



Supporting Information

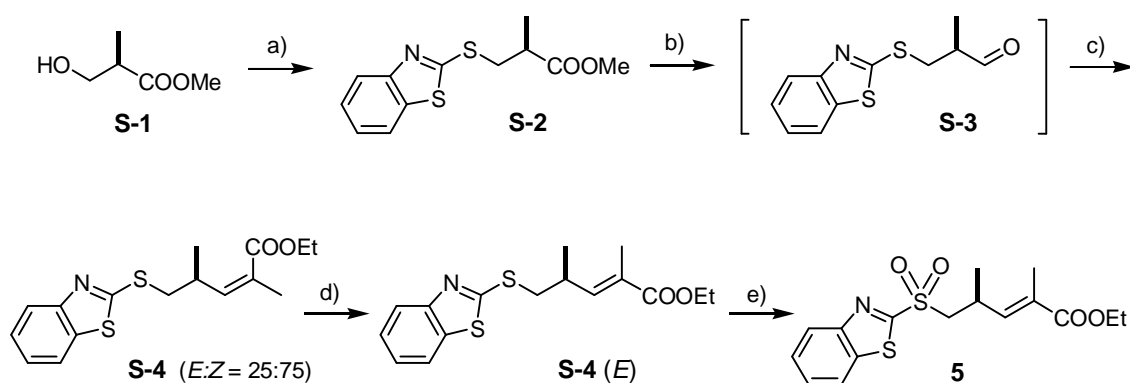
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Studies on lejimalide B. Preparation of the Seco-Acid and Identification of the Molecule's "Achilles Heel"

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Preparation of Sulfone 5



Scheme S-1. a) Benzothiazol-2-thiol (BTSH), PPh₃, DEAD, THF, quant; b) Dibal-H, CH₂Cl₂, -78°C; c) 2-phosphonopropionic acid triethylester, LiHMDS, THF, -78°C → -40°C, 80% (over both steps); d) PhSSPh (0.5 eq.), AIBN cat., THF, reflux, quant.; e) Mo₇O₂₄(NH₄)₆·4 H₂O cat., aq. H₂O₂, EtOH, 98%.

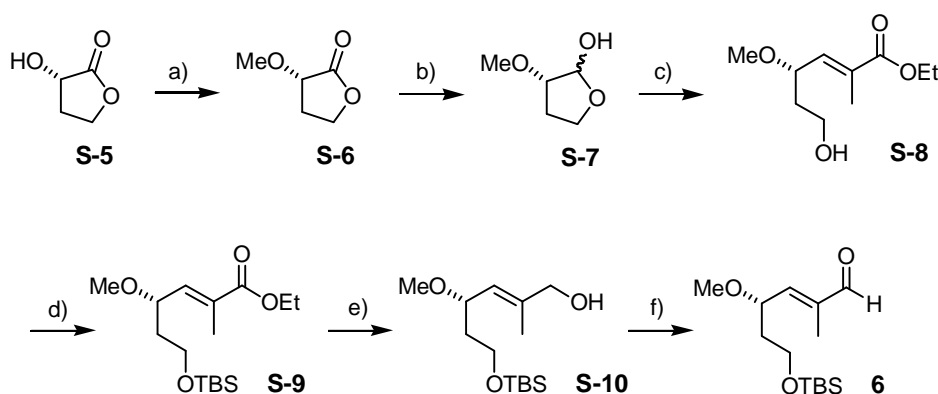
The preparation of the required building blocks commenced with a Mitsunobu reaction¹ of Roche ester **S-1** with 2-mercapto-benzothiazole (BTSH), furnishing product **S-2** which was reduced with Dibal-H to afford the corresponding aldehyde **S-3**. Despite considerable experimentation, olefination of crude **S-3** by a Horner-Wadsworth-Emmons reaction

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¹ O. Mitsunobu, *Synthesis* **1981**, 1-28.

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 protocol² 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



Scheme S-2. a) Ag_2O , MeI, MeCN, reflux; b) Dibal-H, CH_2Cl_2 , -78°C ; c) $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{COOEt}$, toluene, 70°C , 62% (over 3 steps); d) TBSCl, Et_3N , DMAP cat., CH_2Cl_2 , RT, 99%; e) Dibal-H, CH_2Cl_2 , -78°C , 95%; f) DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_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 MeI and Ag_2O . Subsequent Dibal-H reduction gave lactol S-7

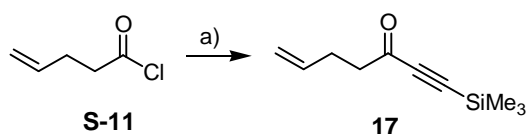
² M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essinfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, 25, 2183-2186.

³ For a related case see: A. J. Clark, J. M. Ellard, *Tetrahedron Lett.* **1998**, 39, 6033-6036.

⁴ M. T. Mendlik, M. Cottard, T. Rein, P. Helquist, *Tetrahedron Lett.* **1997**, 38, 6375-6378.

which was immediately subjected to a standard Wittig reaction with the stabilized ylide $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{COOEt}$ 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. a) Bis(trimethylsilyl)acetylene, AlCl_3 , CH_2Cl_2 , 0°C , 83%.

Ketone **17** as the substrate for the Noyori transfer hydrogenation was prepared by an AlCl_3 -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

⁵ R. Suzuki, H. Tsukuda, N. Watanabe, Y. Kuwatani, I. Ueda, *Tetrahedron* **1998**, *54*, 2477-2496.