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Desymmetrisation of dialdehydes: (+)-(*S*) and (−)-(*R*) *nor*-methyl mevaldate as versatile synthetic intermediates

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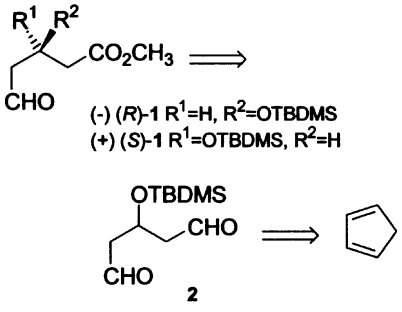
Abstract—Desymmetrisation of 3-(*t*-butyldimethylsilyloxy)pentanedial **2** may be carried out by monoacetalisation with (*R*)- or (*S*)-2-phenylethanol. The products may be elaborated to *nor*-methyl mevaldate derivatives.

The synthetic versatility of 1,3,5 trioxygenated substrates has led to much interest in their enantiocontrolled construction and such derivatives have been obtained through desymmetrisation of anhydrides,[1] enzymatic reductions[2a] and ester hydrolysis,[3] enantioselective catalytic hydrogenation,[4] stereoselective aldol condensation,[4] Sharpless asymmetric epoxidation,[5] and by transformation of other enantiopure precursors.[2b]

In this paper we present the synthesis of (+)-(*S*) and (−)-(*R*) methyl (*t*-butyldimethylsilyl)mevaldate (*R*)- and (*S*)-**1** via desymmetrisation of dialdehyde **2**, readily obtained from cyclopentadiene (Scheme 1). Procedures for obtaining enantiomerically enriched (*R*)-**1** have been reported previously.[2b,3a,5]



Scheme 1.

Desymmetrisation is proving to be a powerful synthetic tool,[6] and dialdehydes have been the focus of a number of studies.[7] We decided to explore the potential for desymmetrisation of dialdehyde **2** via diastereocontrolled acetal formation with chiral alcohols.

Although several approaches to analogues of dialdehyde **2** have been reported,[7b,8] we found it to be conveniently prepared through a six-step sequence from cyclopentadiene. The known alcohol **4** was obtained from cyclopentadiene via epoxide **3** in 20% overall yield following the procedure of Crandall.[9] Alcohol **4** was protected as its *t*-butyldimethylsilyl ether **5** in 95% yield (TBDMSCl–imidazole, THF, 0°C) and this was transformed into a 12:1 mixture of diasteroisomeric diols **6** by the method of Matteson, employing catalytic osmium tetroxide in *t*-butanol at reflux with trimethylamine-*N*-oxide as the reoxidant.[10] Cleavage of **6** with sodium periodate in 8:2 dioxane:water, followed by exhaustive extraction with ethyl acetate furnished dial **2**, which forms the cyclic hydrate **7** on standing. In order to achieve reproducible results in the subsequent desymmetrisation step, it was imperative to transform the hydrate back to the dialdehyde by treating with powdered 4 Å molecular sieves in refluxing THF for 2 h (Scheme 2).

A range of chiral alcohols was investigated with 2-phenylethanol showing the highest diastereoselectivity. After refluxing 1.5 equiv. of chiral alcohol with dialdehyde **2** and 4 Å molecular sieves in THF for 18 h, analysis indicated a mixture of monoacetals and starting material.[11] Although these could be isolated and characterised, it was found most convenient to filter the slurry through a pad of Celite®, remove the solvent and

Keywords: desymmetrisation; 3-(*t*-butyldimethylsilyloxy)pentanedial; *nor*-methyl mevaldate.

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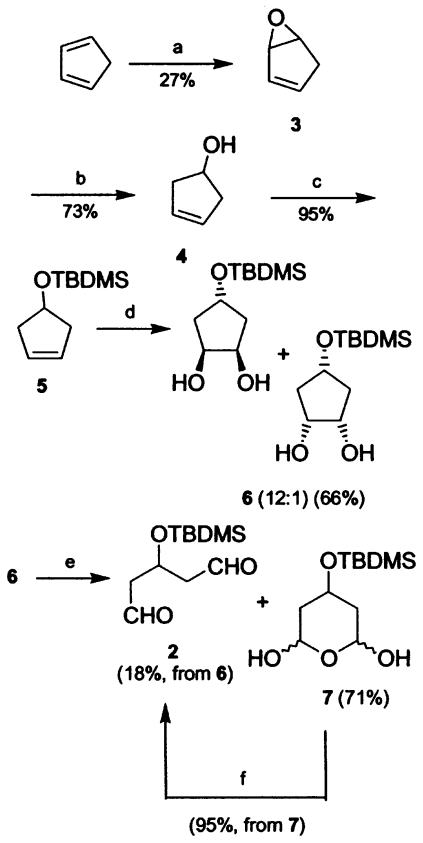


