A Simple Chiral Synthesis of Both (*R*)- and (*S*)-Mevalonolactones from a Single Precursor *via* Diastereocontrolled Oxygenation

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A synthesis of (*R*)- and (*S*)-mevalonolactones (**10**) has been developed from the common chiral lactone precursor (**1**) by diastereocontrolled oxygenation with a molybdenum peroxide complex.

Although several interesting chiral syntheses of optically active mevalonolactone (**10**) have been described,[1] an oxygenation approach at the chiral centre has not previously been reported. We describe herein a synthesis of both (*R*)- and (*S*)-enantiomers of mevalonolactone (**10**) from a common chiral precursor (**1**) *via* diastereocontrolled oxygenation with oxodiperoxy(pyridine)(hexamethylphosphoric triamide)-molybdenum (MoOPH)[2] at the key stage.

Oxygenation of the lithium enolate generated from the known alkyl γ-lactone (**1**),[3] prepared from (*S*)-glutamic acid[4] or D-mannitol,[5] with 1.5 equiv. of MoOPH[2] at −78 °C in tetrahydrofuran (THF) allowed a diastereoselective reaction at the less hindered face of the molecule to give the hydroxylated product (**2**),† $[\alpha]_D$ + 34.7 ° (*c* 0.60, $CHCl_3$), in 63 % yield, accompanied by a small amount of the separable enantiomer (silica gel column chromatography, 7% yield). When oxygenation was carried out with bubbling molecular oxygen in the presence of triethyl phosphite,[6] virtually no diastereoselection was observed and an equal mixture of both isomeric products was obtained in moderate yield.

Reduction of (**2**) with lithium aluminum hydride (THF, 0 °C) gave the triol (**3**), in nearly quantitative yield, the primary hydroxy group of which was selectively toluene-*p*-sulphonated to give (**4**) using an excess of toluene-*p*-sulphonyl chloride (7.5 equiv.) in pyridine at 0 °C for 6 h. The crude sample of (**4**) was reduced with lithium aluminum hydride (THF, 0 °C) to give the diol (**5**) which on treatment with methanol containing a catalytic amount of hydrochloric acid[7] underwent smooth detritylation to give the triol (**6**), $[\alpha]_D$ + 13.8 ° (*c* 1.0, $CHCl_3$), in 43% overall yield from (**3**).

On sequential 'one-pot' reaction in methanol (ozonolysis at −78 °C, reduction with sodium borohydride, and cleavage with aqueous sodium periodate), (**6**) afforded the (*R*)-lactol (**8**) in 45% overall yield as a mixture of epimers *via* the tetraol (**7**). Compound (**8**) was readily converted into (*R*)-mevalonolactone (**10**), $[\alpha]_D$ − 23.4 ° (*c* 0.32, EtOH) [lit.[1b] $[\alpha]_D$ − 23.0 ° (*c* 6, EtOH)], in 89% yield by treatment with

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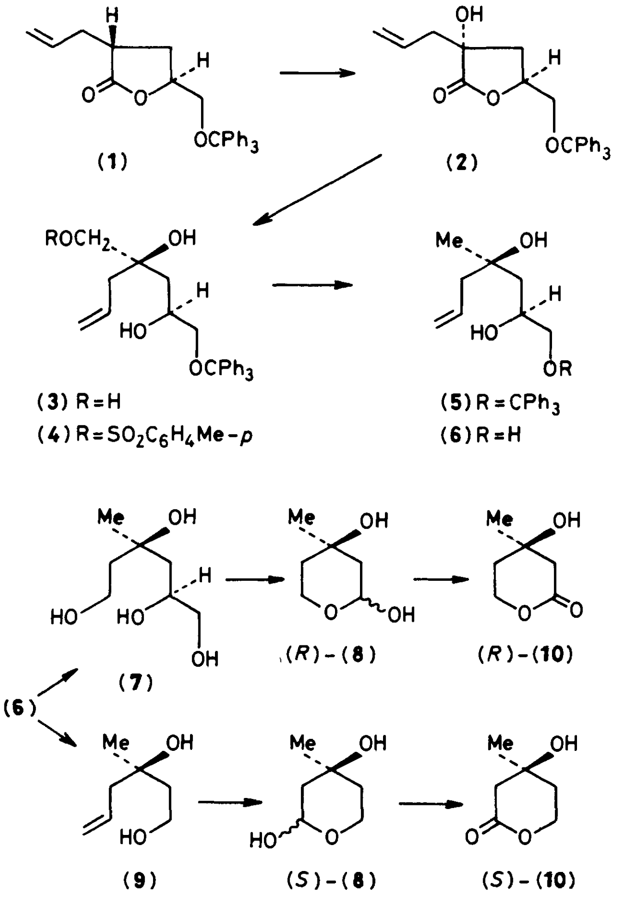
† All new isolated compounds exhibited satisfactory analytical (combustion and/or high resolution mass spectrum) and spectral (i.r., ^{1}H n.m.r., and mass) data.



pyridinium chlorochromate in methylene chloride at room temperature.

On the other hand, sequential 'one-pot' oxidative cleavage ($NaIO_4$) and reduction ($NaBH_4$) of (**6**) in aqueous methanol afforded the diol (**9**), $[\alpha]_D$ + 5.1 ° (*c* 1.4, EtOH), in 92% yield. Ozonolysis of (**9**) (MeOH, −78 °C, then Me_2S, −78 °C to room temp.) yielded the (*S*)-lactol (**8**) as a mixture of epimers. The (*S*)-lactol was then converted into (*S*)-mevalonolactone (**10**), $[\alpha]_D$ + 23.3 ° (*c* 0.98, EtOH) [lit.[1b] $[\alpha]_D$ + 22.8 ° (*c* 10, EtOH)], in 80% yield by oxidation with pyridinium chlorochromate in methylene chloride.

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