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Asymmetric Synthesis of Both Enantiomers of Methyl and t-Butyl 3-Hydroxybutyrates Monitored by Optically Active Sulfoxides.

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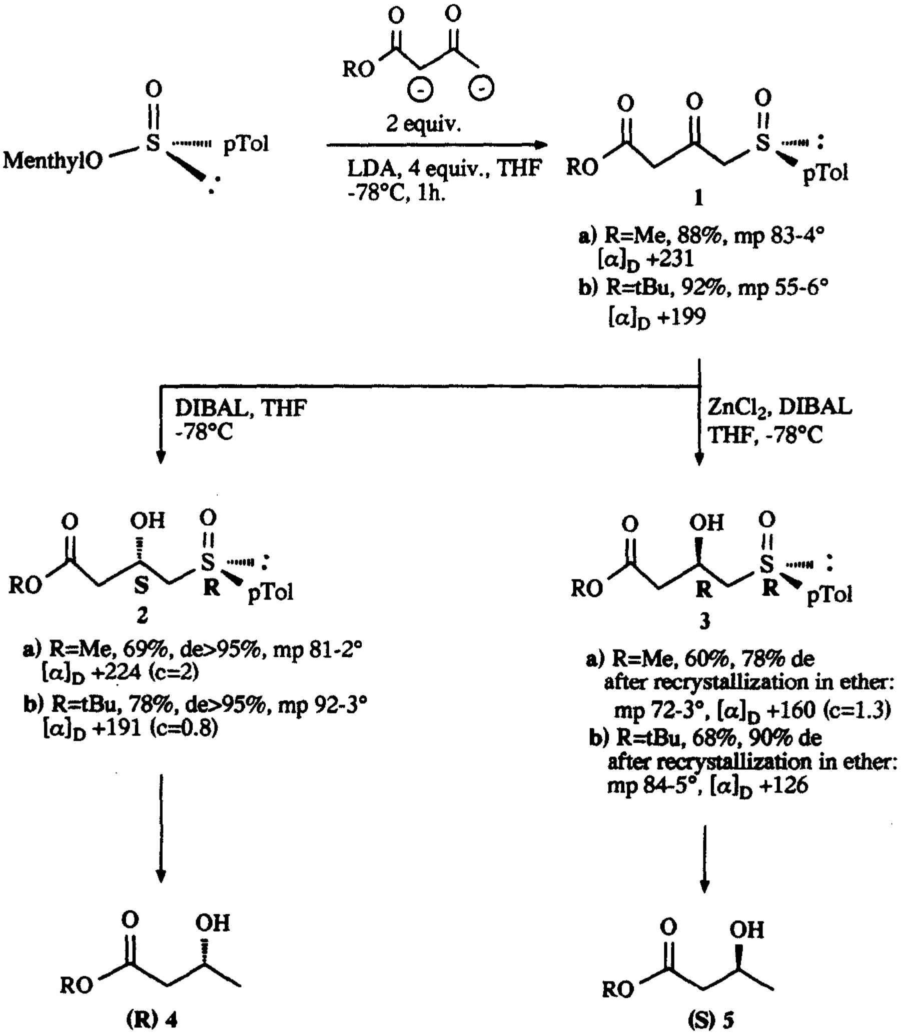
Abstract : Methyl and t-butyl (R) and (S) 3-hydroxybutyrates were prepared by stereoselective reduction of (R) 4-[p-tolylsulfinyl]-3-oxobutyrate, readily available in one step from (-)(S) menthyl p-toluene sulfinate.

Optically active 3-hydroxybutyric acid is a very useful chiral building block for natural product synthesis. Many applications have been reported in the literature : (S)(+) salcatol[1a], (R)(-) lavandulol[1b], (RR) pyrenophorin[1c], colletodiol[1d], (RR)(-) grahamimycin[1d], (R)(+) recifeiolide[1e], griseoviridin[1f], carbomycin B[1g], acosamine[1h], cladospolide A[1i].

In all these syntheses, (R)-3-hydroxybutyric acid was obtained either by optical resolution[2] or from the biopolymer PHB[3], and the (S) enantiomer by yeast reduction of acetoacetate[4]. Only one asymmetric synthesis of methyl 3-hydroxybutyrate was reported by Noyori[5], based on the asymmetric hydrogenation of methyl 3-ketobutyrate.

We report in this paper the asymmetric synthesis of methyl and t-butyl (R) and (S) 3-hydroxybutyrates based on the stereoselective reduction of optically active methyl and t-butyl (R) 4-[p-tolylsulfinyl]-3-oxobutyrates **1a** and **1b**, which can be prepared in one step from (S)(-) menthyl p-toluenesulfinate and commercially available methyl and t-butyl acetoacetates.

We found that (R) 4-sulfinyl-3-oxobutyric esters **1** could be readily prepared, at -78°C, in high yields (88 to 92%) from (-)(S) menthyl p-toluenesulfinate[6] and the dianion of the corresponding acetoacetate, obtained with LDA in THF at 0°C. It was shown by ^1H NMR that in $CDCl_3$ the carbonyl in **1** was partially enolized (about 30%) : the AB pattern at 3.97 ppm corresponding to the methylene group α to the sulfoxide was partially replaced by a singlet at 5.1 ppm due to one vinylic hydrogen.



