Stereoselective Total Synthesis of ent-EI-1941-2 and Epi-ent-EI-1941-2

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ABSTRACT

The first asymmetric total syntheses of ent-EI-1941-2 and epi-ent-EI-1941-2 have been accomplished, starting from a chiral epoxy iodoquinone 6, a key intermediate in our total syntheses of epoxyquinols A and B. A key step in the preparation of ent-EI-1941-2 is an intramolecular carboxypalladation via a 6-endo cyclization mode, followed by β-hydride elimination, while carboxymercuration is a key step in the synthesis of epi-ent-EI-1941-2.

Interleukin-1β (IL-1β) converting enzyme (ICE) is a cysteine protease that cleaves a biologically inactive 31 KDa precursor to biologically active IL-1β,1 an important mediator in the pathogenesis of rheumatoid arthritis, septic shock, inflammation, and other physiological conditions.2 Therefore, it is thought that ICE inhibitors would be useful as antiinflammatory drugs. Koizumi and co-workers have isolated EI-1941-1 (1), EI-1941-2 (2), and EI-1941-3 (3) from culture broths of Farrowia sp., the first two of which selectively inhibit human recombinant ICE activity with IC50 values of 0.086 and 0.006 μM, respectively.3 Just recently, the relative and absolute stereochemistries of EI-1941-1 and -2 have been determined by X-ray crystallographic analysis of the p-bromobenzoyl ester of EI-1941-2.4 Structurally, EI-1941-1 and EI-1941-2 (Figure 1) have an epoxyquinone core, and due to our interest in the synthesis of such epoxyquinone derivatives, including ECH5 and its dimers, epoxyquinols A and B,6 we set out to accomplish the first asymmetric total synthesis of ent-EI-1941-2, the achievement of which will be disclosed in this paper.

A retrosynthetic analysis of EI-1941-2 is depicted in Scheme 1. At the time that we started this project,
relative and absolute stereochemistries were not known. As most of the epoxyquinol natural products have a trans relationship between the epoxide and the 4-hydroxy group on the cyclohexenone,7 a synthetic route by which the two diastereomers (EI-1941-2 and epi-EI-1941-2) can be generated with high optical purity was undertaken in order to determine the relative and absolute stereochemistries. EI-1941-2 and its epimer were to be prepared from diene carboxylic acid via 6-endo-electrocyclization8 or carboxy metalation via the 6-endo mode. 4 was to be synthesized from iodo compound 5 via the Suzuki coupling reaction, while we planned to produce 5 from the R-iodocyclohexanone derivative 6, a key chiral intermediate in our total synthesis of epoxyquinols A and B, which is prepared by a sequence in which the Diels–Alder reaction of furan is one of the key steps.6c,d

The synthesis starts from the chiral iodocyclohexenone 6, easily prepared in a large quantity by our reported method6c,d (Scheme 2). Cleavage of the acetonide on acid treatment gave diol 7. Selective oxidation of the primary alcohol with excess MnO2 in CH3CN gave aldehyde 8, the secondary alcohol of which was protected using TBSOTf and 2,6-lutidine, affording 9 in 72% yield over two steps. Oxidation of this aldehyde to the carboxylic acid was successfully performed under Kraus’ conditions.9 The carboxylic acid was protected as its para-methoxybenzyl ester 10 in 85% yield. Introduction of the side chain by a Suzuki coupling reaction with (E)-1-pentenylborate 10 and Ag2O in the presence of a catalytic amount of Pd(PhCN)2Cl2 and Ph3As11 afforded 11t in 97% yield. Acid treatment then gave carboxylic acid 4t in excellent yield. The isomer with the (Z)-side chain 4c was prepared in good yield by a Stille coupling reaction using (Z)-1-tributylpentenylstannane 12 in the presence of a catalytic amount of Pd(PhCN)2Cl2 and Ph3As,13 followed by the acid treatment (eq 1).

Next we examined the key cyclization of diene carboxylic acid 4t via the 6-endo mode, and the results under several

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reaction conditions are summarized in Table 1. In our previous syntheses of epoxyquinols A and B, the key step is a biomimetic cascade reaction composed of sequential oxidation, 6π-electrocyclization, and Diels–Alder dimerization⁶⁵ (eq 2).

