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Asymmetric Synthesis of both Enantiomers of 2.5-Hexane Diol and 2.6-Heptane Diol Induced by Chiral Sulfoxides.

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***Abstract** : both enantiomers of 2,5-hexane diol and 2,6-heptane diol have been prepared respectively by stereoselective reduction of optically active diketodisulfoxides and ketosulfoxides.*

Optically active 2,5-dimethylpyrrolidine has been employed frequently as a chiral auxiliary of C_2 symmetry in enantioselective reactions. (R,R) and (S,S)-2,5-hexane diols [1] are the usual precursors of 2,5-dimethylpyrrolidine [2]. Similarly, (R,R) and (S,S)-2,6-heptane diols can be considered as precursors of optically active 2,6-dimethylpiperidine.

We report in this paper the enantioselective synthesis of both enantiomers of 2,5-hexane diol , **1** and 2,6-heptane diol , **2** based on the stereoselective reduction of β-ketosulfoxides [3].

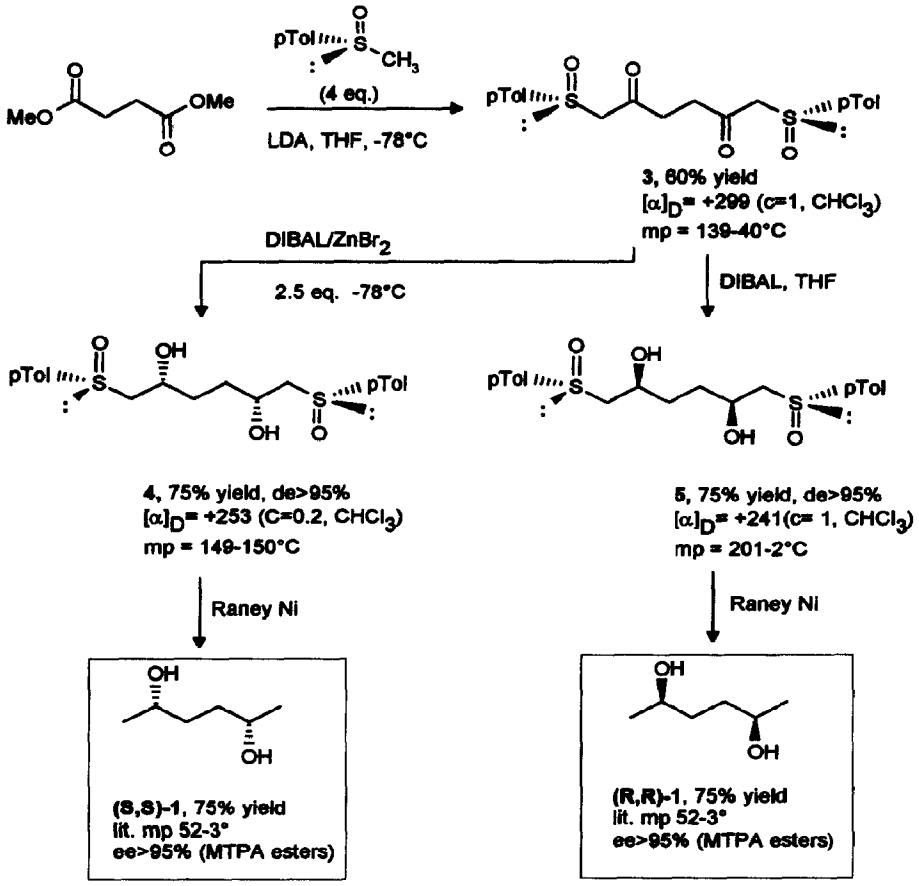
The C_2 symmetry of the diol **1** allows their synthesis by reduction of the corresponding diketodisulfoxide **3** either with DIBAL or $ZnBr_2$/DIBAL [4].

(R,R)-Diketodisulfoxide **3** was readily prepared from methyl succinate and (+)-(R) methyl p-tolylsulfoxide [5] (scheme I). DIBAL reduction of **3** gave as expected only one diastereomer, **5**, as shown by its NMR spectrum having only one set of signals, particularly for the AB protons α to the sulfoxide groups [6]. It must be pointed out that the diketodisulfoxide **3** must be added to the DIBAL solution (reverse addition) [3d].

The stereochemistry of the hydroxylic centers was expected to be (S,S) from our preceeding results [3] and confirmed by desulfurization to the known (R,R) 2,5-hexane diol [1a, 2c]

$ZnBr_2$/DIBAL reduction of **3** afforded similarly only the other diastereomer **4** as the unique product [7] which after desulfurization with Raney Nickel lead to the known (S,S) 2,5-hexane diol [1a, 2b,c].

