Synthesis of the ester side chains of some potently antileukemic harringtonia alkaloids from chiral citrates†

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The selective reduction of one of the three carboxyl groups of two chiral citric acid derivatives to the corresponding aldehydes, under Rosenmund conditions, are reported together with the application of these aldehydes to the syntheses of the ester side chains of some potently antileukemic *Cephalotaxus* alkaloids *e.g.* anhydroharringtonine.

The potent antileukemic activity of some of the *Cephalotaxus* alkaloids, *e.g.* **1a–c**, has led to considerable medicinal interest in these compounds.[1] In particular homoharringtonine **1c** has reached phase III clinical trials[2] in the USA against chronic myelogenous leukemia while in China it is reported to be used as a front-line therapy for acute myeloid leukemia[1b] and has shown activity against the chloroquinine resistant *Plasmodium f.* malaria parasite *in vitro* (Fig. 1).[3]

The limited availability of these alkaloids has engendered much interest in their partial synthesis from the more abundant but inactive cephalotaxine **2** and a number of synthetic approaches to the side chains have been described.[1] The critical problem is the coupling of the highly hindered secondary alcohol of **2** to the side chains, a situation exacerbated by the neopentylic character of these acids. Esterification of **2** with acids bearing an adjacent sp^2 centre, *e.g.* a ketone, followed by elaboration of the side chain *via* a Reformatsky reaction has attracted much interest.[1] In contrast, Kelly *et al.* discovered that reducing the steric hindrance of the acids by utilising a cyclic form allows intact side chains, potentially enantiomerically enriched, to be coupled.[4] Robin's recent disclosure of an effective means of achieving this for the preparation of homoharringtonine **1c** represents an important step forward.[1d]

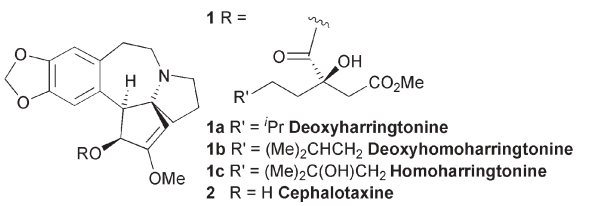

Fig. 1 Structures of some antileukemic harringtonia alkaloids.

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Herein are reported efforts to employ chiral citrates, *e.g.* **3**, to the synthesis of the side chain of **1b**, to Robin's acid **4** and to the related anhydroharringtonine side chain **5** (Fig. 2). The more recently isolated anhydroharringtonine has been found to be amongst the most active of these compounds against P-388 leukemia cells *in vitro*.[5]

Retrosynthetic analysis of **4/5** is representative of the approach adopted (Fig. 2). Key points involve the selective reduction of the carboxylic acid in **3/6** to the corresponding aldehyde **7/8**, the addition of three extra carbons with concomitant deoxygenation and selective cleavage of the dioxolanone ring in the presence of the methyl ester to give **9/10**. Successful acid mediated cyclisation can be anticipated based on earlier work.[1d]

We recently reported on a resolution procedure for obtaining multigram quantities of either enantiomer of the citric acid derivative **3** and its homologation to **6** *en route* to (*R*)-(−)-homocitric acid γ-lactone.[6] Our initial requirement was to selectively reduce the carboxylic acid group to the aldehyde oxidation level and we have found the Rosenmund reduction to be particularly suitable for this role as over-reduction to the corresponding alcohol leads to cyclisation and the aldehyde product **8** proved very sensitive.

The Rosenmund reduction has been largely superseded by metal hydride reagents.[7] In large measure this appears to be due to problems of inconsistent results, with many different catalyst 'poisons' employed to produce a more reliable deactivated palladium surface. Studies by Maier *et al.* have shown that a key role of 'poisons' is to facilitate a rearrangement of the surface morphology of the palladium with an attendant drop in surface area and that the same effect can be achieved by heating the Pd/C catalyst in refluxing xylene under an atmosphere of hydrogen.[8,9] This catalyst was found to be effective for the reduction of simple aliphatic and aromatic aldehydes at room temperature. Thus we first converted **6** into its corresponding acid chloride, in essentially