1

a) R=Me, 88%, mp 83-4°
$[\alpha]_D$ +231
b) R=tBu, 92%, mp 55-6°
$[\alpha]_D$ +199

2

a) R=Me, 69%, de>95%, mp 81-2°
$[\alpha]_D$ +224 (c=2)
b) R=tBu, 78%, de>95%, mp 92-3°
$[\alpha]_D$ +191 (c=0.8)

3

a) R=Me, 60%, 78% de
after recrystallization in ether:
mp 72-3°, $[\alpha]_D$ +160 (c=1.3)
b) R=tBu, 68%, 90% de
after recrystallization in ether:
mp 84-5°, $[\alpha]_D$ +126

(R) 4

a) R=Me, 90%, $[\alpha]_D$ -47
(lit.[3b] $[\alpha]_D$ -48), 97% ee.
b) R=tBu, 82%, $[\alpha]_D$ -36
(lit.[3b] $[\alpha]_D$ -36).

(S) 5

a) R=Me, 81%, $[\alpha]_D$ +47
97% ee.
b) R=tBu, 85%, $[\alpha]_D$ -35
98% ee.

**yields are given for isolated products, all $[\alpha]_D$ in $CHCl_3$, at c=1 unless otherwise indicated.*

The reduction of the ß-ketosulfoxides 1 was carried out by the method we already described[7]. With DIBAL in THF, (SR) ß-hydroxysulfoxides **2a** and **2b** were obtained in 69% and 78% respectively. A diastereoselectivity, higher than 95%, was determined by proton NMR from the methoxy singlet in **2a** and from the methylene group α to the ester group in **2b** [giving a doublet in the (SR) diastereomer and an AB pattern in the (RR) diastereomer][8]. Desulfurization with Raney Nickel gave methyl (R)(-) 3-hydroxybutyrate **4a** in 90% yield and t-butyl (R)(-) 3-hydroxybutyrate **4b** in 82% yield. The optical rotation of these known hydroxyesters confirm their high optical purity and absolute configuration[3b].

Reduction of 1 with DIBAL in presence of zinc chloride yielded the (RR) ß-hydroxysulfoxides **3a** and **3b** respectively in 60 and 68% yield and 78 and 90% de[9]. The lower de observed in that cases could be due to a competitive chelation of the sulfinyl oxygen and the ester group in the chelate formed with zinc chloride[7]. This competition is however less efficient in the case of the bulky t-butyl ester. One recrystallization in ether gave optically pure β-hydroxysulfoxides 3, as shown by NMR. Finally desulfurization of **3a** and **3b** lead to methyl and t-butyl (S)(+) 3-hydroxybutyrates in more than 80% yield.

It can be noted also that the chemical yields for the reduction step with DIBAL or $ZnCl_2$/DIBAL are not as high as usual and that always some starting ß-ketosulfoxide is recovered (between 15 to 20%). This is probably due to the presence of some enolized ß-ketosulfoxide as we mentioned earlier, which is not reduced in the reaction conditions, being quenched immediately by DIBAL as an aluminium salt.

In conclusion the method we described in this paper allowed the preparation of optically pure t-butyl (R) 3-hydroxybutyrate in 3 steps from t-butyl acetoacetate. For the (S) enantiomer one recrystallisation of the ß-hydroxysulfoxide **3b** in ether is necessary to get the optically pure isomer.

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8) ^{1}H NMR ($CDCl_3$, 200MHz) of **2a**: δ: 7.52 and 7.32 (AA'BB', 4 arom. H, J=8.2Hz), 4.6 (X of ABX, 1H, H_3), 4.5 (broad s, 1H, OH), 3.65 (s, 3H, OCH_3), 2.91 (AB of ABX, 2H, H_4, J_{AB}=13.5Hz, J_{AX}=9.5Hz, J_{BX}=2.5Hz, $\Delta\nu$=46Hz), 2.56 (d, 2H, H_2, J=6.1Hz), 2.40 (s, 3H, CH_3).
^{1}H NMR ($CDCl_3$, 200MHz) of **2b**: δ: 7.54 and 7.34 (AA'BB', 4 arom. H, J=8Hz), 4.5 (X of ABX, 1H, H_3), 4.1 (d, 1H, OH, J=3.45Hz), 2.87 (AB of ABX, 2H, H_4, J_{AB}=13.4Hz, J_{AX}=9.8Hz, J_{BX}=2.3Hz, $\Delta\nu$=45.4Hz), 2.46 (d, 2H, H_2, J=6.3Hz), 2.42 (s,3H,CH_3), 1.42 (s,9H, tButyl).

9) ^{1}H NMR ($CDCl_3$, 200MHz) of **3a**: δ : 7.53 and 7.31 (AA'BB', 4 arom. H, J=8.2Hz), 4.5 (X of ABX, 1H, H_3), 4.2 (broad s, 1H, OH), 3.66 (s, 3H, OCH_3), 2.98 (AB of ABX, 2H, H_4, J_{AB}=13.1Hz, J_{AX}=8Hz, J_{BX}=3.9Hz, $\Delta\nu$=29Hz), 2.63 (AB of ABX, 2H, H_2, J_{AB}=16Hz, J_{AX}=7Hz, J_{BX}=5Hz, $\Delta\nu$=19.7Hz), 2.4 (s, 3H, CH_3).
^{1}H NMR (CDCl3, 200MHz) of **3b**: δ : 7.54 and 7.32 (AA'BB', 4arom. H, J=8.2Hz), 4.4 (X of ABX, 1H, H_3), 4.1 (broad s, 1H, OH), 2.96 (AB of ABX, 2H, H_4, J_{AB}=13.1Hz, J_{AX}=8Hz, J_{BX}=3.9Hz, $\Delta\nu$=33Hz), 2.54 (AB of ABX, 2H, H_2, J_{AB}=16.4Hz, J_{AX}=7.3Hz, J_{BX}=5.3Hz, $\Delta\nu$=22Hz), 2.4 (s, 3H, CH_3), 1.42 (s, 9H, t-Butyl).

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