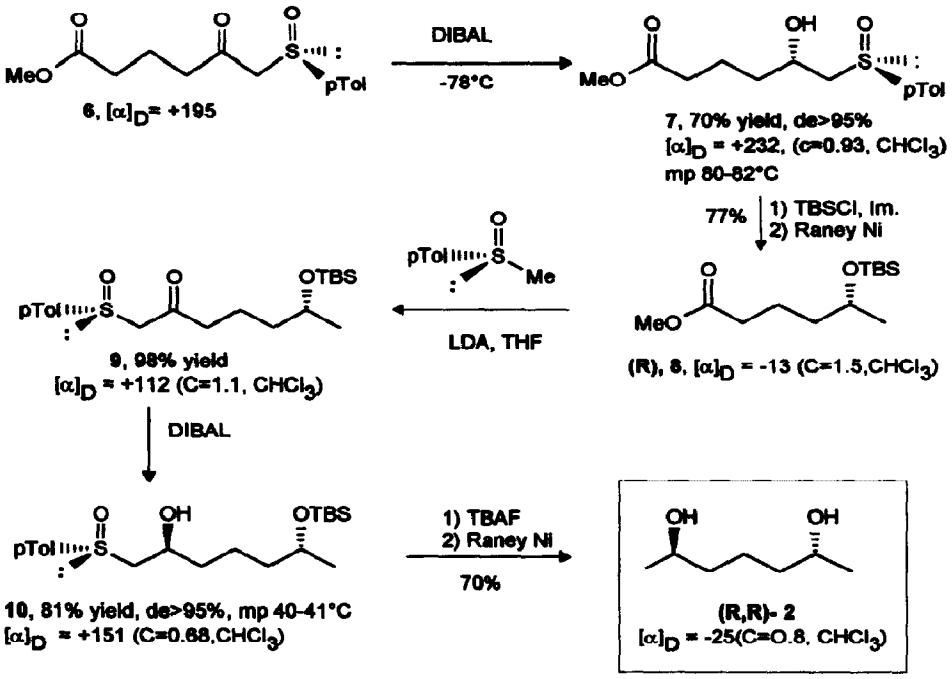
Scheme I



The same methodology could not be used to prepare optically pure 2,6-heptane diol because it was impossible to synthesize the corresponding diketodisulfoxide from methyl glutarate. The reaction of this diester with 2 equivalents of (+)-(R) methyl p-tolylsulfoxide anion gave mainly cyclized products in this strongly basic medium. Therefore the synthetic approach was modified to a multi step process : introduction of a first ketosulfoxide functionality from glutaric anhydride, reduction of the carbonyl, desulfurization and introduction of the second ketosulfoxide moiety.

The synthesis of the ketosulfoxide **6** was already reported for the enantioselective reduction of zearalenone [8]. Reduction of the ketosulfoxide **6** with DIBAL gave the β-hydroxysulfoxide **7** with an S configuration at the hydroxylic center [3] (d.e > 95%, deduced from the NMR spectrum [9]) (scheme II). The (R) hydroxyester **8** was obtained by protecting the OH group with a TBS group followed by desulfurization. (R)-**8** was finally reacted with (+)(R) methyl p-tolylsulfoxide and the resulting ketosulfoxide **9** reduced with DIBAL (d.e > 95%, determined by NMR [10]), deprotected with TBAF and desulfurized to give (R,R)-2,6-heptane diol **2**.

Scheme II



(S,S) 2,6-heptane diol 2 was obtained by a very similar route. The reduction with $ZnBr_2$/DIBAL of the ketosulfoxide 6 and subsequent transformation to (+) methyl (5S)- [tert-butyldimethylsilyl) oxy] hexanoate 11 (scheme III) was already described [8]. The ester 11 was then allowed to react with (+)-(R) methyl p-tolyl sulfoxide anion to give the ketosulfoxide 12 in 94% yield, which was then reduced with $ZnCl_2$/DIBAL to the hydroxysulfoxide 13 (with the (R) configuration at the new hydroxylic center [3] , d.e > 95%, determined by NMR [11]). Finally (S,S)-2,6-heptane diol 2 was obtained by removing the protecting group followed by desulfurization.

