# Enantioselective Synthesis of the Lactone Moiety of the Mevinic Acids using D-Xylose as a Chiral Precursor

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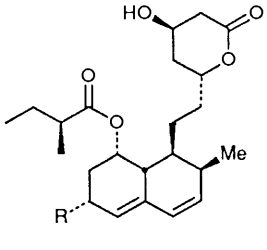
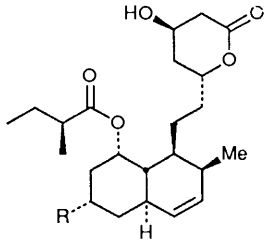
Homologation of the lactone **14** easily obtained from D-xylose afforded the pyranone **15**, a key chiral synthon for the lactone portion of mevinic acids.

Interest in mevinic acids **1**–**4** and their analogues is justified by their powerful activity as inhibitors of HMG-CoA reductase, an enzyme which controls the rate-limiting step of cholesterogenesis.[1] Work carried out in this area has led to several total syntheses of mevinic acids[2] and their structural analogues[2a,3] as well as some useful chiral synthons for their preparation.[4] From a structural point of view mevinic acids consist of a hydronaphthalene and a lactone unit, the latter seeming to be essential for their biological activity.



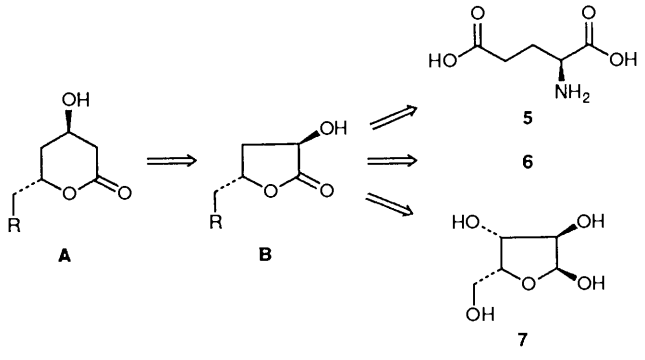
**1** R = H (compactin)
**2** R = Me (mevinolin)



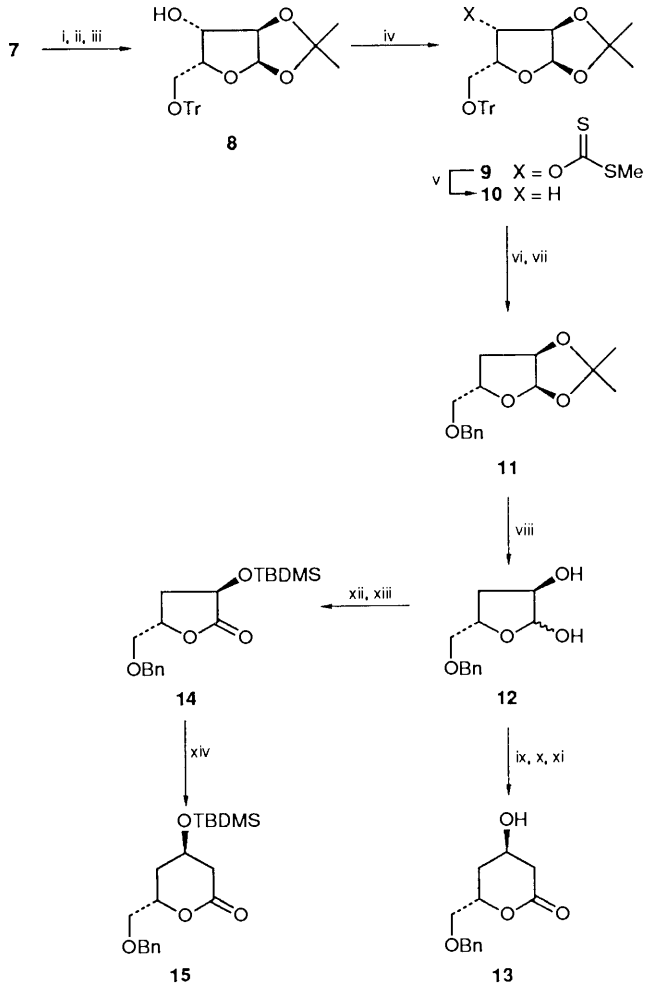
**3** R = H (dihydrocompactin)
**4** R = Me (dihydromevinolin)

We report here a simple synthesis of (4*R*,6*S*)-6-benzyloxymethyl-4-t-butyldimethylsilyloxytetrahydro-2-pyrone **15** a building block for compounds **1**–**4** and their cogeners. In our retrosynthetic analysis (Scheme 1) we envisaged in structure **B** a useful intermediate for the synthesis of **A** by a simple homologation of the butyrolactone structure. In turn, the five-membered lactone **B** can be obtained either from L-glutamic acid[5], D-glucose[4h,6] or D-xylose[7] **7**.

