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ASYMMETRIC SYNTHESIS OF (3R-TRANS)- AND (3S-CIS)-HYDROXY-5-PENTANOLIDES

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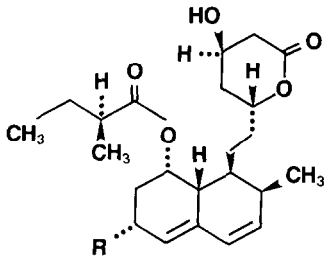
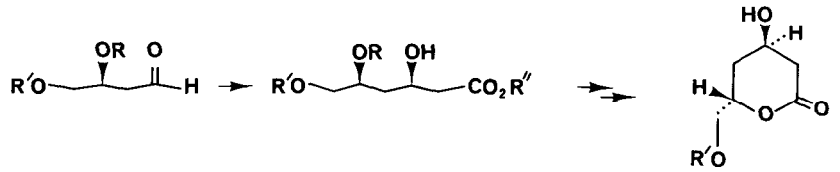
Abstract: The synthesis of optically active lactones 11a and 11b is reported, utilizing chiral aldehyde 7 as the key intermediate.

Inhibition of HMG-CoA reductase is a well-recognized property of compactin[1] 1a, mevinolin[2] 1b and their analogues. As part of a program[3] directed at the



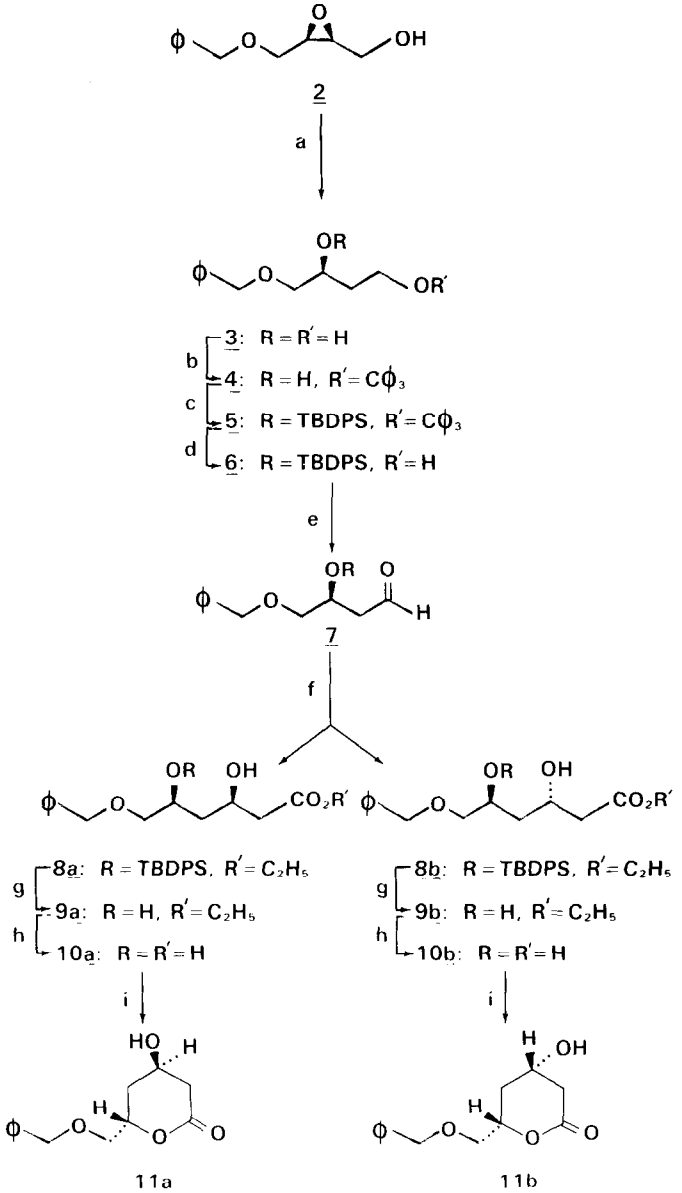
1a, R = H
1b, R = CH_3

synthesis of β-hydroxy-δ-lactones with the relative and absolute configuration of these natural products, we have examined the feasibility of asymmetric synthesis by the strategy shown below. In the present communication we wish to describe an efficient synthesis of aldehyde 7 and its conversion to the two chiral lactones 11.