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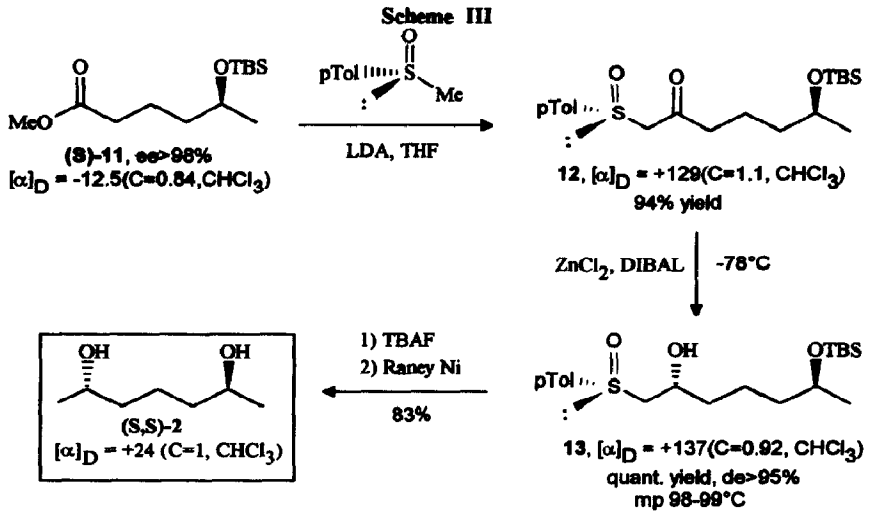
Scheme III



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6) ^{1}H NMR of **5** ($CDCl_3$, 200 MHz): δ: 1.56-1.90 (m, 4H, CH_2CO), 2.44 (s, 6H, Me), 2.94 (m, 4H, CH_2S), 4.41 (m, 2H, CHCO), 5.62 (br.s, 2H, OH), 7.27-7.44 (AA'BB', 8H, J= 8 Hz, arom.H). The ^{13}C NMR gave also only one set of signals corresponding to one diastereomer.

7) ^{1}H NMR of **4** ($CDCl_3$, 200 MHz): δ: 1.6-1.8 (m, 4H, CH_2CO), 2.45 (s, 6H, Me), 2.88 (AB of ABX, 4H, J_{AB}= 13Hz, J_{AX}= 9.5 Hz, J_{BX}=3 Hz, Δν = 40 Hz, CH_2S), 4.35 (m, 2H, X of ABX, CHCO), 4.5 (br.s, 2H, OH), 7.27-7.49 (AA'BB', 8H, J= 8 Hz, arom.H). The ^{13}C NMR gave also only one set of signals corresponding to one diasteromer.

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9) ^{1}H NMR of **7** ($CDCl_3$, 200 MHz): δ: -.1.4-1.8 (m,4H, H-3, H-4), 2.3 (t, 2H, J= 7 Hz, H-2), 2.42 (s, 3H, Me), 2.82 (AB of ABX, 2H, J_{AB}= 13 Hz, J_{AX}= 10 Hz, J_{BX}= 2Hz, Δν= 72 Hz, H-6), 3.65 (s, 3H, OMe), 4.2 (m, X of ABX, 1H, H-5), 7.36-7.5 (AA'BB', 4H, J= 8 Hz, arom.). The ^{13}C NMR gave also only one set of signals corresponding to one diastereomer.

10) ^{1}H NMR of **10** ($CDCl_3$, 200 MHz): δ: 0.01 and -0.008 (s, 6H, Me_2Si), 0.84 (s, 9H, tBuSi), 1.06 (d, 3H, J= 6 Hz, H-7), 1.2-1.6 (m, 6H, H-3, H-4, H-5), 2.41 (s, 3H, Me), 2.85 (AB of ABX, 2H, J_{AB}= 13 Hz, J_{AX}= 10 Hz, J_{BX}= 2Hz, Δν= 67 Hz , H-1), 3.69 (m, X of ABX, 1H, H-6), 4.05 (d, 1H, J= 3 Hz, OH), 4.13 (m, 1H, H-2), 7.32-7.5 (AA'BB', J= 8 Hz, 4H, arom.). The ^{13}C NMR gave also only one set of signals corresponding to one diastereomer.

11) ^{1}H NMR of **13** ($CDCl_3$, 200 MHz): δ: 0.03 (s, 6H, Me_2Si), 0.86 (s, 9H, tBuSi), 1.10 (d, 3H, J= 6 Hz, H-7), 1.35-1.6 (m, 6H, H-3, H-4, H-5), 2.41 (s, 3H, Me), 2.83 (AB of ABX, 2H, H-1, J_{AB}= 13 Hz, J_{AX}= 9 Hz, J_{BX}= 2Hz, Δν= 33 Hz), 3.76 (m, X of ABX, 1H, H-6), 3.83 (d, 1H, J= 2 Hz, OH), 4.27 (m, 1H, H-2), 7.33-7.53 (AA'BB', 4H, J= 8 Hz, arom.). The ^{13}C NMR gave also only one set of signals corresponding to one diastereomer.

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