A Facile Chiral Synthesis of (+)-Prelog–Djerassi Lactonic Acid Methyl Ester using Five-membered Heterocyclic Chiral Reagents

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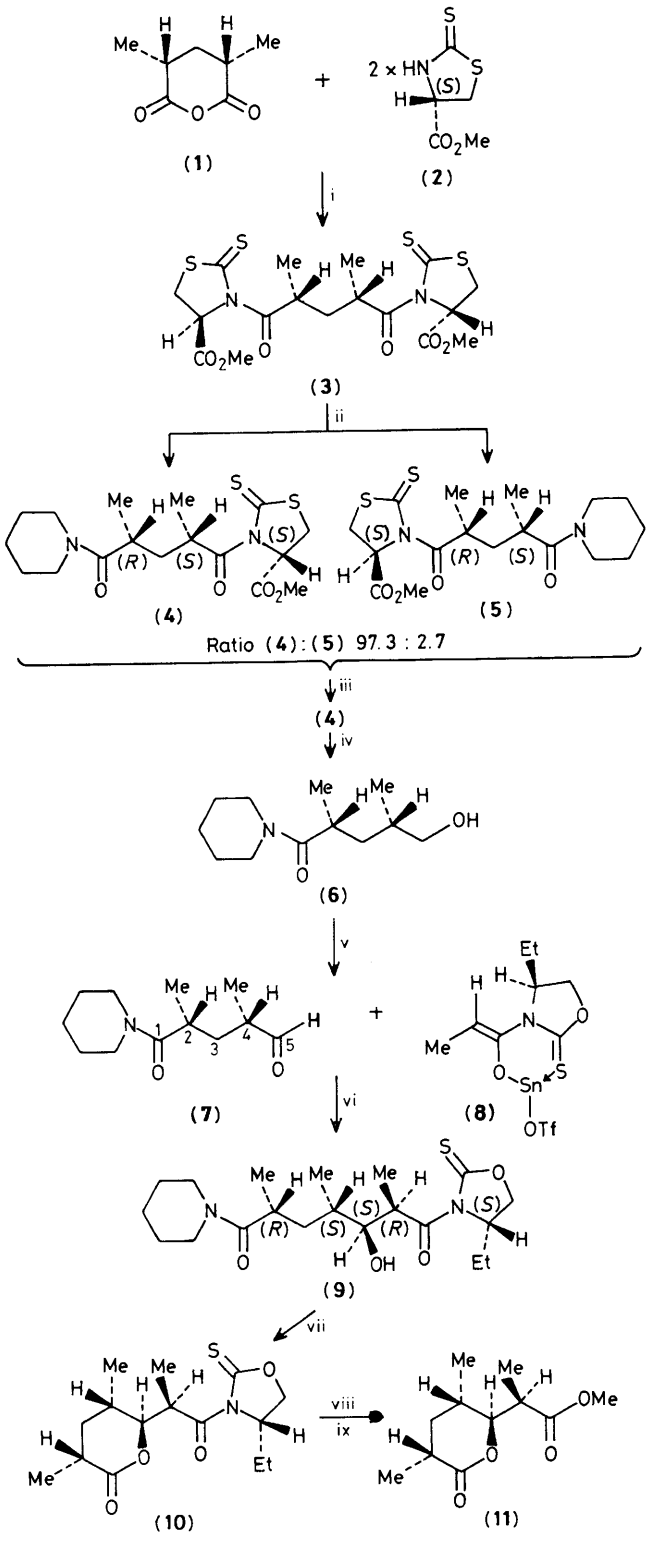
A chiral synthesis of (+)-Prelog–Djerassi lactonic acid methyl ester (**11**) *via* a series of short steps has been performed using new chiral induction methods.

In preliminary reports, we have described a highly stereoselective differentiation between two identical carboxy groups in the prochiral σ-symmetrical dicarboxylic acids using 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione[1] and a stereoselective synthesis of aldols using chiral 1,3-oxazolidine-2-thione derivatives.[2] We now report the application of these methods to the synthesis of (+)-Prelog–Djerassi lactonic acid methyl ester (**11**) *via* a series of short steps (Scheme 1).

