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Synthesis of (S) 2-Ethyl-2-methylpentanoic Acid from the Formate Ester of (S) Ethyl 2-Formyl-3-hydroxy-2-methylpropionate

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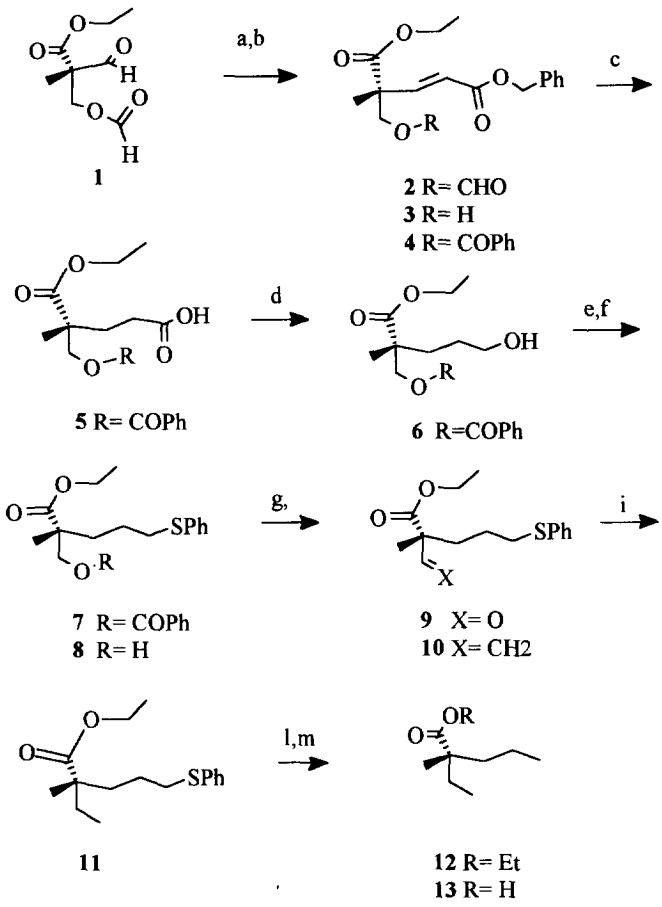
Abstract: The synthesis of (S) 2-ethyl-2-methylpentanoic acid **13** from the C-5 aldehydo ester **1**, obtained through a baker's yeast transformation, *via* C-2 and C-1 chain elongations by means of olefin-forming reactions is reported. Copyright © 1996 Elsevier Science Ltd

Racemate resolution by crystallisation techniques is probably considered to be the most important method for the synthesis of pure enantiomers.[1] Indeed, this approach was used in the fifties for the preparation of a set of optically active trialkylacetic acids required in mechanistic studies.[2,3,4] However, considerable difficulties were encountered. In particular, enantiomerically pure (+)-2-ethyl-2-methylpentanoic acid (3-methylhexane-3-carboxylic acid) was obtained after 40 crystallisations of the brucine salt.[3] Reportedly, the attempts to produce the (-)-acid by crystallisation of the salts with quinine, cinchonine, strycnine and (-)-phenylethylamine was unsuccessful.[4] More recently,[5] the (-)-acid, possessing 23% optical purity, was obtained by asymmetric alkylation of N,N-disubstituted amides derived from ephedrine.

In light of current interest in the preparation of relatively small, highly functionalized, optically active and synthetically useful molecules by means of isolated enzymes and microorganisms,[6] we reported previously on the production of the C-5 (S) aldehydo ester **1** and of its (R) enantiomer.[7] Such molecules, containing a carbon atom directly bound to four carbon atoms in different oxidation states, were obtained through a short sequence, involving in the key step the use of baker's yeast. As a further example of the synthetic significance of these studies we now report on the direct preparation of enantiomerically pure (S)-(-)-2-ethyl-2-methylpentanoic acid **13** from **1**, apparently not accessible through the available methodologies.[4,5]

The conversion of **1**, $[\alpha]^{20}_{D}$ -14.5° (c 1, $CHCl_3$),[7] into **13** (Scheme 1) involves two chain elongations as key steps, achieved through olefin forming reactions onto aldehydic species. The first one, performed with $Ph_3P{=}CHCO_2CH_2C_6H_5$, led to **2**, $[\alpha]^{20}_{D}$ +0.2° (c 1, $CHCl_3$). The formate ester obtained in the subsequent step

resulted rather labile, thus it was substituted with the benzoate ester. To this end, **2** was hydrolyzed and the resulting carbinol **3** was converted into benzoate ester **4**, $[\alpha]^{20}_{D}$ -8.2° (c 1, $CHCl_3$). Catalytic hydrogenation of the diester **4** saturated the double bond and at the same time regioselectively revealed the carboxyl moiety present at position 5 of the glutarate framework providing **5**.



