Enantioselective Synthesis of (*S*)- and (*R*)-6-(2,3-Dihydroxypropyl)-1,3-dioxin-4-ones: the Versatile Building Blocks of Four- and Six-carbon Backbones

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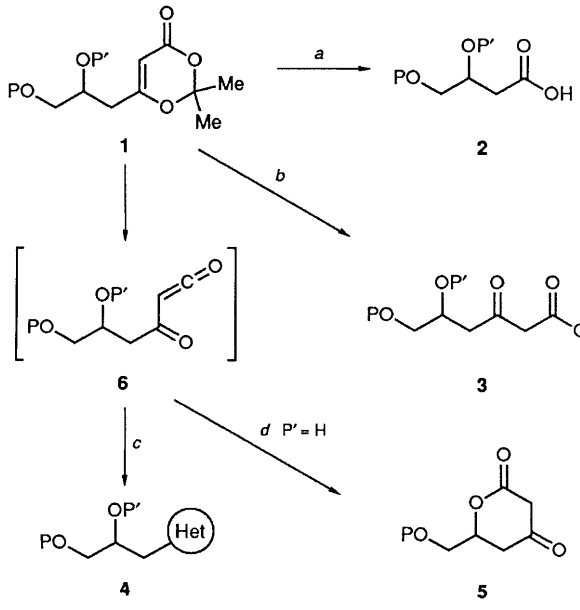
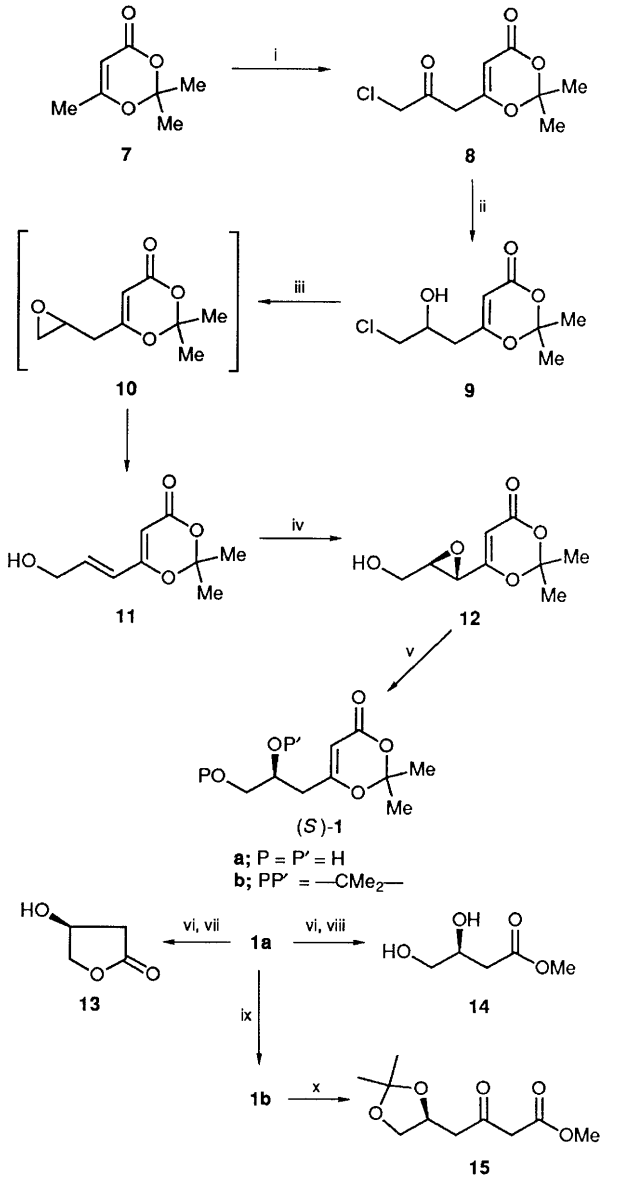
The Sharpless asymmetric epoxidation of 2,2-dimethyl-6-(3-hydroxy-1-propenyl)-1,3-dioxin-4-one using titanium tetraisopropoxide–diisopropyl tartrate followed by catalytic hydrogenation affords the title compounds as enantiomerically pure compounds, which act as versatile four- and six-carbon building blocks.