The starting material in our present study was the epoxide[4] 2, the optical purity of which was determined to be 92% (ee) by the Anderson-Shapiro method.[5] The epoxide was opened[6] with Red-Al® to give 3. Tritylation of diol 3 with triphenylmethyl chloride in the presence of pyridine in CH_2Cl_2 gave the monotrityl derivative 4, which on treatment with t-butyldiphenylsilyl (TBDPS) chloride and imidazole in DMF afforded the silyl compound 5 in quantitative yield. Removal of the trityl group (trifluoroacetic acid, CH_2Cl_2, H_2O, -20 °C),

followed by oxidation of 6 (PCC, 4-A molecular sieves[7], CH_2Cl_2), resulted in a high yield of the desired optically active aldehyde 7[8], $[\alpha]_D^{25}$ -18.3° (c = 18.83 in $CHCl_3$).



a: Red-Al®, THF, 0 °C; **b:** ϕ_3CCl, CH_2Cl_2, pyridine, 20 °C; **c:** t-Buϕ_2SiCl, DMF, imidazole, 20 °C; **d:** CF_3CO_2H, CH_2Cl_2, H_2O, -20 °C; **e:** pyridinium chlorochromate, molecular sieves, CH_2Cl_2, 20 °C; **f:** Zn, $(C_2H_5)_2AlCl$, $BrCH_2CO_2C_2H_5$, THF, 15 °C; **g:** Bu_4NF, CH_3CO_2H, THF, 20 °C; **h:** 1 N NaOH, dioxane, 5 °C; **i:** refluxing toluene.

Having achieved the objective of making aldehyde 7 by an efficient synthetic route, we next turned our attention to examine the utility of 7 as a precursor to optically active β-hydroxy-δ-lactones. Initial attempts to make aldol product 8 from compound 7 using classical Reformatsky conditions ($BrCH_2COOC_2H_5$, Zn, I_2, THF) met with no success. The use of ultrasound[9] in combination with the above reaction conditions (40 °C, 18 h) did produce the desired aldol 8, albeit in poor yield (10%). However, the use of diethylaluminium chloride[10] along with Zn brought a dramatic increase in the yield (85%) of 8 as well as a significant decrease in the reaction time (20 min) and temperature (15 °C). Chlorotitanium triisopropoxide was also found to be an effective reagent in these condensations.[11] Under all the above aldol reaction conditions the ratio of the two diastereoisomers that were formed was found to be approximately 1:1 as evidenced by HPLC analysis. The pure 8a, $[\alpha]_D^{25}$ -14.6° (c = 1.08 in $CHCl_3$), and 8b, $[\alpha]_D^{25}$ -17.4° (c = 0.94 in $CHCl_3$), were separated by HPLC and were converted into the respective lactones 11a, $[\alpha]_D^{25}$ +6.54° (c = 1.56 in $CHCl_3$), and 11b, $[\alpha]_D^{25}$ +13.86° (c = 1.06 in $CHCl_3$), in a three step sequence (a. desilylation 8 → 9: Bu_4NF, CH_3COOH, THF, 20 °C; b. hydrolysis 9 → 10: 1 N NaOH, dioxane, 5 °C; c. lactonization 10 → 11: refluxing toluene). The structures 11a and 11b were assigned to the two isomeric lactones unambiguously on the basis of their NMR spectroscopic data.[8]

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8. Satisfactory analytical data were obtained for all the new compounds.

The spectral data for some of the key intermediates are as follows.

Compound 7: oil, $[\alpha]_D^{25}$ -18.3° (c = 18.8 in $CHCl_3$); IR (CH_2Cl_2): 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.72 (t, J = 1 Hz, 1H), 7.10-7.70 (m, 15H), 4.34 (s, 2H), 4.31 (m, 1H), 3.42 (m, 2H), 2.61 (m, 2H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 201.11, 137.95, 135.89, 135.78, 133.77, 133.29, 129.93, 129.77, 128.30, 127.76, 127.60, 73.59, 73.21, 68.33, 48.67, 26.94, 19.25.

