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Semi-syntheses of the 11-hydroxyrotenoids sumatrol and villosinol†

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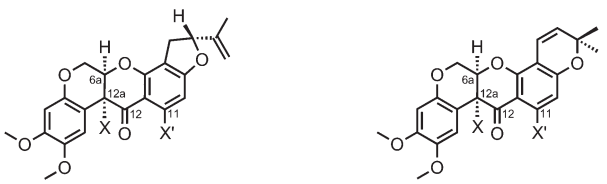
We describe semi-syntheses of the 11-hydroxyrotenoids sumatrol (1) and villosinol (2), starting from rotenone (5), using an oxime-directed C_{11}–H functionalisation approach. Thus, rotenone (5) was converted into rotenone oxime (6), which gave dimeric palladacycle 7 following reaction with $Na_2PdCl_4{\cdot}3H_2O$. Controlled, divergent, oxidation of palladacycle 7 with either $Pb(OAc)_4$ or $K_2Cr_2O_7$ afforded the 11-acetoxylated intermediates 9 and 13, respectively, which were transformed into sumatrol (1) and villosinol (2).

The 11-hydroxyrotenoid sumatrol (**1**, Fig. 1) was first isolated from *Derris malaccenis* in 1935 by Cahn and Boam[1] and was named in 1937 by Robertson and Rusby.[2] The latter pair successfully established the constitutional features of sumatrol (**1**), but could not definitively assign its skeletal structure and proposed instead two possible isomeric forms.[2–4] This structural ambiguity was resolved in 1961 by Crombie and Peace,[5] who succeeded in proving its skeletal structure and determining its absolute stereochemistry in conjunction with Djerassi and co-workers.[6] Villosinol (**2**, Fig. 1), the 12aβ-hydroxylated counterpart of sumatrol (**1**), was first isolated from *Tephrosia villosa* in 1976 by Sarma and co-workers[7] and was successfully characterised using the latest available spectroscopic techniques.

Since their initial isolations sumatrol (**1**) and villosinol (**2**) have been found in extracts from *Tephrosia pentaphylla*,[8] *Indigofera tinctoria*,[9] *Lonchocarpus* aff. *fluvialis*,[10] and, most recently, *Tephrosia toxicaria*.[11] Extracts from these plants have been shown to be toxic to fish,[10,11] insects,[9–11] bacteria,[11] and human cancer cells,[10] and, while mechanisms of action have not yet been identified, it is possible, if not probable, that their bioactivities relate to their rotenoid constituents. It is known, for example, that sumatrol (**1**) is a powerful inhibitor of mitochondrial complex I,[12] an important target in anti-cancer studies,[13] and it is likely that villosinol (**2**), given its structural similarity with sumatrol (**1**), also inhibits this vital enzyme.

As part of an investigation into the chemistry and biochemistry of the natural rotenoids underway in our laboratory, we sought synthetic routes to enantiomerically pure sumatrol (**1**) and villosinol (**2**). Neither sumatrol (**1**) nor villosinol (**2**) have been synthesised to date, and, in fact, of the prenylated 11-hydroxyrotenoids, only α-toxicarol (**3**, Fig. 1) and 12aβ-hydroxy-α-toxicarol (**4**, Fig. 1) have been prepared; the former semi-synthetically from sumatrol (**1**),[14] the latter by oxidation of α-toxicarol (**3**).[15] Given this lack of synthetic precedent, we considered that a semi-synthetic route starting from inexpensive natural rotenone (**5**, Scheme 1), proceeding *via* an oxime or *O*-acetyl oxime-directed palladium-catalysed or mediated C_{11}–H bond oxidation step,[16–18] might offer a naturally stereocontrolled means of rapidly accessing these molecules. While conceptually appealing, we felt that the C_{11}–O bond-forming reaction, involving oxidation of an envisaged palladacylic intermediate followed by reductive elimination from a putative Pd^{IV} species,[18] would likely present a formidable challenge as rotenoids frequently undergo oxidation at the C_{6a}–C_{12a} ring junction upon exposure to oxidants.[19] This challenge would have to be overcome and a practical solution found. If successful, however, we reasoned that it might then be possible to apply this approach to the preparation of additional 11-hydroxyrotenoids from other rotenoid precur-



1 X = H X' = OH
2 X = OH X' = OH

3 X = H X' = OH
4 X = OH X' = OH

Fig. 1 The 11-hydroxyrotenoids sumatrol (**1**), villosinol (**2**), α-toxicarol (**3**), and 12aβ-hydroxy-α-toxicarol (**4**).