Scheme 1

Reagents: a) $Ph_3P{=}CHCO_2CH_2C_6H_5/CHCl_3$ r.t.; then, EtOH/HCl, 40°C; (71%). b) PhCOCl, Py, DMAP, 10°C; (89%). c) H_2 , Pd/C 5%/EtOH-AcOH. d) $BH_3.Me_2S$/THF, 10°C; (79% from **8**). e) PhSSPh, Ph_3P/DME, reflux; (71%). f) EtOH, HCl, reflux; (82%). g) DMSO, $(CF_3CO)_2O$, Et_3N, -60°C; (89%). h) $CH_2I_2/Me_3Al/Zn$, 0°C; (77%). i) H_2, Pd/C 5%/EtOH-AcOH. l) Raney/Ni, reflux; (88% from **10**). m) KOH, MeOH, reflux: (82%).

The free carboxyl group of the hemiester **5** was reduced by means of ($BH_3.Me_2S$) to the primary carbinol **6**, $[\alpha]^{20}_D$ -6.6° (c 1, $CHCl_3$). The removal of the oxygen function of **6**, which would allow the formation of the *n*-propyl chain of desired **13**, involved oxygen-sulfur exchange, followed by reductive desulfurization. The first goal was achieved by treating the carbinol **6** with $PhSSPh/Ph_3P$[8] to provide the mixed sulfide **7**, $[\alpha]^{20}_D$ -1.9° (c 1, $CHCl_3$) in high yield. The diester **7** was selectively hydrolyzed by treatment with warm ethanolic hydrochloric acid providing the monoester **8**, $[\alpha]^{20}_D$ +8.5° (c 1, $CHCl_3$) and ethyl benzoate. The primary carbinol present in **8** was oxidized under Swern conditions to the aldehyde **9**, $[\alpha]^{20}_D$ +6.2° (c 1, $CHCl_3$).

The latter alkyl disubstituted malonaldehyde was submitted to the second C=C bond forming reaction of the sequence, designed to eventually provide the ethyl moiety of **13**. Thus, the olefination with $CH_2I_2/Me_3Al/Zn$[9] provided **10**, $[\alpha]^{20}_D$ -8.9° (c 1, $CHCl_3$), possessing the C-8 carbon framework of the desired acid **13**. This material became accessible from **10** by simple functional group manipulation. Accordingly, the vinyl acetate **10** was submitted to catalytic hydrogenation providing **11**, yielding, in turn, on Raney-Ni desulfurization, the ester **12**, $[\alpha]^{20}_D$ -24° (c 1, $CHCl_3$), bearing the required methyl, ethyl and *n*-propyl substituents attached to the C-2 acetate framework. The (S) acid **13**, $[\alpha]^{20}_D$ -19.6° (c 1, EtOH) was obtained from **12** upon basic hydrolysis. The R enantiomer, obtained by Bleazard and Rothstein[3] from the brucine salt after a large number of recrystallizations, showed $[\alpha]^{20}_D$ 19.7° (c 1, EtOH). We use this value of $[\alpha]^{20}_D$ as the criterion for optical purity of **13.** The overall yield (not optimized) of the sequence leading to **13** from **1** was *ca.* 15%.

Thus, the direct incorporation of the chiral center of baker's yeast-produced **1** in the enantiomerically pure trialkyl acetic acid **13** further supports the significance of the set of materials produced by enzymic transformation of non-conventional substrates as synthetic enantiomerically pure intermediates.[10] In this particular case, the value of the results is enhanced by the fact that the chiral C-5 starting material becomes accessible in the yeast transformation in both enantiomeric forms.[7]

Experimental Section

Benzyl, Ethyl Ester of (R) 4-methyl-4-hydroxymethylpent-2-endioic Acid (3). The aldehyde (**1**),[7] 15 g (0.08 mol), in $CHCl_3$, (100 ml), was stirred at r.t. for 1 h with $Ph_3P{=}CHCO_2CH_2Ph$, 39 g (0.095 mol). The reaction mixture was evaporated and the residue taken up with EtOH saturated with HCl gas. After 30 min the reaction mixture was evaporated to dryness and the residue was chromatographed on SiO_2, eluting with AcOEt/hexane to

give the unsaturated mixed ester (**3**) as an oil, (16.5 g, 71%), $[\alpha]^{20}_D$ +0.2° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J= 8.2 Hz); 1.36 (s, 3H); 2.82 (bt, 1H); 3.72 (bt, 2H); 4.18 (q, 2H, J= 8.2 Hz); 5.18 (s, 2H); 6.0 (d, 1H, J= 16.8 Hz); 7.11 (d, 1H, J= 16.8 Hz); 7.32 (s, 5H). Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.92; H, 6.78.

