to the study of structure/allelopathic activity, performed on a wide variety of podolactone-related structures.[4] As a result, dilactone **8** was considered as a leading agent for the elaboration of natural herbicides. This finding justifies the development of new synthetic strategies allowing both high-scale multigram-preparation of this kind of molecule, and the subsequent preparation and biological screening of new derivatives.

Continuing the strategy of synthesising podolactones from available natural diterpenes, the first synthesis of the recently described oidiolactone C (**9**)[5] from *trans*-communic acid **1**, via intermediate **6**, has been achieved using organopalladium complex chemistry in the key steps (Scheme 1). Thus, **9** can be synthesised from **8** via regio- and stereoselective oxidation of conjugated diene **6**. In addition, the key step in the transformation of **1** into **6** lies in the removal of an allylic trifluoroacetate with Pd(0) complexes.

The transformation of acid **1** into diester **2** has been described by our group, showing a 72% yielding ratio (Scheme 2). Its allylic hydroxylation on C-7 was achieved using SeO_2 (0.5 equiv.) and *t*-BuOOH as reoxidant,[6] alcohol **3** being stereoselectively obtained (60%) and peroxide **13a**

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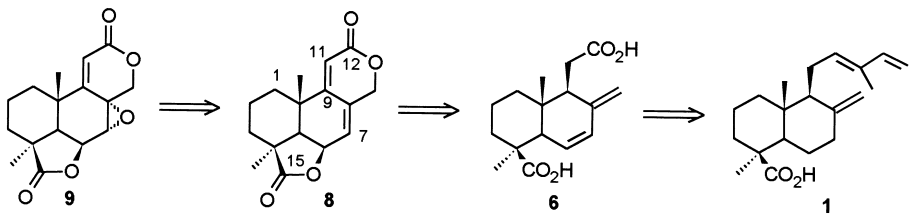
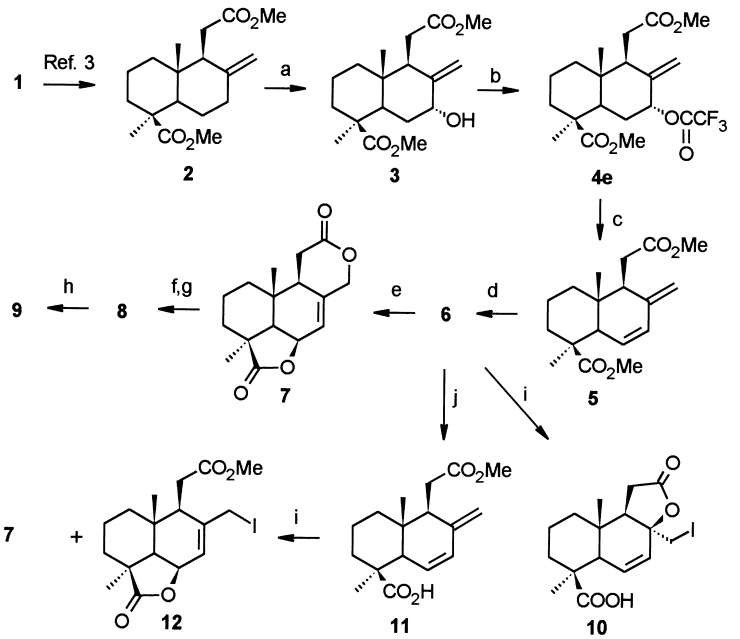


Scheme 1.

isolated as a byproduct (Fig. 1). Increasing the concentration of SeO_2 resulted in shorter reaction times and lower yields. On the other hand, variations on *t*-BuOOH concentration did not affect the final yield. Hydroxylation using only SeO_2 led to worse results, mainly due to the formation of selenium dimer **13b** (30%), which did not evolve to the targeted hydroxylated intermediates. In order to obtain the key-intermediate **5**[†] derivatives **4a** and **4b** were subjected to elimination processes unsuccessfully, diene **5** being obtained in negligible yields (5–10%). Knowing that



Scheme 2. Reagents and conditions: (a) SeO_2, *t*-BuOOH; CH_2Cl_2, rt, 9 h, 60%; (b) $(CF_3CO)_2O$, DMAP, CH_2Cl_2, 0°C, 30 min, 90%; (c) $Pd(PPh_3)_4$, K_2CO_3, toluene, 50°C, 9 h, 70%; (d) $CH_3(CH_2)_2SNa$, DMF, 50°C, 24 h, 85%; (e) $Pd(OAc)_2$, AcOH/acetone, benzoquinone, rt, 7 days, 70%; (f) LDA, THF, –78°C, 30 min; TMSCl, –78°C, 30 min; PhSeCl, –78°C, 1 h; (g) H_2O_2, py, CH_2Cl_2, rt, 80% two-step yield; (h) dimethyldioxirane, acetone, rt, 24 h, 80%; (i) I_2, CH_3CN, –20°C, 7 h, 100% for **10**; (j) MeOH, *t*-BuOMe, carbonyldiimidazole, rt, 24 h, 90%