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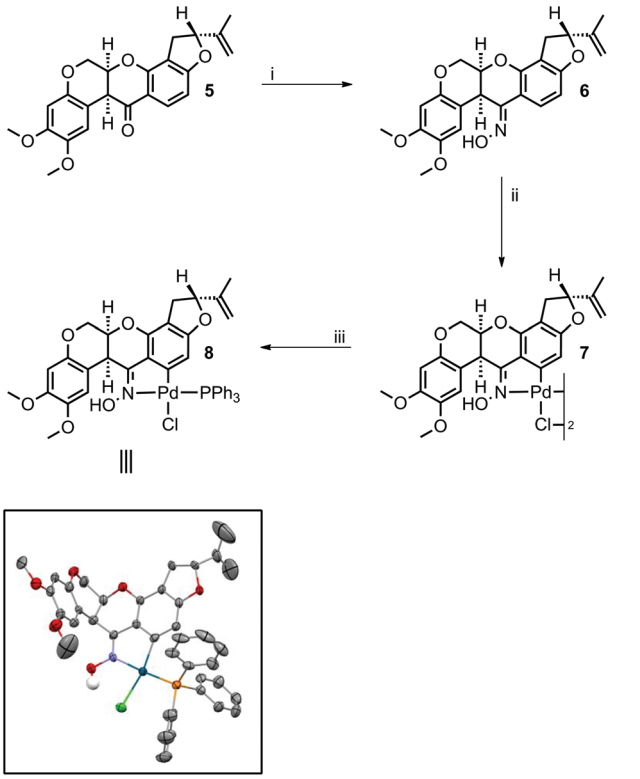
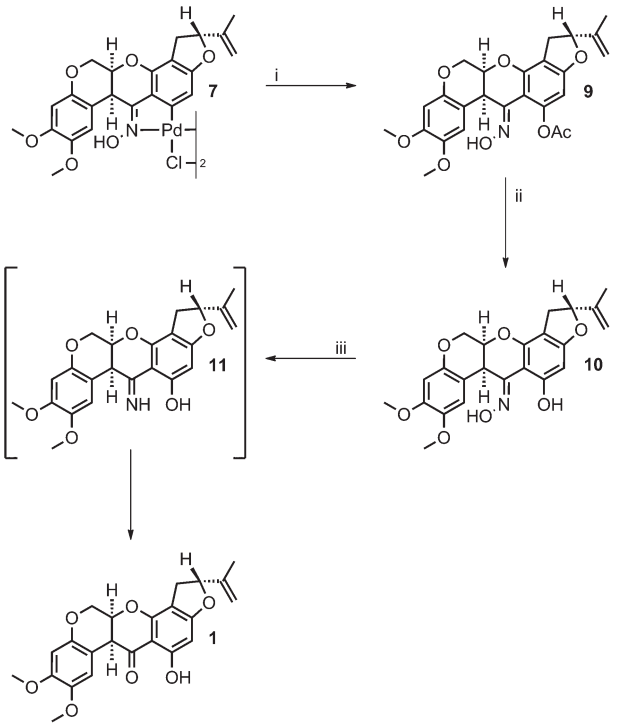
†Electronic supplementary information (ESI) available: General methods, synthetic procedures for all compounds and ^1H and ^{13}C NMR spectra; X-ray crystal structure of **8**. CCDC 1859235. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob01919c



Scheme 1 Reagents and conditions: i. $NH_2OH{\cdot}HCl$, NaOAc, ethanol, reflux, 18 h, 74%; ii. $Na_2PdCl_4{\cdot}3H_2O$, NaOAc, AcOH, rt, 4 d, 92%; iii. PPh_3, THF, rt, 18 h, 88%. The X-ray crystal structure of triphenylphosphine complex **8** shows displacement ellipsoids at 50% probability for non-H atoms. The solvent molecule (THF) has been removed for clarity.



Scheme 2 Reagents and conditions: i. Pyridine, THF, rt, 10 min, *then* Pb $(OAc)_4$, AcOH, 0 °C, 2 h, *then* $NaBH_4$, $NaHCO_3$, H_2O, 21% over 3 steps; ii. Na_2CO_3, MeOH, rt, 18 h, 78%; iii. $TiCl_3$ (12 wt% solution in HCl), NH_4OAc, 1 : 1 THF–H_2O, rt, 0.5 h, 40%.

sors. In this way, potentially lengthy total syntheses could, in future, be avoided in favour of shorter semi-syntheses.