Benzyl, Ethyl Ester of (R) 4-methyl-4-benzoyloxymethylpent-2-endioic Acid (4). To a solution in CH_2Cl_2 (50 ml) of product (**3**), 16 g (0.055 mol) in the presence of pyridine (10 ml) and 4-dimethylaminopyridine, 0.1 g, benzoylchloride, 9.3 g (0.07 mol) was added dropwise at 0 °C under stirring. After standing overnight, the reaction mixture was washed with cold dil. HCl, 3% $NaHCO_3$ and water. The residue obtained upon evaporation of the dried organic phase was chromatographed on SiO_2 to provide the benzoate ester (**4**) (19.3 g, 89%), oil, $[\alpha]^{20}_D$ -8.2° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, J= 7.3 Hz); 1.48 (s, 3H); 4.19 (q, 2H, J= 7.3 Hz); 4.49 (s, 2H); 5.2 (s, 2H); 6.06 (d, 1H, J= 15.6 Hz); 7.2 (d, 1H, J= 15.6 Hz); 7.3-7.6 (m, 8H); 7.97 (d, 2H). Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.70; H, 6.11.

(R) Ethyl 2-methyl-2-benzoyloxymethyl-5-hydroxypentanoate (6). The diester (**4**), 19 g (0.048 mol) in EtOH/acetic acid 1:1 (100 ml) was stirred in H_2 in the presence of 5% Pd/C, 0.5 g. At the end of the absorption, the reaction mixture was filtered and the solvent evaporated. The residue, 14.2 g, in anhydrous THF (150 ml) at 0 °C under nitrogen was treated with 10M BH_3-Me_2S, 6 ml (0.06 mol). After 2 h, water (20 ml) was carefully added, followed by K_2CO_3, 4 g. The reaction mixture was extracted with Et_2O (3 x 100 ml). The residue obtained upon evaporation of the dried organic phase provided upon chromatography the hydroxy ester (**6**), (11.2 g, 79%), $[\alpha]^{20}_D$ -6.6 (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, J= 7.2 Hz); 1.32 (s, 3H); 1.5-1.9 (m, 4H); 2.4 (sb, 1H); 3.63 (t, 2H); 4.17 (q, 2H, J= 7.2 Hz); 4.33 (d, 1H, J= 9.6 Hz); 4.45 (d, 1H, J= 9.6 Hz); 7.43 (t, 2H); 7.55 (m, 3H); 8.0 (m, 2H). Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.15; H, 7.79.

(R) Ethyl 2-Methyl-2-benzoyloxymethyl-5-thiophenylpentanoate (7). A solution in 1,2-dimethoxyethane (100 ml) of carbinol (**6**), 11 g (0.037 mol), Ph_3P, 45 g (0.18 mol) and diphenyldisulfide, 40 g (0.18 mol), was refluxed under nitrogen for 16 h. The residue obtained upon evaporation of the solvent was chromatographed to provide the sulfide (**7**), (10.1 g, 71%), $[\alpha]^{20}_D$ -1.9° (c 1, $CHCl_3$), and 2 g of unreacted starting material. ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, J= 6.8 Hz); 1.28 (s, 3H); 1.55-1.95 (m, 4H); 2.91 (t, 2H); 4.12 (q, 2H, J= 6.8 Hz); 4.3 (d, 1H, J= 11.4 Hz); 4.4 (d, 1H, J= 11.4 Hz); 7.1-7.6 (m, 8H); 8.0 (d, 2H). Anal. Calcd. for $C_{22}H_{26}O_4S$: C, 68.39; H, 6.74. Found: C, 68.42; H, 6.65.

(R) Ethyl 2-Methyl-2-hydroxymethyl-5-thiophenylpentanoate (8). The sulfide (**7**), 10 g (0.026 mol) in EtOH (80 ml) was treated with HCl (gas) and the saturated mixture was refluxed for 6 h. The solution was concentrated to small volume, taken up with AcOEt (150 ml) and washed with water and 3% $NaHCO_3$. The residue obtained upon evaporation of the organic phase was chromatographed to provide carbinol (**8**), (6 g, 82%), $[\alpha]^{20}_D$ 8.5° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H); 1.22 (t, 3H, J 5.5 Hz); 1.55-1.8 (m, 4H); 2.37 (bt, 1H); 2.88 (t, 2H); 3.5 (m, 4H); 3.62 (m, 1H); 4.12 (q, 2H, J 5.5 Hz); 7.3 (m, 5H). Anal. Calcd. for $C_{15}H_{22}O_3S$: C, 63.83; H, 7.80. Found: C, 63.72; H, 7.83.

