Studies on Iljimalide B. Preparation of the Seco-Acid and Identification of the Molecule’s “Achilles Heel”

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Preparation of Sulfone 5

\[
\text{HO-}COO\text{Me} \xrightarrow{a)} \text{S-1} \quad \text{S-2} \xrightarrow{b)} \text{S-3} \xrightarrow{c)} \text{5}
\]

\[
\text{S-4} \quad (E:Z = 25:75) \quad \text{S-4 (E)} \quad \text{S-4} \quad \text{COOEt}
\]

**Scheme S-1.** a) Benzothiazol-2-thiol (BTSH), PPh\(_3\), DEAD, THF, quant; b) Dibal-H, CH\(_2\)Cl\(_2\), −78°C; c) 2-phosphonopropionic acid triethylster, LiHMDS, THF, −78°C → −40°C, 80% (over both steps); d) PhSSPh (0.5 eq.), AIBN cat., THF, reflux, quant.; e) Mo\(_7\)O\(_{24}\)(NH\(_4\))\(_6\)\(_4\) H\(_2\)O cat., aq. H\(_2\)O\(_2\), EtOH, 98%.

The preparation of the required building blocks commenced with a Mitsunobu reaction\(^1\) of Roche ester S-1 with 2-mercapto-benzothiazole (BTSH), furnishing product S-2 which was reduced with Dibal-H to afford the corresponding aldehyde S-3. Despite considerable experimentation, olefination of crude S-3 by a Horner-Wadsworth-Emmons reaction

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invariably delivered the \((Z)\)-rather than the required \((E)\)-isomer as the major product. The best results were obtained with LiHMDS (1.2 equiv.) as the base (80%, \(Z:E = 75:25\)), whereas the choice of other bases or the application of the Masamune-Roush protocol\(^2\) led to largely inferior yields. The unfavorable stereochemical outcome of the reaction was conveniently corrected by isomerization of the crude mixture of \(S-4\) with PhSSPh/AIBN in refluxing THF.\(^3\) Although this process was rather slow (4d), the required product was obtained in geometrically almost pure form (\(E:Z = 95:5\)). Subsequent oxidation of the sulfide group gave sulfone \(5\) which reacted smoothly with aldehyde \(6\) (see below) to give alkene \(7\) as described in the Text of the paper.

**Preparation of Aldehyde 6**

\[
\begin{align*}
S-5 & \xrightarrow{a)} S-6 \xrightarrow{b)} S-7 \xrightarrow{c)} S-8 \\
d) & \xrightarrow{d)} S-9 \xrightarrow{e)} S-10 \xrightarrow{f)} 6
\end{align*}
\]

**Scheme S-2.** a) \(\text{Ag}_2\text{O}, \text{Mel, MeCN, reflux}\); b) Dibal-H, CH\(_2\)Cl\(_2\), \(-78^\circ\text{C}\); c) Ph\(_3\)P=\(\text{C(\text{Me})COOEt}, \text{toluene, 70}^\circ\text{C, 62\% (over 3 steps)}\); d) TBSCI, Et\(_3\)N, DMAP cat., CH\(_2\)Cl\(_2\), RT, 99%; e) Dibal-H, CH\(_2\)Cl\(_2\), \(-78^\circ\text{C, 95\%}\); f) DMSO, (COCl\(_2\), Et\(_3\)N, CH\(_2\)Cl\(_2\), \(-78^\circ\text{C} \rightarrow \text{RT, 95\%}\).

Aldehyde \(6\) was prepared on large scale from commercial lactone \(S-5\) by adapting a literature route.\(^4\) Specifically, compound \(S-5\) was converted into the corresponding methyl ether \(S-6\) on treatment with \(\text{Mel and Ag}_2\text{O}\). Subsequent Dibal-H reduction gave lactol \(S-7\)

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which was immediately subjected to a standard Wittig reaction with the stabilized ylide Ph₃P=C(Me)COOEt to give enoate S-8 as a single isomer. Protection of the -OH group as a TBS-ether prior to reduction of the ester in S-9 and reoxidation of the primary alcohol of the resulting product S-10 readily furnished the required aldehyde 6.

**Preparation of Ketone 17**

![Scheme S-3](image)

**Scheme S-3.** a) Bis(trimethylsilyl)acetylene, AlCl₃, CH₂Cl₂, 0°C, 83%.

Ketone 17 as the substrate for the Noyori transfer hydrogenation was prepared by an AlCl₃-mediated reaction of acid chloride S-11 with commercial bis-trimethylsilylethyne. The required mono-substitution product was obtained in 83% yield on a >16 g scale after convenient purification by Kugelrohr distillation.⁵

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