Carbohydrates used as precursors in the synthesis of enantiomerically pure compounds are often initially structurally modified and/or several of their chiral centres inverted before use. In this context, D-xylose has the advantage of having a carbon skeleton of the right stereochemistry so that deoxygenation at C-3 is the only substantial modification necessary before its use in synthesis of the lactone **B**. Selective protection–deprotection of D-xylose **7** (Scheme 2) afforded a diol that could



**Scheme 1**



**Scheme 2** *Reagents and conditions*: i, $CH_3COCH_3$, $CuSO_4$ (anhydrous), 25 h r.t., 85%; ii, 75% AcOH, r.t. 24 h, 90%; iii. TrCl, Py, 16 h, 95%; iv, NaH, $CS_2$, MeI, THF, 88%; v, 1.2 eq. $Bu_3SnH$, AIBN, $C_6H_6$ reflux 1 h, 78%; vi, $H_2$, 10% Pd/C, EtOH, t.r. 12 h, 100%; vii, NaH, BnBr, THF, r.t. 2 h, 95%; viii, 3.2M HCl–dioxane (1:1), r.t. 2 h, 90%; ix, NaH, $Ph_3P^+CH_2SPhCl^-$, DMF–$Me_2SO$ (2:3), 0 °C, 70%; x, $HgCl_2$, HgO, $CH_3CN$–$H_2O$ (3:5:1), 65 °C, 55%; xi, *N*-iodosuccinimide, $Bu_4NI$, $CH_2Cl_2$, r.t., 75%; xii, $Ag_2CO_3$/Celite, $C_6H_6$, reflux 2 h, 80%; xiii, TBDMSCl–imidazole, $CH_2Cl_2$, r.t. 1 h, 90%; xiv, 4 eq. $LiCHBr_2$, THF, −90 °C then HCl sat. in $Et_2O$ until pH ~6, 78%

be selectively tritylated at the primary hydroxy group to give compound **8**. This was transformed into its xanthate **9** and then deoxygenated by the method of Barton[8] to give the deoxy product **10** ($[\alpha]_D^{25}$ −14.1, *c* 3.7 in $CHCl_3$). The conversion of **10** into the benzyl ether derivative **11**, achieved in very high yield, was necessary in order to ensure the subsequent selective cleavage of the acetonide group. The latter was removed under acidic conditions (3.2M HCl–dioxane, 1:1) to give the lactol **12**.

This was converted into the β-hydroxy-δ-lactone **13** by a method elaborated by Lee on a similar substrate.[6]

Treatment of the lactol **12** with $Ph_3P^+CH_2SPhCl^-$ resulted in the corresponding open-chain thio enol ether which could be hydrolysed with mercury salts ($HgCl_2$–HgO) in aqueous acetonitrile. During this process the six-member ring lactol was formed and its subsequent oxidation with *N*-iodosuccinimide gave the lactone **13** in 31% yield from **12**. Alternatively the lactol **12** could be oxidised to the corresponding lactone with $Ag_2CO_3$–Celite (Fetizon reagent) and the resulting α-hydroxy lactone protected as a TBDMS ether **14** ($[\alpha]_D^{25}$ +36.1, *c* 2.35 in $CHCl_3$). We were aware that few methods are available in the literature to realize this key step and indeed the use of the method of Kowalski,[9] the most promising, gave only a complex mixture of products. Fortunately after several attempts, we found the optimum conditions to afford the desired product **15** in 78% yield. In order to confirm its structure, the lactone **15** was desilylated ($Bu_4NF$, THF) to give an alcohol which was identical with compound **13** and the spectroscopic data of which agreed with those in the literature.[4i]

## Experimental

(4R,6S)-6-*Benzyloxymethyl*-4-*t*-*butyldimethylsilyloxytetrahydro*-2-*pyrone* **15**.—To a stirred solution of $LiCHBr_2$[9] (4 equiv., 1.07 g, 6 mmol) in dry THF (10 ml) at −90 °C compound **14** (0.5 g, 1.5 mmol) dissolved in dry THF (10 ml) was added dropwise. After the mixture had been stirred at −90 °C for 10 min, a saturated solution of HCl in $Et_2O$ was added until the mixture reached pH = 6. It was then allowed to warm to room temperature when it was diluted with $Et_2O$ (120 ml), washed with saturated brine, and dried ($MgSO_4$). Chromatography of the residue on a silica gel column (hexane–EtOAc, 9:1) afforded the title product as an oil (0.41 g, 78%); $[\alpha]_D^{25}$ −18° (*c* 1, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1735; δ(300 MHz, $CDCl_3$) 0.10 (s, 3 H), 0.15 (s, 3 H), 0.91 (s, 9 H), 1.95–2.05 (m, 2 H), 2.20–2.30 (m, 1 H), 2.40–2.50 (m, 1 H), 3.43 (dd, 1 H, *J*/Hz 10.5 gem., *J*/Hz 3.5), 3.68 (dd, 1 H, *J*/Hz 10.5 gem., *J*/Hz 3.5), 4.48–4.52 (m, 1 H), 4.58 (d, 1 H, *J*/Hz 11.5), 4.60–4.68 (m, 1 H), 4.65 (d, 1 H, *J*/Hz 11.5) and 7.30–7.35 (m, 5 H); *m*/*z* 350 ($M^+$), 281, 271, 139, 91 and 75 (Found: C, 65.05; H, 8.7. $C_{19}H_{30}O_4Si$ requires C, 65.10; H, 8.62)

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