(R) Ethyl 2-Methyl-2-formyl-5-thiophenylpentanoate (9). A solution of DMSO, 2.8 ml (0.04 mol) in CH_2Cl_2 (20 ml) was cooled to -60 °C and treated under stirring with trifluoroacetic acid anhydride, 4.2 ml (0.03 mol). After 10 min the carbinol (**8**) was added, 5.2 g (0.018 mol) in CH_2Cl_2 (20 ml). The mixture was kept at the above temp. for 30 min. and then treated with Et_3N, 8 ml. After 30 min the temperature was slowly raised to 23 °C and the reaction mixture was washed with water, dried and evaporated to give, after chromatography, the aldehyde (**9**), (4.5 g, 89%), $[\alpha]^{20}_D$ 6.2° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H, J 7.2 Hz); 1.28 (s, 3H); 1.51-1.61 (m, 2H); 1.78-2.10 (m, 2H); 2.91 (t, 2H); 4.17 (q, 2H, J 7.2 Hz); 7.31 (m, 5H); 9.68 (s, 1H). Anal. Calc. for $C_{15}H_{20}O_3S$: C, 64.29; H, 7.14. Found: C, 64.18; H, 7.24.

(R) Ethyl 2-Methyl-2-vinyl-5-thiophenylpentanoate (10). To a suspension of Zn, 6 g, diiodomethane, 6.4 g (0.024 mol) in THF (50 ml) was added Me_3Al (1M in hexane, 4.8 ml) at 25 °C under N_2. After 30 min a solution of the aldehyde (**9**), 2 g (0.007 mol) in THF (20 ml) wass added at 0 °C to the above mixture. After 1 h of stirring the reaction mixture was diluted with Et_2O (150 ml) and washed with dil. HCl and 10% Na_2SO_3. The residue obtained upon evaporation of the solvent, upon chromatography, provided (**10**), (1.5 g, 77%), $[\alpha]^{20}_D$ -8.9° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.18-1.27 (t + s, 6H); 1.45-1.9 (m, 4H); 2.9 (t, 2H); 4.1 (q, 2H); 5.0-5.1 (m, 2H); 5.8 (dd, 1H, J_1 11 Hz, J_2= 17 Hz); 7.3 (m, 5H). Anal. Calcd. for $C_{16}H_{22}O_2S$: C, 69.06; H, 7.91. Found: C, 69.15; H, 7.89.

(S) Ethyl 2-Methyl-2-ethylpentanoate (12). Product (**10**), 1.3 g (0.005 mol), and 5% Pd/C, 0.2 g, in EtOH (50 ml) were stirred under H_2 atmosphere to provide, after filtration of the catalyst and evaporation of the solvent, the sulfide (**11**), which was dissolved in EtOH (10 ml) and boiled for 5 min with 3 g of Raney/Ni. The reaction mixture was filtered and the residue obtained upon evaporation of the solvent was distilled bulb-to-bulb at ca. 100 mm/Hg to provide the ester (**12**), (0.76 g, 88%), oil, $[\alpha]^{20}_D$ -24° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.82 (t, 3H, J 7.7 Hz); 0.89 (t, 3H, J 7.4 Hz); 1.09 (s, 3H); 1.24 (t, 3H, J 7.2 Hz); 1.25-1.73 (m, 6H); 4.11 (q, 2H, J 7.2 Hz) 0.75-0.95 (t + t, 6H); 1.1 (s, 3H); 1.25 (t, 3H); 1.3-1.8 (m, 6H); 4.12 (q, 2H). Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.81; H, 11.65.

(S) 2-Methyl-2-ethylpentanoic Acid (13). A solution of the ester (**12**), 0.5 g (0.003 mol) in MeOH saturated with KOH (10 ml) was refluxed for 3 h. The solution was concentrated, diluted with cold water and extracted with ether (10 ml). The aqueous phase was acidified with HCl and extracted with CH_2Cl_2 (3 x 20 ml). The residue obtained upon evaporation of the dried organic extract was distilled bulb-to-bulb at 40 mm/Hg to provide the acid (**13**), (0.35 g, 82%), oil, $[\alpha]^{20}_D$ -19° (c 1, EtOH). ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J 7.5 Hz); 0.91 (t, 3H, J 7.4 Hz); 1.12 (s, 3H); 1.76-1.17 (m, 6H); 11.6 (s broad, 1H). Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.15; H, 11.89.

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