[†] Compound **5**: δ_H (400 MHz, $CDCl_3$) 6.13–6.07 (2H, m, H-6, H-7), 4.86 (1H, d, $J=1.6$ Hz, H-13), 4.67 (1H, br s, H′-13), 3.67 (3H, s, OMe), 3.58 (3H, s, OMe), 2.68 (1H, br d, $J=9.2$ Hz), 2.53 (1H, dd, $J=3.4$, 16.2 Hz), 2.35 (1H, dd, $J=9.4$, 16.2 Hz), 2.26 (1H, br s), 2.22 (1H, br d, $J=13.4$ Hz), 1.82 (1H, qt, $J\approx3.7$, 13.7 Hz), 1.64–1.51 (2H, m), 1.27 (3H, s, H-14), 1.24–1.15 (1H, m), 1.07 (1H, dt, $J=4.15$, 13.5 Hz), 0.477 (3H, s, H-16); δ_C (100 MHz, $CDCl_3$) 176.8, 174.1, 145.2, 129.0, 128.0, 110.2, 55.2, 51.6, 51.1, 48.6, 43.3, 38.0, 37.0, 36.9, 30.8, 27.7, 19.5, 11.7; HR FAB MS: MNa^+, found: 329.1730. $C_{18}H_{26}O_4Na$ requires: 329.1729.

allylic acetates and carbonates in the absence of nucleophiles lead, via β-hydride elimination, to conjugated dienes after being exposed to Pd(0),[7] we subjected compounds **4c** and **4d** to the presence of $Pd(PPh_3)_4$, but unfortunately no reaction took place. Finally, this elimination was accomplished by treating the trifluoroacetate **4e** with $Pd(PPh_3)_4$ catalyst in the presence of K_2CO_3. Under these conditions, diene **5** was obtained in a 70% yield.[8] Other catalysts such as $PdCl_2(PPh_3)_2$, $Pd_2dba_3{\cdot}dba/2PPh_3$ and $Pd(OAc)_2/2PPh_3$ led to lower yields. The better aptitude of trifluoroacetate as a leaving group with respect to carbonate and acetate could account for the reaction taking place. It is worth noting that this work constitutes one of the few examples of the use of allylic trifluoroacetates to afford conjugated dienes.[9,10]

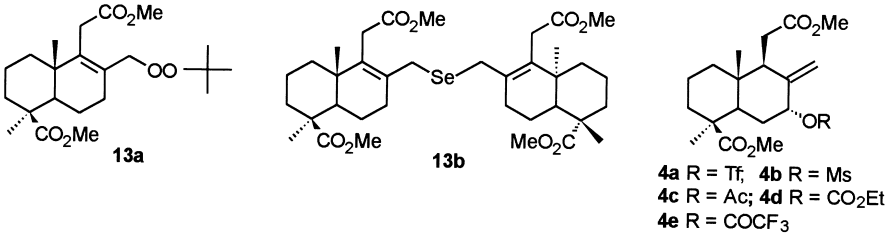


Figure 1.

Compound **5** was saponified using sodium propanothiolate in DMF to give **6** (85%). Bislactonisation of **6** was first essayed by treating the diacid with iodine in acetonitrile, leading quantitatively to γ-monolactone **10**‡ (derived from a 5-*exo-trig* cyclisation). To prevent the formation of **10**, compound **6** was selectively esterified on C-12 to obtain **11** (90%), which was then subjected to iodolactonisation conditions as above to give the iodoester **12**§ along with the desired **7**¶ in a ratio of 4:1 (determinated by ^1H NMR), respectively. These compounds could not be separated by column chromatography due to the instability of **12**. Attempts to transform **12** into **7** were unsuccessful. The preparation of the bislactonisation compound could be efficiently accomplished via a 1,4-regioselective oxidation of the conjugated diene **6** using Pd(II) as the catalyst and employing benzoquinone as a reoxidant.[11] Although this reaction has been used intramolecularly for the formation of bicycles, only one example of an intramolecular nucleophilic attack of a

