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An Efficient Asymmetric Synthesis of the Mercaptopyrrolidine Side Chain of an Important β-Methyl Carbapenem Antibiotic

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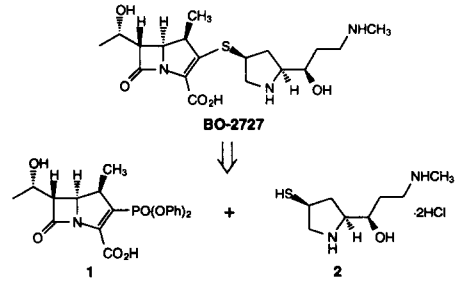
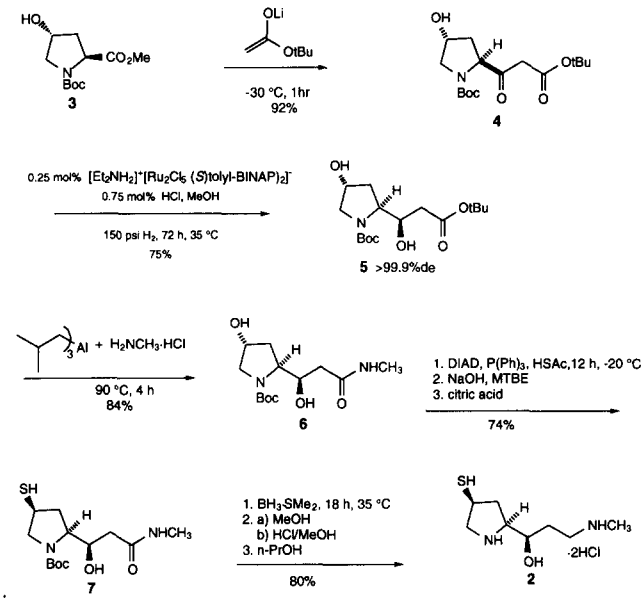
Abstract: *An efficient asymmetric synthesis of the mercaptopyrrolidine side chain 2 1s described. The β-ketoester 4 is hydrogenated diastereoselectively to give the (R)-β-hydroxyester 5. The remaining functional groups are installed via a thiol Mitsunobu reaction and a reduction of a secondary amide to produce 2 in 34% overall yield from BOC-L-trans-4-hydroxyproline methylester 3 (Scheme 1).* © 1997 Elsevier Science Ltd.

BO-2727[1] is an important β-methyl carbapenem antibiotic candidate that obviates the coadministration of the β-lactamase inhibitor cilistatin[2] and is currently in extended clinical trials in Japan. In a retrosynthetic analysis, BO-2727 can be divided into two intermediates, the β-methyl β-lactam moiety **1** and the mercaptopyrrolidine side chain **2**. This paper describes an efficient asymmetric synthesis of the side chain **2**, from the readily avaible BOC-*L*-trans-4-hydroxyproline methylester **3**. The synthesis is highlighted by an asymmetric hydrogenation of a β-keto ester, a selective thiol Mitsunobu reaction[3] and a borane reduction/deprotection/crystallization sequence that produces **2** in 34% overall yield from **3** (Scheme 1). The synthesis is free of chromatographic purifications and is amenable to kilo-scale production.



To convert the key intermediate β-ketoester **4** to **2**, the C-3 hydroxyl group, the C-6 thiol moiety and the secondary methyl amine have to be installed stereo- and regioselectively. Preparation of the β-keto ester **4** via the Claisen condensation[4] required five equivalents of the enolate of *t* -butyl acetate, formed with lithium hexamethyldisilylazide in tetrahydrofuran at -40 °C. One equivalent of the lithium enolate was used to form the lithium alkoxide of **3**, which served as an *in situ* alcohol protecting group. Excess of the enolate was required to compensate for the loss of the reagent due to decomposition to ketene and *t*-butylacetoacetate as well as subsequent deprotonation of the product **4**. With the addition of the methyl ester **3** to the enolate at -30 °C, the reaction was complete in 30 minutes. The reaction was quenched by the addition of a citric acid solution and the product was extracted into tetrahydrofuran/heptanes. Due to the instability of the β-keto ester **4** (crude

reaction mixtures of **4** showed 14% decomposition to methyl ketone in 42h at 40 °C), temperatures were maintained below 35 °C throughout the isolation and vacuum distillation. β-Keto ester **4** was isolated in 92% yield (98 wt% purity) by crystallization by addition of heptanes.



