Synthesis of anti and syn hydroxy-iso-evoninic acids†

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Received 26th March 2012, Accepted 9th May 2012
DOI: 10.1039/c2ob25625h

The first synthesis of hydroxy-iso-evoninic acid (2), a pyridyl diacid found as a macrodilactone bridging ligand in bioactive Celastraceae sesquiterpenoid-based natural products, has been achieved in 9 steps and an overall yield of 26%. The synthesis utilizes a benzilic ester rearrangement (BER) and a late stage benzylic oxidation to give access to all four stereoisomers whose absolute stereochemistry was assigned following chromatographic separation and anomalous dispersion X-ray crystallography.

Celastraceae herbaceous perennials grow in temperate regions of the world and have been highly valued for centuries because their extracts exhibit an astonishingly wide range of medicinal properties and have been widely used in both traditional medicine1 and agriculture.2 Sesquiterpenoids are the most diverse class of constituents, all being based on dihydro-β-agarofuran skeleton displaying diverse degrees of oxidation and a plethora of esterification motifs, frequently incorporating unusual nicotinic acid based esterifying ligands.3 Hydroxy-iso-evoninic acid (2) is one of these esterifying ligands; it contains an α-hydroxy-3-butyric acid side-chain at C-4 giving it two chiral centres including the quaternary hydroxyl group α to the carboxylic acid. This ligand forms a 14-membered macrodilactone bridge between the C-3 and C-13 hydroxy groups of the most highly oxygenated dihydro-β-agarofuran core, (−)-euonyminol (1),4 in nine biologically active natural products.5–12

Three of these nine natural products [hypoglaunine A (3), hypoglaunine B (4) and triptonine B (5)] are of particular interest for their anti-HIV activity (EC50 values ≤0.13 μg mL−1) and unusually high therapeutic indexes (TI > 769) (Fig. 1).12,13

Although their mechanism of action is currently unknown, it has been reported that the α-hydroxy group in the hydroxy-iso-evoninate ligand is important for their high potency (although not an absolute requirement).12

To date, hydroxy-iso-evoninic acid has only been isolated as a constituent of parent macrodilactone sesquiterpenoids; no spectral data for the isolated diacid has been reported.1 H and 13C NMR data for these natural products suggest that in all cases hydroxy-iso-evoninic acid exists as the same stereoisomer but the relative and absolute stereochemistry of the C-2 and C-3 stereocentres have yet to be assigned.

Herein we report the first synthesis of hydroxy-iso-evoninic acid (2). Single enantiomers of each of the anti and syn diastereoisomers (2a and 2b) have been separated and their absolute stereochemistry determined.

The key step in our retrosynthetic strategy was envisaged to be the formation of quaternary α-hydroxy methyl ester 6 by means of a benzilic ester rearrangement (BER)14 of diketone 7. This diketone was envisioned to be accessed by oxidation of allylic picoline 8 which itself was to be prepared by allylation of 4-bromo picoline15 (Scheme 1).

Since 4-metallated pyridines are frequently rather labile, and indeed 4-bromo-3-picoline itself requires refrigeration following its 4-step synthesis from 3-picoline (35% yield),15 we sought an efficient method for directly coupling this aryl halide with an allylic moiety. Of several methods investigated, Pd(0)-catalyzed coupling with 2-acetoxy-3-ene in the presence of (Bu3Sn)2 was uniquely successful.16 However, the yield was low (39%) and was not dramatically improved by preformation of the allyl stannane17 (54% yield); furthermore, separation of the product...
from tin-containing by-products was tedious. Consequently, we were inspired to explore whether direct 4-allylation of 3-picoline could be achieved by extending the scope of an interesting phosphonate ester mediated protocol for 4-alkylation of pyridine reported by Akiba et al. in 1981\(^1\) (Scheme 2).