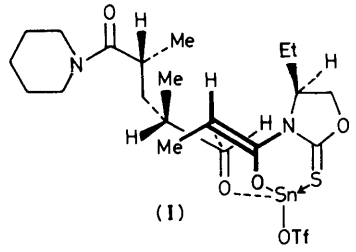
The condensation reaction between *meso*-2,4-dimethylglutaric acid anhydride (**1**) and 2 mol equiv. of 4(*S*)-methoxycarbonyl-1,3-thiazolidine-2-thione [4(*S*)-MCTT] (**2**)† in the presence of dicyclohexylcarbodi-imide (DCC) in pyridine gave 4(*S*)-MCTT diamide (**3**) {$[\alpha]_D^{20}$ + 167.9° (*c* 2.96, $CHCl_3$)} in 67.2% yield. Aminolysis of (**3**) with 1 mol equiv. of piperidine at −20 °C in CH_2Cl_2 proceeded with high selectivity to afford a solid mixture (74.0% yield) of diastereoisomers (**4**) and (**5**) in a 97.3 : 2.7 ratio (h.p.l.c. analysis[1]). Recrystallization of the solid mixture from CH_2Cl_2–hexane gave pure compound (**4**) in 67.7% yield from (**3**) {yellow plates; m.p. 118.5—119 °C; $[\alpha]_D^{20}$ + 118.9° (*c* 1.41, $CHCl_3$)}. The monitored reduction[3] of (**4**) with $NaBH_4$ in aq. tetrahydrofuran (THF) gave a 91.1% yield of alcohol (**6**), which was oxidized with pyridine–sulphur trioxide complex[4] in the presence of Et_3N in dimethyl sulphoxide (DMSO)–THF (1 : 1) at 0 °C for 1 h to afford a mixture of aldehyde (**7**) and its C-4 epimeric aldehyde in a 91.7 : 8.3 ratio (g.l.c. analysis) (total 63.5% yield).‡

† 4(*S*)-MCTT was readily synthesized from D-cysteine methyl ester hydrochloride and CS_2 in the presence of Et_3N in CH_2Cl_2 in 84.6% yield {colourless oil; $[\alpha]_D^{20}$ + 71.68° (*c* 3.739, $CHCl_3$)}.

‡ A crosslinked 5% phenyl methyl silicone 25 m capillary column was used for g.l.c. analysis.



Scheme 1. *Reagents and conditions:* i, DCC–pyridine, CH_2Cl_2; ii, piperidine, CH_2Cl_2, −20 °C; iii, recrystallization from CH_2Cl_2–hexane; iv, $NaBH_4$–aq. THF; v, pyridine–sulphur trioxide complex, Et_3N, DMSO–THF (1:2), 0 °C; vi, CH_2Cl_2, −78 °C; vii, 3 M HCl–benzene (1:1), 80 °C; viii, 0.5 M LiOH, THF, 0 °C; ix, CH_2N_2, Et_2O.



Aldol type condensation between aldehyde (**7**) [diastereoisomeric purity (d.p.) = 91.7%] and the tin–enolate (**8**)[2] prepared from 3-propanoyl-4(*S*)-ethyl-1,3-oxazolidine-2-thione and tin(II) trifluoromethanesulphonate in the presence of *N*-ethylpiperidine was performed in CH_2Cl_2 at −78 °C for 30 min to furnish the desired product (**9**) together with other minor diastereoisomers in a 92.0:8.0 ratio (h.p.l.c. analysis[1]) (total 74.2% yield). This highly stereoselective aldol reaction proceeds according to a reaction process *via* a Felkin type transition state (I) (Tf = CF_3SO_2).[5]

Compound (**9**) (d.p. = 92%) was heated at 80 °C for 7 h in benzene–3 M HCl (1:1) to give δ-lactone (**10**) [d.p. = 94.7% (h.p.l.c. analysis), 56.7% yield], which on treatment with 0.5 M LiOH in THF at room temperature for 5 min gave a carboxylic acid. Its methyl ester (CH_2N_2) was purified on a silica gel column [benzene–AcOEt (7:3)] to afford pure (+)-Prelog–Djerassi lactonic acid methyl ester (**11**) in 53.3% yield from (**10**) {colourless needles from Et_2O–hexane; m.p. 77.5—78.0 °C; $[\alpha]_D^{20}$ + 38.67° (*c* 0.75, $CHCl_3$)}. All physical data of the synthesized compound (**11**) were shown to be identical with those of an authentic sample.[6]

Thus, a simplified new chiral synthesis of (+)-Prelog–Djerassi lactonic acid methyl ester[7] has been accomplished and this procedure will have useful applications in the synthesis of macrolide and polyether antibiotics.

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