Compound 8a: oil, $[\alpha]_D^{25}$ -14.6° (c = 1.08 in $CHCl_3$); IR (CH_2Cl_2): 3500 (OH), 1730 (ester CO) cm^{-1}; ^1H NMR (C_6D_6): δ 7.80 (m, 4H), 7.00-7.25 (m, 11H + H from C_6D_5H), 4.36 (m, 1H), 4.26 (m, 1H), 4.12 (q, J = 12 Hz, 2H), 3.86 (q, J = 7 Hz, 2H), 3.38 (d, J = 5 Hz, 2H), 3.20 (d, J = 3 Hz, 1H), 2.21 (m, 2H), 1.79 (m, 2H), 1.18 (s, 9H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR (C_6D_6): δ 172.13, 73.86, 72.99, 70.50, 65.14, 60.15, 41.68, 41.35, 26.94, 19.25, 13.94 (phenyl carbon signals are overlapped with those of solvent); DCI MS (isobutane): m/e (%), 521 (28, MH^+), 444 (21), 443 (53), 385 (38), 365 (32), 353 (35), 295 (51), 275 (70), 273 (29), 265 (20), 257 (38), 229 (24), 221 (23), 207 (34), 199 (43), 187 (39), 181 (52), 179 (20), 161 (100), 157 (69), 155 (56), 133 (22), 117 (22), 115 (24), 107 (36), 105 (27).

Compound 8b: oil; $[\alpha]_D^{25}$ -17.4° (c = 0.94 in $CHCl_3$); IR (CH_2Cl_2): 3500 (OH), 1725 (ester CO) cm^{-1}; ^1H NMR (C_6D_6): δ 7.83 (m, 4H), 7.00-7.25 (m, 11H + H from C_6D_5H), 4.46 (m, 1H), 4.36 (m, 1H), 4.06 (s, 2H), 3.87 (q, J = 7 Hz, 2H), 3.32 (m, 2H), 3.10 (d, J = 3 Hz, 1H), 2.29 (dd, J = 16 and 8 Hz, 1H), 2.20 (dd, J = 16 and 4 Hz, 1H), 1.72 (m, 2H), 1.19 (s, 9H), 0.89 (t, J = 7 Hz, 3H); ^{13}C NMR (C_6D_6): δ 171.96, 73.85, 72.85, 70.26, 64.91, 60.15, 42.14, 41.06, 26.95, 19.31, 13.96; DCI MS (isobutane): m/e (%), 521 (9, MH^+), 386 (29), 385 (100), 365 (81), 341 (21), 335 (21), 295 (60), 275 (78), 273 (36), 257 (40), 221 (53), 217 (25), 207 (22), 199 (60), 181 (32), 179 (29), 175 (20), 161 (30), 157 (73), 155 (28), 133 (29), 131 (28), 129 (21), 121 (26), 119 (28), 117 (31), 115 (28), 107 (57), 105 (39).

Compound 11a: oil, $[\alpha]_D^{25}$ +6.54° (c = 1.56 in $CHCl_3$); IR (CH_2Cl_2): 3580 (OH), 1735 (lactone CO) cm^{-1}; ^1H NMR (C_6D_6): δ 7.00-7.25 (m, 5H + H from C_6D_5H), 4.60 (m, 1H), 4.21 (q, J = 12 Hz, 2H), 3.65 (b, 1H), 3.27 (dd, J = 14 and 3 Hz, 1H), 3.13 (dd, J = 14 and 4 Hz, 1H), 2.28 (dd, J = 17 and 3 Hz, 1H), 2.21 (b, 1H), 2.10 (dd, J = 17 and 4 Hz, 1H), 1.38 (m, 2H); ^{13}C NMR (C_6D_6): δ 169.26, 74.71, 73.49, 71.97, 62.63, 38.92, 32.11; DCI MS (isobutane): m/e (%), 237 (100, MH^+), 219 (50), 147 (15), 131 (10), 129 (34), 107 (29), 97 (10).

Compound 11b: oil, $[\alpha]_D^{25}$ +13.9° (c = 1.06 in $CHCl_3$); IR (CH_2Cl_2): 3580 (OH), 1735 (lactone CO) cm^{-1}; ^1H NMR (C_6D_6): δ 7.00-7.25 (m, 5H + H from C_6D_5H), 4.25 (s, 2H), 3.71 (m, 1H), 3.42 (m, 1H), 3.18 (d, J = 5 Hz, 2H), 2.32 (dd, J = 17 and 5 Hz, 1H), 2.14 (dd, J = 17 and 7 Hz, 1H), 1.90 (b, 1H), 1.55 (m, 1H), 1.30 (m, 1H); ^{13}C NMR (C_6D_6): δ 169.17, 75.68, 73.54, 71.82, 63.47, 39.73, 34.16; DCI MS (isobutane): m/e (%), 237 (100, MH^+), 219 (33), 131 (18), 129 (31), 111 (11), 107 (49).

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11. Partial transesterification was found to be a major problem in the condensations involving chlorotitanium triisopropoxide.

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