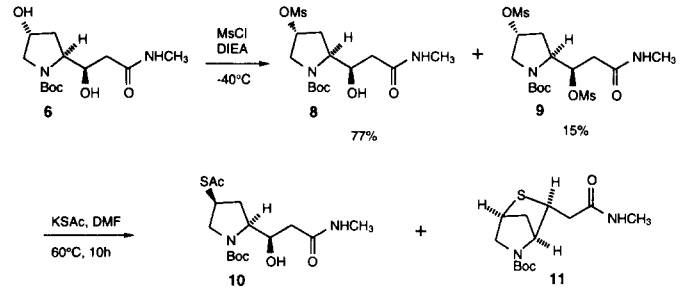
Scheme 1

The second step in the synthesis generates the desired (*R*)-β-hydroxy ester **5**. An asymmetric bioreduction process for this conversion has alresdy been described,[5] but a more robust process amenable to hundreds of kilos was needed. Noyori and coworkers reported that the asymmetric hydrogenation of statine β-keto ester analogs gives the matched (>99:1 diastereoselectivity) and the mismatched (85:15 diastereoselectivity) (*R*)/(*S*)-β-hydroxy esters with (*R*)-BINAP and (*S*)-BINAP respectively.[6] Hydrogenation of **4** with the $RuCl_2\{[(R)\text{-BINAP}]\}_2{\cdot}Et_2NH$ catalyst (matched case) and the $RuCl_2\{[(S)\text{-BINAP}]\}_2{\cdot}Et_2NH$ catalyst (mismatched case) generated the undesired (*S*) β-hydroxy ester in >99:1 diastereoselectivity and the desired (*R*) β-hydroxy ester in 88:12 diastereoselectivity respectively. For the large scale reaction the commercially availble (*S*)-tolylBINAP ligand (purchased from Takasago) was used. The β-keto ester **4** was dissolved in methanol (1.5 mL MeOH/1.0 g **4**) and the solution was purged with nitrogen prior to addition of the $RuCl_2\{[(S)\text{-tolylBINAP}]\}_2{\cdot}Et_2NH$ catalyst (0.25 mol%), and hydrogen chloride (0.75 mol%). The amount of hydrogen chloride, volume of dry methanol, and temperature were minimized to reduce the rate of transesterification of the starting material and the product to their respective methyl esters without hindering the rate of hydrogenation. Thorough degassing of the methanol and β-ketoester solution before the addition of the catalyst and HCl eliminates the risk of catalyst oxidation. The reaction progressed to completion in 72 h at 35 °C and 150 psi hydrogen. The (*R*) β-hydroxy ester **5** was crystallized directly from the reaction mixture by the addition of water (75% yield in >99.9% de).

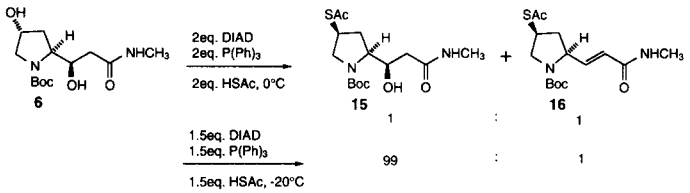
Amidation of the (*R*) β-hydroxy ester **5** with the Weinreb reagent (*iso*-butyl chloro methylamine aluminum) generated the diol amide **6** in 84% yield and >97wt % purity.[7] The Weinreb reagent was prepared from the reaction of 3.1 eq. of triisobutylaluminum (0.87M in hexane) and 3.1 eq. of methylamine

hydrochloride in THF giving a 2:1 hexanes:tetrahydrofuran solution. The hexane must be removed prior to reaction with the (*R*) β-hydroxy ester **5** in order to prevent gel formation. Likewise, triisobutylaluminum was chosen over triethylaluminum due to gel formation with the latter reagent even in THF. The concentration of the Weinreb reagent in the THF solution was quantified by a use-test (percent conversion of **5** to **6**) due to the lack of an alternative assay method. The reaction was quenched and extracted with saturated aqueous sodium potassium tartrate solution due to the high water solubility of the diol amide **6**. Diol amide **6** crystallized during azeotropic distillation with isopropyl acetate (IPAc).

Conversion of diol amide **6** to the desired thiol amide **7** requires the selective activation of the C-7 hydroxyl in the presence of the C-3 hydroxyl and subsequent displacement with a thiol nucleophile. Initially the hydroxyl was activated as the mesylate **8**, but bis-mesylation occurred in 15-20% yield.[8] Displacement of the mesylates with potassium thiol acetate generated two major products: the desired thiol amide **10** and the bicyclic sulfide **11**. Attempts to remove the bicyclic sulfide **11** and/or the bis-mesylate **9** were unsuccessful.



Selective activation and thiol displacement of the C-7 hydroxyl group was most efficiently accomplished via the thiol-Mitsunobu reaction.[3] Initially the thiol-Mitsunobu reaction was perfomed at 0 °C in THF with 2 eq. diisopropyl azodicarboxylate, 2 eq. $P(Ph)_3$ and 2 eq. of thiolacetic acid. Two products were formed in 85% yield: the desired thiol acetate **15** and the α,β-unsaturated amide **16**. However, when the temperature was lowered to -20 °C, the desired thiol acetate was produced with >99:1 selectivity.



The resulting thiolacetate was saponified with aqueous NaOH, which allowed easy separation of the desired sodium thiolate from the non water soluble by-products, triphenylphosphine oxide and diisopropylhydrazodicarboxylate. The reaction was run with approximately 1.5 equivalents each of triphenylphosphine, diisopropylazodicarboxylate, and thiolacetic acid; the excess reagents were quenched by the addition of methanol prior to saponification with NaOH.

Unmasking of the methyl amine surrogate, **7**, was accomplished via reduction with borane dimethylsulfide (2.4 eq.) in dimethoxyethane at 35°C for 18h (>95% conversion as determined by ^1H NMR).[8] Excess borane was quenched by the addition of methanol and 6.8 equivalents of HCl was bubbled into the

mixture (HCl effects both t-BOC deprotection and hydrolyzes the intermediate boron complexes). After concentration via simple distillation [removes boron as $B(OMe)_3$] and crystallization from *n*-PrOH, bis-HCl salt **2** (95% purity by ^1H NMR) was isolated in 80% yield from thiol amide **7**.

In summary we have described an efficient asymmetric synthesis of the bis-HCl salt of side chain **2** from **3** in 34% overall yield. This robust process was implemented to produce 225 Kg of (*R*) β-hydroxy ester **5** and a portion was carried through to generate 25 Kg of the bis-HCl salt **2**.

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