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A Highly Stereoselective Route to the Four Stereoisomers of a Six-Carbon Synthon

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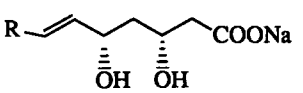
Abstract. The syntheses of chiral synthons **13-16** are described utilizing the chiral pool approach starting from either *S*- or *R*-malic acid

Suitably substituted 3,5-dihydroxy-6(E)-heptenoates **1** are potent HMG-CoA reductase inhibitors[1] and they are related to other hypocholesterolemic agents like compactin[2] and mevinolin[3] in having a β,δ-dihydroxy acid (or β-hydroxy-δ-lactone) as a common structural feature Heptenoates of the type **1** were generally



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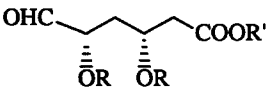

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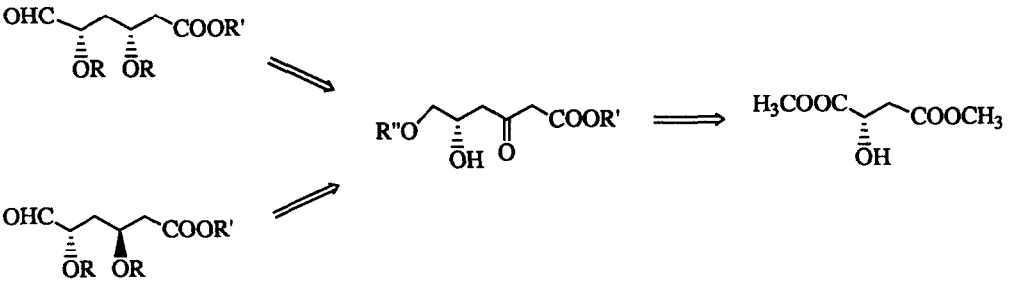
made, in the racemic form, by a linear approach involving the addition of the dianion derived from acetoacetate to a conjugated aldehyde During our investigations for an efficient and stereoselective synthesis of **1** and related compounds, we presented a unique strategy utilizing **2**, a racemic but diastereomerically pure acyclic synthon derived from 1,3,5-*cis*-cyclohexane triol[4]. In the present communication[5], we describe the syntheses of all four stereoisomers of **2** in optically pure form

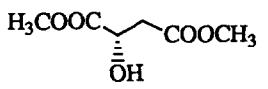
The general strategy for the construction of the desired six-carbon synthons was based on the retrosynthetic analysis shown in the scheme The key step in the present synthesis is the conversion of the optically pure δ-hydroxy-β-ketoester, derived from *S*- or *R*-malic acid, selectively to either the 1,3-*syn*-diol utilizing our *syn*-selective reduction methodology[6] or to the 1,3-*anti*-diol using the hydroxy-directed reduction method of

Evans[7] Thus *S*-malic acid was expected to give the *syn*-(3*R*, 5*S*)- and the *anti*-(3*S*, 5*S*)-synthons, and *R*-malic acid to provide the corresponding enantiomers



Scheme

Reduction of *S*-dimethyl malate **3** with BH_3 SMe_2 following Moriwaki's procedure[8,9] provided diol **4** which was converted (trityl chloride/pyridine in CH_2Cl_2, 0 to 25 °C, 18 h) into the trityl derivative **5**, mp 80-82 °C, $[\alpha]_D$ −5 52° (*c* = 1, CH_2Cl_2) in 85% yield Compound **5** on treatment with 4 4 equivalents of *t*-butyl lithioacetate[10] in THF at −78 to 0 °C gave the hydroxyketoester **6** as an oil, $[\alpha]_D$ −8 68° (*c* = 2 65, CH_2Cl_2),



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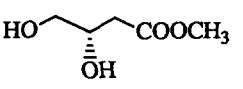

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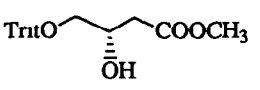

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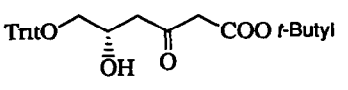