‡ Compound **10**: δ_H (400 MHz, $CDCl_3$) 6.60 (1H, dd, $J=1.9$, 10.3 Hz, H-6), 5.75 (1H, dd, $J=3$, 10.3 Hz, H-7), 3.32 (1H, d, $J=10.4$ Hz, H-13), 3.28 (1H, d, $J=10.4$ Hz, H′-13), 2.84 (1H, dd, $J=9.3$, 18.6 Hz, H-11), 2.47 (1H, d, $J=18.6$ Hz, H′-11), 2.35 (1H, d, $J=9.1$ Hz, H-9), 2.27 (1H, br d, $J=13.5$ Hz), 1.93 (1H, t, $J=2.5$ Hz, H-5), 1.89–1.74 (1H, m), 1.68 (1H, br d, $J=13$ Hz), 1.56–1.51 (1H, m), 1.34 (3H, s, H-14), 1.06 (2H, dq, $J=4$, 13.6 Hz), 0.71 (3H, s, H-16); δ_C (100 MHz, $CDCl_3$) 182.7, 175.5, 134.8, 123.4, 82.7, 51.6, 50.2, 43.0, 37.6, 36.9, 36.8, 31.0, 28.2, 18.7, 13.3, 12.3; HR CI MS: MH^+, found: 405.0562. $C_{16}H_{22}O_4I$ requires: 405.0563.

§ Compound **12**: δ_H (400 MHz, $CDCl_3$) 6.25 (1H, dd, $J=2.5$, 4.4 Hz, H-7), 4.80 (1H, m, H-6), 4.02 (1H, d, $J=9.7$ Hz, H-13), 3.95 (1H, d, $J=9.7$ Hz, H′-13), 3.74 (3H, s, OMe), 2.83 (1H, m), 2.55 (1H, dd, $J=7.3$, 16.4 Hz, H-11), 2.41 (1H, dd, $J=4.5$, 16.4 Hz, H′-11), 2.12–2.05 (1H, m), 1.85 (1H, d, $J=5.1$ Hz, H-5), 1.7–1.4 (5H, m), 1.29 (3H, s, H-14), 0.809 (3H, s, H-16); δ_C (100 MHz, $CDCl_3$) 181.7, 173.7, 144.2, 123.5, 72.9, 52.4, 50.7, 46.2, 42.6, 34.1, 33.0, 30.9, 28.0, 24.1, 18.2, 18.0, 7.0; HR CI MS: MH^+, found: 419.0718. $C_{17}H_{24}O_4I$ requires: 419.0719.

¶ Compound **7**: δ_H (300 MHz, $CDCl_3$) 6.03 (1H, m, H-7), 4.93 (1H, m, H-6), 4.80 (1H, d, $J=14.2$ Hz, H-13), 4.72 (1H, dd, $J=1.2$, 14.2 Hz, H′-13), 2.61 (1H, m), 2.43–2.31 (2H, m), 2.19–2.09 (1H, m), 1.82 (1H, d, $J=5.1$ Hz, H-5), 1.79–1.68 (1H, m), 1.65–1.46 (3H, m), 1.32 (3H, s, H-14), 1.26 (1H, dd, $J=6.1$, 11.7 Hz), 0.85 (3H, s, H-16); δ_C (75 MHz, $CDCl_3$) 181.3, 172.4, 138.4, 119.2, 72.2, 69.9, 51.2, 44.9, 42.5, 33.6, 32.3, 29.2, 27.8, 24.2, 17.6, 17.5; HR FAB MS: MNa^+, found: 299.1254. $C_{16}H_{20}O_4Na$ requires: 299.1259.

carboxylate leading to a monolactone has been described.[12] Therefore, when diacid **6** was treated with $Pd(OAc)_2$ (10 mol%) in AcOH/acetone and in the presence of benzoquinone, dilactone **7** was obtained in a 70% yield.[8] The last step of the synthetic sequence, the introduction of the $\Delta^{9,11}$ double bond in **7**, was achieved by elimination of the 11-phenylselenoxide intermediate[2c] (80%). The preparation of **9** was completed by treating **8** with dimethyldioxirane (80%), after noticing only a slight transformation of **8** into the desired epoxide when **8** was exposed to MCPBA (24 h, refluxed $CHCl_3$, 10%).

In conclusion, as herein reported, we developed an efficient synthesis of intermediate **8** (seven steps from **2**, 18% overall yield) and compound **9** (eight steps, 14% overall yield), using as key steps the formation of conjugated dienes via elimination of allylic trifluoroacetates and a bislactonisation process catalysed by Pd, which is the first example described of biscyclisation in this kind of oxidation.

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