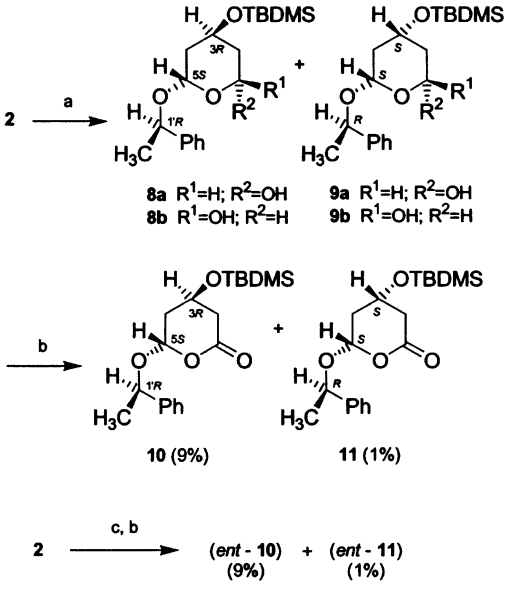
Scheme 2. *Reagents and conditions*: (a) CH_3CO_3H, CH_3CO_2Na, Na_2CO_3, CH_2Cl_2, $T<10°C$; (b) $LiAlH_4$, Et_2O, 0°C; (c) TBDMSCl, imidazole, THF, 0°C; (d) OsO_4, $(CH_3)_3NO$, pyr, *t*-BuOH, H_2O, reflux; (e) $NaIO_4$, dioxane/H_2O (8:2), rt; (f) 4 Å mol. sieves, THF, reflux.

treat the residue with PCC in CH_2Cl_2 overnight.[12] By this means (*R*)-2-phenylethanol furnished the readily separable lactones **10** and **11** in 9 and 1% overall isolated yields, respectively.[13] (*S*)-2-Phenylethanol likewise gave *ent*-**10** and *ent*-**11** in the same yields (Scheme 3). Treatment of lactones **10** and *ent*-**10** with MeONa in MeOH at −35°C for 18 h, yielded (*R*)-**1** and (*S*)-**1** in 76% yield, possessing specific rotations of −10.5 ($c=$ 1.5, $CHCl_3$), and +10.7 ($c=0.475$, $CHCl_3$), respectively,[14] together with (*R*)-2-phenylethanol and (*S*)-2-phenylethanol, recovered in 64% yield and possessing the same specific rotations as the starting materials (Scheme 4).[15,16]

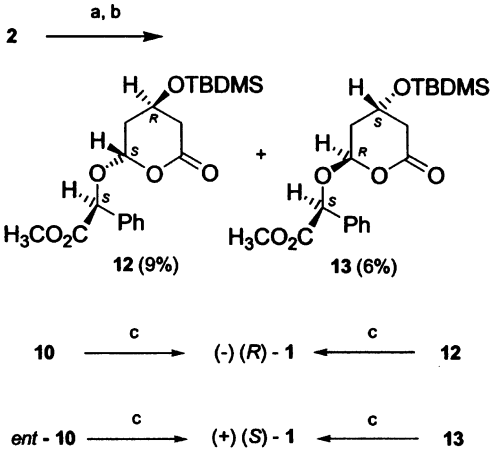
Confirmation of the absolute stereochemistries of (*R*)-**1** and (*S*)-**1** and those of the parent compounds **10** and *ent*-**10**, at C-3, was achieved via lactones **12** and **13**, obtained from treatment of compound **2** with (*S*)-methyl mandelate in THF under reflux, followed by oxidation of the crude mixture with PCC. Compounds **12** and **13** furnished crystals suitable for X-ray crystallographic analysis, establishing the absolute configuration at C-3 in lactones **12** and **13** as (*R*) and (*S*), respectively (Fig. 1).[17] Subsequent treatment of lactone **12** with MeOH/MeONa yielded (*R*)-**1**; whereas lactone **13** gave (*S*)-**1** (Scheme 4).