Formation of the ethyl formate salt of 3-picoline activated the pyridyl ring for nucleophilic addition of triethylphosphite, which occurred exclusively at the 4-position to form phosphonate ester 9 when the reaction was performed in MeCN.\(^2\) Subsequent, sequential addition of n-BuLi (1 equiv., to deprotonate at the 4-position), (E)-2-bromopent-3-ene (to effect 4-alkylation), and further n-BuLi (2 equiv., to remove the phosphonate and formate esters and rearomatise) gave 4-allyl-3-picoline 8 in 53\% yield. Accounting for the fact that this approach circumvents the need to prepare 4-bromo-3-picoline, or handle toxic tin reagents, this one-pot reaction was considered well-suited to deliver sufficient material for the remainder of the synthesis.

Surprisingly, a variety of conditions that we explored to effect dihydroxylation of alkene 8 were unsuccessful,\(^19\)-\(^22\) and led only to products of C–C bond cleavage or decomposition. Epoxidation then hydrolytic ring-opening of alkene 8 was therefore considered as an alternative strategy (Scheme 3). Direct epoxidation using e.g. m-CPBA and Sharpless AD conditions resulted in concomitant pyridine-N-oxide formation, but treatment of alkene 8 with NBS cleanly afforded the corresponding bromohydrin 10 as a mixture of regio- and diastereoisomers. Addition of base to this mixture resulted in ring-closure to epoxide 11 (dr 52 : 48) which was smoothly hydrolysed using aqueous perchloric acid to give 1,2-diol 12 (dr 52 : 48, 70\% yield over 3 steps). Oxidation of this diol mixture with IBX resulted in glycol-bond cleavage, however, this cleavage could be avoided by instead employing a Swern oxidation to afford desired diketone 7 in 95\% yield providing aqueous work-up was avoided and the crude material was held at \(-78 ^\circ\)C until it was loaded onto a flash column for purification.\(^23\) Use of a more hindered base or changing the electrophilic activator did not improve the stability of the product in the reaction mixture.

Promotion of a BER of diketone 7 was investigated under both basic conditions and in the presence of Lewis acids\(^24\) (Table 1).

In the presence of CuCl no rearrangement occurred and only decomposition products were observed, likely caused by the coordination of copper to the pyridyl nitrogen (Table 1, entry 1). However, the requisite BER was promoted by Lewis acids Ca(OH)\(_2\) and ZnCl\(_2\) (entries 2 and 3), and both promoters showed selectivity for the syn-diastereoisomer 6b. Interestingly, when switching to basic promoters (entries 4, 5 and 6), the BER reactions were similarly clean but a switch in the favoured diastereomeric ratios was calculated from \(^1\)H NMR integration. Syn and anti refer to the relative stereochemistry of the two methyl groups.

<table>
<thead>
<tr>
<th>Entry</th>
<th>BER promoter</th>
<th>6a : 6b(^\text{a}) (anti : syn)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ca(OH)(_2)</td>
<td>45 : 55</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl(_2)</td>
<td>35 : 65</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>0.05 M BaO</td>
<td>57 : 43</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>0.05 M NaOMe</td>
<td>57 : 43</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>0.10 M NaOMe</td>
<td>66 : 34</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^{a}\) 1 equiv., MeOH, 40 °C. \(^{b}\) All reactions were complete within 16 h, diastereomeric ratios were calculated from \(^1\)H NMR integration. Syn and anti refer to the relative stereochemistry of the two methyl groups.

High levels of diastereoselectivity are frequently observed in BERs of cyclic systems,\(^25\)-\(^27\) but in acyclic cases diastereoselectivity is difficult to control. To the best of our knowledge, Burke et al. are the only group who have reported attempts to influence the diastereoselectivity of an acyclic rearrangement.\(^28\) They found that for one particular Cu(OAc)\(_2\) promoted BER, the diastereoselectivity was moderately dependent on the concentration of Cu(OAc)\(_2\) (100 mol% Cu(II) dr 2.1 : 1 cf. 1 mol% Cu(II) dr 4.2 : 1). However, it appears that this is not a general situation and there are no reports where the conditions are tunable to favour either of the diastereomers as achieved here for ester 6a vs. 6b.