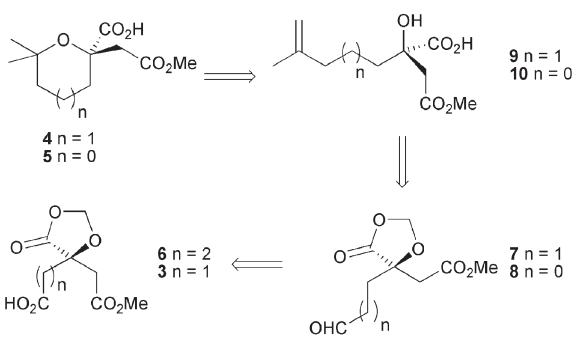
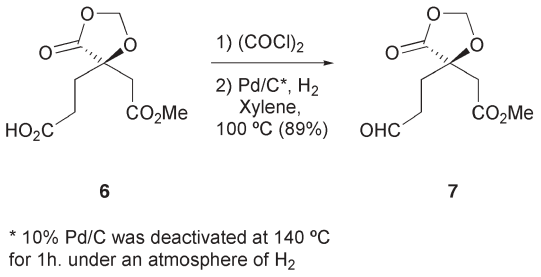


Fig. 2 Retrosynthetic analysis of some harringtonine esters to a citrate.

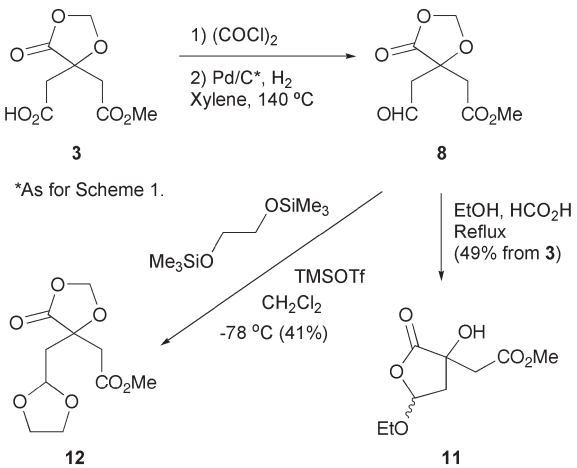


Scheme 1 Rosenmund reduction of homocitrate **6**.

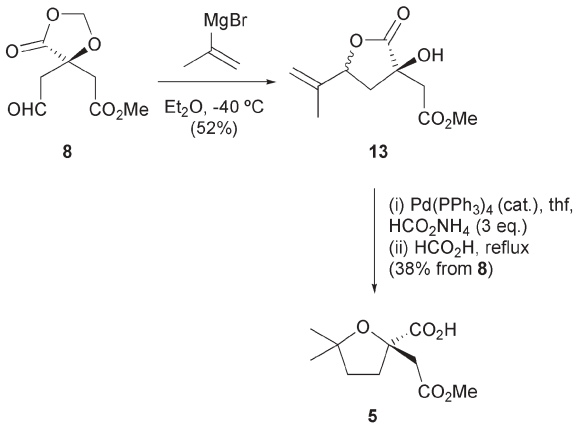
quantitative yield, by treatment with neat oxalyl chloride. Having prepared the Pd-catalyst according to Maier's protocol,[10] we found that for this substrate the reduction had to be carried out at 100 °C with 2.5% catalyst to deliver a consistent yield of 89%. Lower temperatures or less catalyst led to poor yields and increased amounts of impurities (Scheme 1).

Reduction of citrate **3** was initially more troublesome as the aldehyde **8** exhibited poor stability to chromatography on silica, alumina or Florisil® with a *ca.* 40% recovery. However, analysis of the ^{1}H NMR indicated that when the reduction was carried out at 140 °C with a flow of hydrogen[11] and 2.3% of the Pd/C catalyst **8** was obtained in good purity and in nearly quantitative yield. For characterisation purposes we sought a suitable protecting group for the aldehyde. Experiments with racemic **8** showed that attempts to form an acyclic acetal using EtOH–HCO_2H gave the pseudolactone **11**. Protection as a dioxolane under the Noyori conditions, however, delivered crystalline **12** in 41% yield after chromatography on silica (Scheme 2).[12]

The conversion of **7** or **8** to the side chains detailed above requires the addition of three carbons and a selective cleavage of the dioxolanone ring in the presence of the methyl ester. Early studies by Nau have shown that this type of chemoselective cleavage can be a low yielding transformation.[13] Taking note of the facile formation of the psuedolactone **11** when **8** was treated with EtOH (Scheme 2) we considered that addition of an organometallic reagent to aldehyde **8** might achieve this. Thus, addition of isopropenylmagnesium bromide at −40 °C in Et_2O afforded **13** in 52% yield as a 2 : 1 mixture of diastereoisomers.[14,15] The allylic γ-lactone moiety in **13** sets up a palladium(0) mediated hydrogenolysis of the unwanted carbon–oxygen bond. Subsequent



Scheme 2 Rosenmund reduction of **3**.