On the basis of the facile 6π-electrocyclization observed for a dienal,⁶⁶ we expected that the same type of 6π-electrocyclization would proceed in the case of diene carboxylic acid 4t or ester 11t (eq 3). On the basis of this assumption, 4t and 11t were refluxed in toluene, but this led to complete recovery of the starting materials (entry 1). Acid catalysts do not promote the 6π-electrocyclization, and once again the starting material was completely recovered (entry 2). The conversion of carboxylic acid 4t to its sodium carboxylate resulted in decomposition of the starting material (entry 3). As we had found that the 6π-electrocyclization of 4t scarcely proceeds at all, intramolecular additions of the carboxylic acid onto the alkene activated with iodine or metal salts were examined, though diastereoselectivity and alternate reaction modes such as 6-endo or 5-exo are possible problems with this approach. In fact, iodolactonization proceeded in the 6-endo mode with low yield (entry 4), while in the case of carboxymercuration using Hg(OTf)₂,¹⁴ the 6-endo cyclized product was obtained in excellent yield as a single isomer,¹⁵ albeit with the incorrect side-chain relative stereochemistry for the natural product in the reaction of (E)-isomer 4t (vide infra, entry 5), while the undesired 5-exo cyclization was observed in that of the (Z)-isomer 4c (entry 6). Unlike these unsuccessful results, the 7,8-dihydro-6H-isochroman-1,5-dione structure 16 was formed when palladium(II) was used as a catalyst. That is, when 4t was treated with p-benzoquinone and a catalytic amount of Pd(PhCN)₂Cl₂,¹⁶ carboxypalladation proceeded, followed by the β-hydride elimination, affording 16 in 70% yield (entry 7).

The remaining steps are reduction of the double bond and deprotection. Hydrogenation of 16 under an H₂ atmosphere in the presence of Pd/C or Pd(OH)₂ did not proceed. As the keto group might be the cause of this reluctance to undergo hydrogenation, it was reduced with NaBH₄ in MeOH to afford alcohols 17 and 18 in 91% yield and equal amounts,¹⁷ which were separated by column chromatography. Hydrogenation of α-alcohol 17 proceeded smoothly and stereoselectively, affording an inseparable mixture of 19 and 20 in excellent yield (95%) and with 6:7:1 diastereoselectivity, which was oxidized with MnO₂, affording ketones 21 and 22 in 92% yield in the same ratio. Though hydrogenation of β-alcohol 18 proceeded slowly, the reduced products 23 and 24 were obtained in 96% yield with the desired isomer predominating (4:6:1 diastereoselectivity). Oxidation of alcohols 23 and 24 with MnO₂ gave 21 and 22 in 75% yield.

(15) Origin of the stereoselective formation of 14 is not clear at the moment.

Table 1. Intramolecular Cyclization of 4t and 4c

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent</th>
<th>SM</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene, reflux, 12 h</td>
<td>4t</td>
<td>NR *</td>
</tr>
<tr>
<td>2</td>
<td>TFA/CH₂Cl₂, RT, 1 h</td>
<td>4t</td>
<td>NR *</td>
</tr>
<tr>
<td>3</td>
<td>NaH, THF, RT, 12 h</td>
<td>4t</td>
<td>Decomposition of 4t</td>
</tr>
<tr>
<td>4</td>
<td>NIS, NaHCO₃, THF/H₂O, RT, 1 h</td>
<td>4t</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1) Hg(OTf)₂, MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl</td>
<td>4t</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1) Hg(OTf)₂, MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl</td>
<td>4c</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pd(PhCN)₂Cl₂, p-benzoquinone THF, RT, 24 h</td>
<td>4t</td>
<td></td>
</tr>
</tbody>
</table>

* Starting material.  * No reaction.  * TFA/CH₂Cl₂ = 1:10.  * 10 mol % was employed.
in a 4.6:1 ratio, and these were easily separated by thin-layer chromatography.

Removal of the TBS group of 21 afforded ent-EI-1941-2 in 86% yield. Synthetic ent-EI-1941-2 exhibited properties identical to those of the natural product except for the optical rotation, which was of opposite sign, indicating that the synthetic compound is the enantiomer of EI-1941-2.3,4

Epi-ent-EI-1941-2 was also prepared stereoselectively from carboxymercurated derivative 14. Though conventional de-mercuration using Bu3SnH in the presence of AIBN18 did not work, affording 4t, we found that the treatment of 14 with Zn powder in MeOH and AcOH19 gave β,γ-unsaturated lactone 25. After removal of the TBS group, to give alcohol 26, treatment of this with a catalytic amount of amine isomerized the double bond to provide epi-ent-EI-1941-2 in 67% yield (Scheme 4).

In summary, we have accomplished the first asymmetric total synthesis of ent-EI-1941-2 and epi-ent-EI-1941-2, starting from the chiral epoxy iodoquinone 6, a key intermediate in our total synthesis of epoxyquinols A and B. A key step is the intramolecular, metal-mediated carboxylation of an alkene via the 6-endo cyclization mode, in which Pd(II) gave a 2H-pyran-2-one via β-hydride elimination, affording ent-EI-1941-2 after stereoselective hydrogenation, while Hg(OTf)2 afforded a carboxymercurated product of side-chain relative stereochemistry opposite to that of the natural product, leading eventually to epi-ent-EI-1941-2 with high diastereoselectivity. We are currently investigating the synthesis of the natural enantiomer EI-1941-2, as well as that of EI-1941-1, the full accounts of which will be described shortly.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of 1H and 13C NMR and IR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.


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