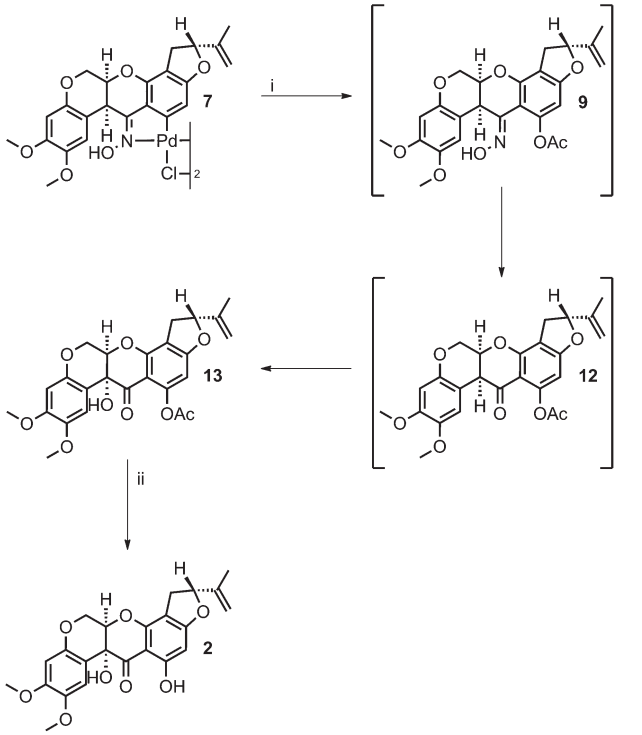
Herein, we describe the first semi-syntheses of the 11-hydroxyrotenoids sumatrol (**1**) and villosinol (**2**), starting from rotenone (**5**), enabled by the preparation and controlled, divergent, oxidation of a dimeric palladacycle derived from rotenone oxime (**6**, Scheme 1).

Starting from rotenone oxime (**6**, Scheme 1), which was prepared using the method described by Harper in 74% yield,[20] we began our investigations by trialling a range of palladium-catalysed C–H acetoxylation conditions. Our aim was to find a suitable combination of catalyst and oxidant to yield 11-*O*-acetyl rotenone oxime (**9**, Scheme 2), or a derivative thereof. Unfortunately, all attempts to bring about the desired 11-acetoxylation of rotenone oxime (**6**), using catalytic $Pd(OAc)_2$ and stoichiometric phenyliodonium diacetate (PIDA), failed, likely due to competitive deoximation by the oxidant.[17] Next, rotenone oxime (**6**) was *O*-acetylated in 1 : 1 acetic anhydride-acetic acid, using the method described by Neufeldt and Sanford,[17] and the *O*-acetyl oxime intermediate (not shown) formed *in situ* was then heated with catalytic $Pd(OAc)_2$ and stoichiometric PIDA as before. While the *O*-acetyl oxime intermediate was certainly more stable than rotenone oxime (**6**) under these conditions, both the catalyst and intermediate were ultimately decomposed. We suggest that these outcomes reflect the intrinsic instability of the rotenoid intermediate towards oxidation,[19] and, as we were unable to obtain any 11-acetoxylated products from the reaction, an alternative approach was therefore sought.

Undeterred, we attempted preparative cyclopalladation of rotenone oxime (**6**), adapting the well-established methods described by Baldwin[21,22] and Sutherland.[23,24] We reasoned that if an isolable palladacycle could be obtained then selective 11-acetoxylation could, in theory, be achieved by careful addition of a stoichiometric amount of oxidant. Pleasingly, treatment of a suspension of rotenone oxime (**6**) and NaOAc (1.2 equivalents) in acetic acid with $Na_2PdCl_4{\cdot}3H_2O$ (1.0 equivalent) afforded the chloride-bridged dimeric palladacycle **7** (Scheme 1) in 92% yield as a bright yellow, near-insoluble, solid. As direct spectroscopic characterisation of palladacycle **7** proved difficult, we resolved to infer its probable structure by preparing a soluble monomeric derivative that could be thoroughly analysed. Thus, a suspension of palladacycle **7** in THF was treated with triphenylphosphine and the desired bridge-cleavage reaction proceeded smoothly to give monomeric complex **8** (Scheme 1) in 88% yield following its precipitation. Triphenylphosphine complex **8** was fully characterised spectroscopically and, unambiguously, by single crystal X-ray crystallography (Scheme 1).‡ The structure of palladacycle **7** was thereby effectively inferred.

Investigations into the 11-acetoxylation of palladacycle 7 with PIDA failed, as did attempted oxidations with inorganic persulfate salts. Instead, 11-acetoxylation was accomplished after again turning to the methods described by Baldwin[21,22] and Sutherland[24] (Scheme 2). Addition of pyridine (2.0 equivalents (1.0 equivalent per equivalent Pd)) to a suspension of dimeric palladacyle 7 in THF gave a homogeneous solution (presumably containing the monomeric pyridine complex derived from 7), which was then treated with a solution of $Pb(OAc)_4$ (2.2 equivalents (1.1 equivalent Pb per equivalent Pd)) in acetic acid at 0 °C. Quenching of the reaction with $NaBH_4$ (2.2 equivalents (1.1 equivalent per equivalent Pd)) at 0 °C followed by work-up and chromatography afforded 11-*O*-acetyl sumatrol oxime (**9**, Scheme 2) in 21% yield. Acetate deprotection with Na_2CO_3 in methanol proceeded smoothly to give sumatrol oxime (**10**, Scheme 2) in 78% yield. Finally, reduction of sumatrol oxime (**10**) with excess $TiCl_3$ in 1 : 1 THF–water buffered with NH_4OAc at 0 °C (ref. 24 and 25) gave sumatrol imine (**11**, Scheme 2), which underwent spontaneous hydrolysis upon work-up to afford sumatrol (**1**) in 40% yield after purification.