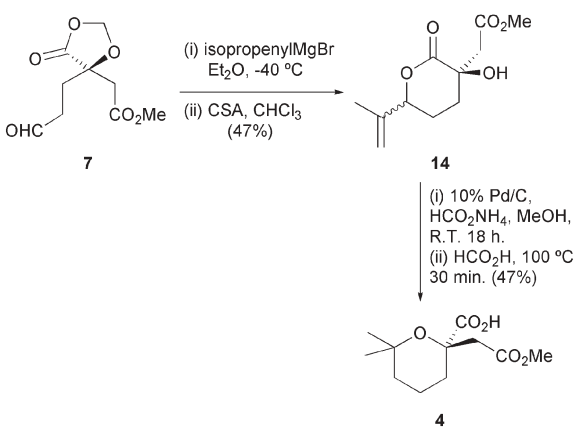
Scheme 3 Synthesis of the anhydroharringtonine side chain.

acid catalysed cyclisation onto the resultant double bond (present as a *ca.* 20 : 1 mixture of regioisomers, favouring the terminal position) afforded the anhydroharringtonine side chain (*R*)-**5** (Scheme 3).[16]

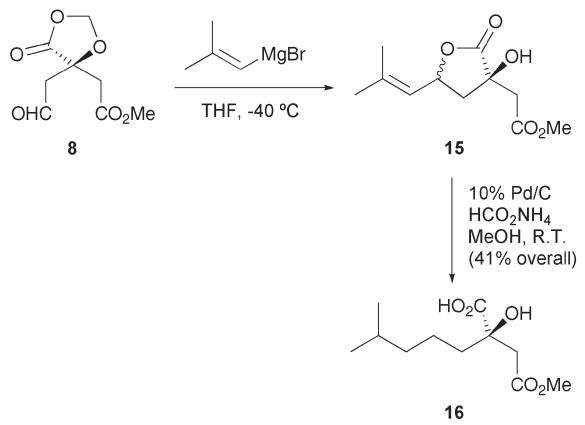
By extending the chemistry above we have prepared Robin's key intermediate **4**. Thus addition of isopropenylmagnesium bromide at −40 °C in Et_2O to **7** afforded a mixture of the desired δ-lactone **14** together with uncyclised material. On treatment of the crude with camphorsulfonic acid complete cyclisation to **14** occurred to bring the overall yield to 47%. In this instance hydrogenolysis was carried out by treatment of **14** with ammonium formate over 10% Pd/C[17] to afford a 1 : 1 mixture of regioisomeric alkenes which, on brief exposure to refluxing formic acid, afforded **4** in 47% yield (Scheme 4).

By contrast when we examined hydrogenolysis of **15**, under the conditions described above, we were unable to stop the reaction before significant saturation of the double bond had occurred. Thus we opted for prolonged treatment and isolated the deoxyhomoharringtonine side chain (*R*)-**16** in a 41% yield from **8** (Scheme 5).

In conclusion, we have carried out a selective reduction of one of the three carboxyl groups in the two citrate derivatives **3** and **6**. The so-formed aldehydes were used to synthesise the deoxyhomoharringtonine and anhydroharringtonine side chain **16** and **5**, and Robin's key intermediate **4** for homoharringtonine **1c**.



Scheme 4 Synthesis of Robin's Acid **4**.



Scheme 5 Synthesis of the deoxyhomoharringtonine side chain **16**.

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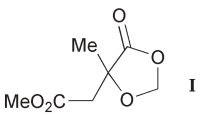

I

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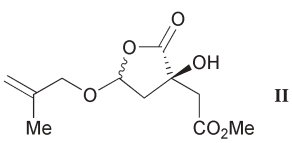

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