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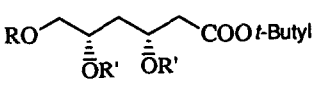
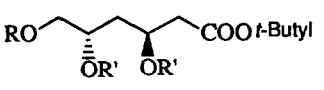


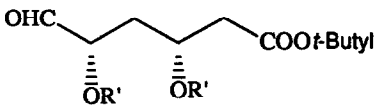
7 R = Trityl, R' = H
8 R = Trityl, R' = *t*-BDPS
9 R = H, R' = *t*-BDPS



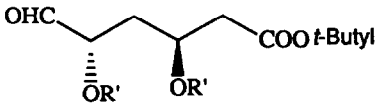
10 R = Trityl, R' = H
11 R = Trityl, R' = *t*-BDPS
12 R = H, R' = *t*-BDPS

in 80% yield Reduction of **6** utilizing the *syn*-selective reduction that we had developed earlier[6] for β-hydroxy-ketones (Et_2BOCH_3, $NaBH_4$, THF/MeOH, −78 °C), gave the *syn*-diol **7** in 80% yield with >99% *de*, mp 89 °C, $[\alpha]_D$ −5 59° (*c* = 1.6, CH_2Cl_2) For achieving higher diastereoselectivity and greater reproducibility, we recommend the use of preformed[6] Et_2BOCH_3 in generating the boron chelates, over the *in situ* methods like Et_3B/air (Narasaka and Pai)[11], or Et_3B/pivalic acid/MeOH (Merck)[12,13], or Et_3B/MeOH (Sandoz)[14]. Treatment of **7** with *t*-butyldiphenyl chlorosilane/imidazole in DMF at 70 °C for 18 h gave **8** (R=trityl, R'=*t*-butyldiphenylsilyl (*t*-BDPS), oil, $[\alpha]_D$ −21 08° (*c* = 1 66, CH_2Cl_2)) and then aqueous trifluoroacetic acid in CH_2Cl_2 at 0 to 25 °C for 2.5 h gave **9** in 70% yield (mp 79-80 °C, $[\alpha]_D$ +8 45° (*c* = 2 13, CH_2Cl_2)). Oxidation of **9** with pyridinium chlorochromate/4A molecular sieve powder in CH_2Cl_2 for 1 h at 25 °C gave the (3*R*, 5*S*)-aldehyde **13**[15], mp 81-82 °C, $[\alpha]_D$ +5 21° (*c* = 5, CH_2Cl_2), in 90% yield Alternatively, the reduction of **6** with $Me_4NHB(OAc)_3$ in THF/AcOH (4:1) at 0 °C for 18 h afforded **10** and **7** in the ratio of 95 5 respectively. Purification of **10** by HPLC followed by a three-step sequence as in the case of the *syn*-isomer **7** gave the (3*S*,5*S*)-aldehyde **14** (**10**, oil, $[\alpha]_D$ +6 67° (*c* = 0 3, CH_2Cl_2), **11**, oil, $[\alpha]_D$ −11 4° (*c* = 0 35, CH_2Cl_2); **12**, oil, $[\alpha]_D$ +28.85° (*c* = 0.52, CH_2Cl_2); and **14**, oil, $[\alpha]_D$ +10 42° (*c* = 0 48, CH_2Cl_2)

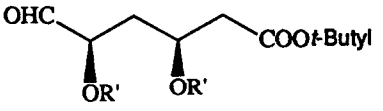
Synthesis of **15**, mp 75-76 °C, $[\alpha]_D$ −4° (*c* = 5, CH_2Cl_2), and **16**, oil, $[\alpha]_D$ −9 4° (*c* = 0 48, CH_2Cl_2), proceeded along the same lines as in the case of **13** and **14** except for the replacement of *S*-malate by *R*-malate



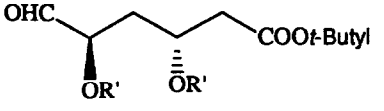
13 R' = *t*-BDPS



14 R' = *t*-BDPS



15 R' = *t*-BDPS



16 R' = *t*-BDPS

The utility of the above chiral synthons **13-16** in the Wittig olefination methodology leading to the syntheses of all the four stereoisomers of different heptenoates of type **1** will be reported in due course of time

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