1,3-Dioxin-4-ones act as versatile synthons in organic synthesis.[1] We have been interested in synthesizing 6-(2,3-dihydroxypropyl)-1,3-dioxin-4-one **1** by focusing our attention on the utilization of the dioxinone moiety as the corresponding β-keto acid and acyl ketene equivalents (Scheme 1). Once **1** is synthesized, the following transformations may be expected. Thus, while oxidative cleavage (path *a*) affords **2**, hydrolysis at the acetal function (path *b*) leads to **3**. Furthermore, by knowing that the 6-electron cycloreversion (by heating[2] or irradiation[3] at 254 nm) of the dioxinones to acylketenes (path *c*) takes place readily, their manipulation either to heterocycles **4** by hetero-Diels–Alder reaction[4] or to inter-[5] and intra-molecular ketene trapping[6] compounds by nucleophiles (*e.g.* formation of **5**) should be expected.

Using readily available 6-methyl derivative **7**† as the starting material, (*S*)-**1** was synthesized as an enantiomerically pure compound. Though reaction steps are longer (5-step), all reactions except for the first one (*ca.* 65%)‡ proceeded in nearly quantitative yields and are suitable for large-scale preparation. Thus, base-catalysed chloroacetylation to **8** followed by sodium borohydride reduction gave **9** (racemic). Treatment of **9** with NaOH–ether (2 mol dm^{-3}) at room temperature gave the allyl alcohol **11** as the sole product. Presumably, the epoxide **10** was formed first, which was then cleaved to the diol. Epoxidation[7,8] of **11** by employing *tert*-butyl hydroperoxide (TBHP) as an oxygen donor and titanium tetraisopropoxide–diisopropyl D-(−)-tartrate (DIPT) as the catalyst, in presence of 4 Å molecular sieves,[9]§ gave the epoxide **12**. ^1H NMR analysis of the Mosher ester in $CDCl_3$ indicated >99% enantiomeric excess (e.e.). Catalytic



Scheme 1 P, P′ = H or an appropriate protecting group



Scheme 2 *Reagent and conditions*: i, lithium diisopropylamide (LDA) (1 equiv.), hexamethylphosphoramide (HMPA) Et_2O, then $ClCH_2COCl$ (0.5 equiv.), −78 °C; ii, sodium borohydride ($NaBH_4$), MeOH; iii, aqueous NaOH (2 mol dm^{-3}); iv, TBHP, diisopropyl D-(−)-tartrate, $Ti(OPr^i)_4$, molecular sieves 4 Å, CH_2Cl_2, −20 °C; v, H_2, Pd/C, AcOEt; vi, O_3 and then Me_2S, −78 °C; vii, CF_3CO_2H, CH_2Cl_2; viii, MeOH, conc. H_2SO_4; ix, $Me_2C(OMe)_2$, $HClO_4$, acetone; x, MeOH, toluene, reflux

† This compound is known as diketene-acetone adduct and is commercially available.

‡ The yield is based on the consumed **7**.

§ Though the results herein were obtained using the stoichiometric conditions,[7] use of the modified conditions[9] have also given satisfactory results. Details will be reported in a full paper.

hydrogenation of **12**, $[\alpha]_D^{22}$ + 36.8° (*c* 1.0, $CHCl_3$), in ethyl acetate afforded the diol (*S*)-(**1a**), $[\alpha]_D^{20}$ −22.8° (*c* 2.16, $CHCl_3$). The absolute structure of the epoxide was determined by its transformation (ozonolysis followed by treatment with trifluoroacetic acid) to (*S*)-3-hydroxy-4-butanolide **13**.[10] Methyl (*S*)-3,4-dihydroxybutanoate **14** was also synthesized in the same manner (ozonolysis followed by methylation). Alternative syntheses of **14** and its use in natural products synthesis as well as transformation to other four-carbon building blocks have been carried out by many researchers.[11]

The diol **1a** also afforded the protected dihydroxy β-keto ester **15**: the six-carbon building block, which is useful for synthesis of HR 780,[12] a synthetic HMG-CoA reductase inhibitor. Though several synthetic methods for **15** are available, none seems to be satisfactory owing to low availability of the starting materials.[13] When the route shown in Scheme 2 was carried out by using L-(+)-DIPT in the epoxidation step, the enantiomer [(*R*)-6-(2,3-dihydroxypropyl)-1,3-dioxin-4-one] was also synthesized with the same efficiency.

We are currently investigating the use of **1** either according to path *c* or even as substrates for pericyclic reactions.[14]

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