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Regioselective Opening of Chiral Hydroxy Epoxides: A Short Route to Muricatacin and its Diastereomer *epi*-Muricatacin

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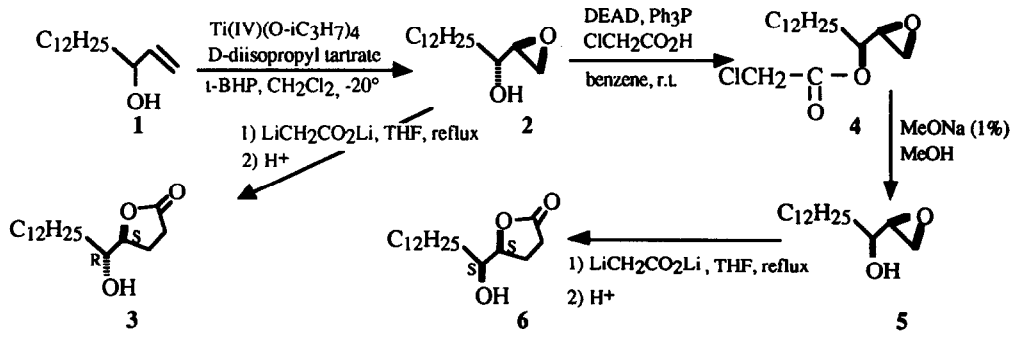
Abstract: The dilithioacetate opening of chiral epoxides, obtained by the Sharpless asymmetric epoxidation procedure, led regiospecifically to the corresponding hydroxy γ-lactones thus opening a short route to epi-muricatacin and muricatacin.

There has been a recent growing interest in the synthesis of substituted hydroxy γ-lactones as important starting material for the synthesis of a variety of natural products, and also as they have been found in many bioactive natural products.[1] Among them muricatacin (**6**) has received a particular interest as a natural antitumor and pesticidal molecule, extracted from the seeds and bark of the tropical plant *Annona muricata*.[2] Recent multistep syntheses of this type of compound include the use of chiral starting material such as carbohydrates,[3a] or amino-acids,[3b] or involve stereoselective reductions of achiral carbonyl substrates.[4] Very recently the asymmetric dihydroxylation of γ, δ-unsaturated esters was described.[5]

As part of our current interest in the asymmetric synthesis of natural products, we describe here a short synthesis of epi-(4S, 5R)-muricatacin and its diastereomer (+)-(4S, 5S)-muricatacin in respectively three and five steps from dodecyl bromide. The allylic alcohol **1**, (Scheme) obtained by the Grignard reaction of dodecyl magnesium bromide with acrolein, was subjected to the Sharpless epoxidation procedure[7] in the conditions of kinetic resolution and in the presence of D-diisopropyl tartrate to give the (2S, 3R) epoxy alcohol **2** (95% resolution yield). The latter when treated with the dilithioacetate dianion[8] gave the intermediate lithium carboxylate which upon acidification[9] led to epi-(4S, 5R)-muricatacin **3** (60% yield, m.p. 68°C, lit.[3b] 67°C, $[\alpha]_D$= +34.5 (c= 0.4 $CHCl_3$), lit.[3b] +32 (c= 2 $CHCl_3$)).



On the other hand, the epoxy alcohol **2** was inverted by the Mitsunobu reaction,[10] using chloroacetic acid[11] to give the (2S, 3S)- epoxy chloroacetate **4** (90% yield). Subsequent deacylation with 1% sodium methoxide in methanol led quantitatively to compound **5**, which was then reacted with dilithium acetate and acidified to give (+)-(4S, 5S)-muricatacin **6** (65% yield, mp. 72°C, lit.[6] 73-74°C, $[\alpha]_D$= +25 (c= 0.6 $CHCl_3$), lit.[6] +23.02° (c= 1.26 $CHCl_3$)). N.m.r. data[12] for **3** and **6** matched with the reported data.[3b, 6]

The configurations of epoxides **2** and **5** were maintained during the nucleophilic attack of the dilithioacetate anion, as confirmed by ^1H and ^{13}C Nmr studies and by ^{31}P Nmr studies of the corresponding phosphonates.[13] No diastereomers could be detected by ^{13}C nmr, and the results of the ^{31}P resonance studies of the phosphonates were consistant with enantiomeric excesses of >98%.

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9. Typical procedure for the opening of the epoxides: To an ice-cooled solution of LDA (10mmol) in THF (20mL), dry acetic acid (0.286 mL, 5mmol) was added with stirring. After 30 min. the epoxy alcohol **5** (0.242g, 1mmol) was added and the mixture stirred overnight under reflux. It was then cooled, acidified with saturated aqueous sodium hydrogen sulfate and extracted with ether (2 x 5mL). The combined extracts were concentrated and treated with p-toluene sulfonic acid (0.05eq in benzene, 10mL, reflux) for 1 hour. The cooled solution was then washed with an aqueous solution of sodium hydrogen carbonate, dried and concentrated. The residue cristallised in a pentane/ether mixture to give (0.185g, 65%) of pure (+)-muricatacin (**6**).
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12. **1**: ^1H NMR: 5.85 (m, 1H), 5.16 (m, 2H), 4.1 (m, 1H), 2.58 (t, J= 6Hz, 1H), 1.6-1.15 (m, 22H), 0.9 (t, J= 6.5Hz, 3H). mp. 25°C. **2**: ^1H NMR: 3.85 (m, 1H), 3.02 (dd, J= 3.1, 7Hz, 1H), 2.81 (dd, J= 2.8, 5.1Hz, 1H), 2.72 (dd, J= 4.8Hz, 1H), 1.7-1.2 (m, 22H), 0.86 (t, J= 6.4Hz, 3H). mp. 38°C, $[\alpha]_D$ -12,1 (c= 1, $CHCl_3$). **4**: ^1H NMR: 4.73 (dd, J= 6.6, 13Hz, 1H), 4.08 (s, 2H), 3.08 (m, 1H), 2.84 (t, J= 4.7Hz, 1H), 2.65 (dd, J= 2.5, 4.7Hz, 1H), 1.7 (m, 2H), 1.6-1.2 (m, 20H), 0.87 (t, J= 6.2Hz, 3H). **5**: ^1H NMR: 3.45 (m,1H), 2.98 (dd, J= 4.4, 8.7Hz, 1H), 2.84 (dd, J= 4.8Hz, 1H), 2.72 (dd, J= 2.8, 4.8Hz, 1H), 1.85 (d, J= 6.4Hz, 1H), 1.6 (m, 2H), 1.5-1.2 (m, 20H), 0.88 (t, J= 6Hz, 3H), mp. 44°C, $[\alpha]_D$= -2 (c= 1, $CHCl_3$). **3**: ^1H NMR: 4.45 (ddd, J= 3.2, 7.3, 10.5Hz, 1H), 3.95 (m, 1H), 2.57 (m, 2H), 2.3-2.0 (m, 2H), 1.8-1.2 (m, 22H), 0.88 (t, J= 6.5Hz, 3H). **6**: ^1H NMR: 4.42 (ddd, 4.6, 7.4, 12Hz, 1H), 3.56 (m, 1H), 2.56 (m, 2H), 2.30-2.0 (m, 2H), 1.55 (m, 2H), 1.45-1,1 (m, 20H), 0.88 (t, J= 6.5Hz, 3H).
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