Completion of the synthesis required hydrolysis of esters 6 and oxidation of the benzyl methyl group to give the required diacids 2 (Scheme 4).
Following successful ester hydrolysis under basic conditions on a 45:55 anti:syn mixture of diastereomers of 6 (89% yield), benzylic oxidation was attempted by refluxing in water with KMnO₄ as was used previously in the synthesis of pyridine based esterifying ligands (−)-evoninic acid⁵⁹ and hydroxy willoidic acid.⁶⁰ Although benzylic oxidation was observed, again products resulting from cleavage of the glycol bond were the major components of the crude reaction mixture. However, performing the benzylic oxidation under basic conditions, as originally reported by Criegee,⁶¹ avoided glycol-bond cleavage and afforded hydroxy-iso-evoninic acids (2) in 95% yield. The diastereomeric ratio was retained during both the hydrolysis and oxidation steps.

As ester diastereoisomers 6a (anti) and 6b (syn) were inseparable by flash chromatography and diacids 2, along with their monoacid precursors, were also found to be inseparable by achiral HPLC, separation by chiral stationary phase (CSP) HPLC was performed on the mixture of all four stereoisomers of ester 6. By using a combination of Chiralcel® OD-H and IC columns, single enantiomers of each of the ester diastereoisomers 6a (anti) and 6b (syn) were isolated (see ESIF).

Assignment of the absolute stereochemistry of each of these esters, (−)-6a and (+)-6b, was achieved by single crystal anomalous dispersion X-ray structure determinations (Fig. 2).§

(−)-(2R,3S)-Ester 6a and (+)-(2S,3S)-ester 6b were then taken separately through the hydrolysis and oxidation steps to obtain (+)-(2R,3S)-hydroxy-iso-evoninic acid (2a, anti) and (+)-(2S,3S)-hydroxy-iso-evoninic acid (2b, syn) (Scheme 5).

Conclusions

In summary, an efficient synthesis of hydroxy-iso-evoninic acid (2) has been developed that gives access to all four possible stereoisomers (9-steps, 4 purifications by flash chromatography, 26% overall yield). The key step in the route is the BER which shows potential for development into a diastereoselective synthesis which can provide selectively either the anti or syn diastereoisomers. By use of CSP-HPLC for the separation of the stereoisomers of ester 6, then further synthetic elaboration of these separated enantiomers, single enantiomers of anti- and syn-hydroxy-iso-evoninic acids [(+)-2a and (+)-2b] were obtained.

We plan to prepare an enantiomerically pure C-3/C-13 diol-model to mimic the (−)-evoninyl core (1) present in the nine natural products which contain hydroxy-iso-evoninic acid as an esterifying ligand (vide supra). Dilactonisation with the four stereoisomers of hydroxy-iso-evoninic acid (2) prepared herein, should then enable assignment of the stereochemistry of the naturally occurring form and allow for development of an asymmetric synthesis starting from the appropriate enantiomer of 4-allyl-3-picoline.⁶²

Acknowledgements

We thank the EPSRC and AstraZeneca for financial support of this work (Industrial CASE award to SAW).

Notes and references

‡ When the reaction was performed using THF (cf. Akiba et al.), a mixture of 4- and 6-phosphonate esters was formed. § Attempts at co-crystallising with single enantiomer chiral pool acids did not result in crystals suitable for X-ray diffraction.

¶ We have been unable to secure a natural sample of any Celastraceae sesquiterpenoid from which to attempt isolation of hydroxy-iso-evoninic acid by hydrolysis.


Scheme 4 Final 2 steps in the synthesis of hydroxy-iso-evoninic acids (2).

Scheme 5 Synthesis of (+)-(2R,3S)-hydroxy-iso-evoninic acid (+)-2a and (+)-(2S,3S)-hydroxy-iso-evoninic acid (+)-2b.

Fig. 2 Molecular structures of (−)-(2R,3S)-ester 6a and (+)-(2S,3S)-ester 6b with absolute configurations assigned via single crystal anomalous dispersion X-ray diffraction.

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