Lastly, inspired by the work of Henry,[26] and in an attempt to build upon our own recent findings,[27,28] we investigated the use of $K_2Cr_2O_7$ as an alternative oxidant to achieve the 11-acetoxylation of palladacycle 7. We wondered whether this oxidant might be capable not only of effecting 11-acetoxylation,[26] but also of sequential oxidative deoximation[29] and diastereoselective Étard-like 12a-hydroxylation.[15,27,28] Thus, a suspension of palladacycle 7 in acetic acid was treated with an aqueous solution of $K_2Cr_2O_7$ (2 equivalents (4 equivalents Cr per equivalent Pd)) at 60 °C. A homogenous solution formed rapidly and analysis of the reaction mixture after 2 h by LCMS revealed 11-*O*-acetyl villosinol (**13**, Scheme 3) to be the major product, several unidentifiable polar by-products having also been formed. Unfortunately, 11-*O*-acetyl villosinol (**13**) was only obtained in 12% yield after precipitation and purification and, as no other product could be isolated from the crude precipitate, it is likely that the starting material underwent substantial decomposition under the reaction conditions. We suggest that intermediate 11-*O*-acetyl villosinol (**13**) was formed *via* a three-step process. Firstly, a chromium-mediated 11-acetoxylation of palladacycle 7 gave 11-*O*-acetyl sumatrol oxime (**9**), secondly, an oxidative deoximation gave sumatrol acetate (**12**), and thirdly, a diastereoselective Étard-like hydroxylation reaction provided the desired 11-*O*-acetyl villosinol (**13**, Scheme 3). Although low yielding, this reaction sequence nevertheless afforded a valuable doubly oxidised and deoximated intermediate that was only one step away from villosinol (**2**). Acetate deprotection using Na_2CO_3 in methanol proceeded cleanly, as before, to give villosinol (**2**) in 85% yield.



Scheme 3 Reagents and conditions: i. $K_2Cr_2O_7$, AcOH, H_2O, 60 °C, 0.5 h *then* rt, 1.5 h, 12%; ii. Na_2CO_3, MeOH, rt, 2 h, 85%.

Conclusions

We have described the first semi-syntheses of sumatrol (**1**) and villosinol (**2**), starting from rotenone (**5**), using a C–H functionalisation approach. The preparation of dimeric palladacycle 7 from rotenone oxime (**6**) made it possible to both effect and control the C_{11}-acetoxylation step, allowing, in the case of sumatrol (**1**), the saturated stereocentres of the C_{6a}–C_{12a} ring junction to survive intact. The structure of dimeric palladacycle 7, which was poorly soluble and difficult to characterise, was inferred from its conversion into the soluble monomeric triphenylphosphine complex **8**, for which an X-ray crystal structure was obtained in addition to spectroscopic data. Having successfully completed the first semi-syntheses of sumatrol (**1**) and villosinol (**2**) there remain two limitations regarding the broader utility of this work; the use of stoichiometric palladium (rendering any synthesis costly) and the use of toxic oxidants (necessitating that extreme care be taken). Limitations aside, by adopting the approach described herein, we have increased the number of rotenoids accessible from rotenone (**5**) and have extended the range of semi-synthesis within this natural product group. Finally, our work could, in principle, be extended to the preparation of related 11-hydroxyrotenoids from appropriate rotenoid precursors. Semi-syntheses of α-toxicarol (**3**) and 12aβ-hydroxy-α-toxicarol (**4**), for example, can now be envisioned, starting from natural deguelin.[27,30]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Crystal data: **8**·THF, $C_{45}H_{45}ClNO_7PPd$, M = 884.64, orthorhombic, a = 9.1935(1), b = 14.7832(2), c = 30.8543(5) Å, U = 4193.39(10) Å^3, T = 180(2) K, space group $P2_12_12_1$, Z = 4, 22 512 reflections measured, 9142 unique (R_{int} = 0.064), which were used in all calculations. The final R_1 was 0.059 ($I > 2\sigma(I)$) and wR_2 was 0.115 (all data). The Flack parameter determined using 2280 quotients was −0.02(2). CCDC 1859235.†

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