With the assignment of the absolute configuration at C-3 on lactones **10** and *ent*-**10** as (*R*) and (*S*), respectively, the relative stereochemistry on compounds **10** and **11** could be established by combination of NOE difference studies and ^1H NMR coupling constants (Fig. 2).

In conclusion, we have shown that dialdehyde **2** may be desymmetrised using chiral alcohols by diastereocontrolled monoacetal formation and the products converted to useful chiral intermediates. Although the conversion in the acetalistion step is not high, the overall procedure constitutes an experimentally expedient means of accessing (*S*)-**1** and (*R*)-**1**.



Scheme 3. *Reagents and conditions*: (a) (+)-(*R*)-1-phenylethanol, 4 Å mol. sieves, THF, reflux, 24 h; (b) PCC, 4 Å mol. sieves, CH_2Cl_2, 18 h; (c) (−)-(*S*)-1-phenylethanol, 4 Å mol. sieves, THF, reflux, 24 h.



Scheme 4. *Reagents and conditions*: (a) (+)-(*S*) methyl mandelate, 4 Å mol. sieves, THF, reflux, 24 h; (b) PCC, 4 Å mol. sieves, CH_2Cl_2, 18 h; (c) MeONa, MeOH, −35°C.

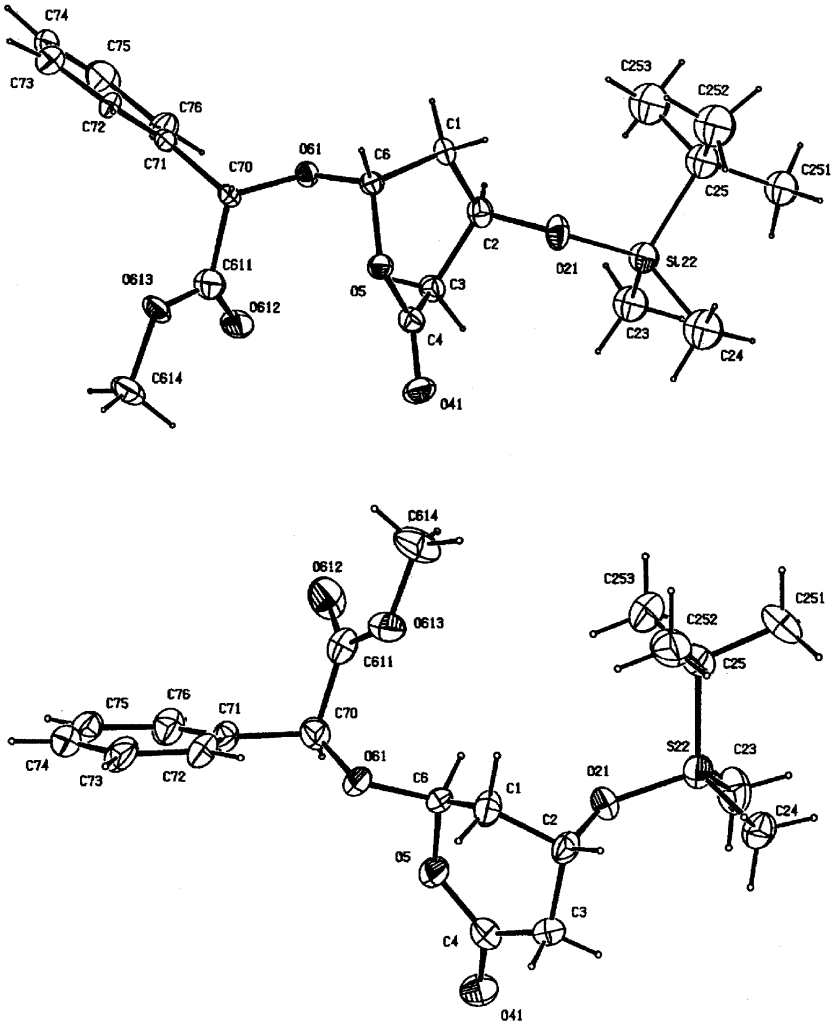


Figure 1. X-Ray for compounds **12** (upper) and **13** (lower) (ORTEP projections).

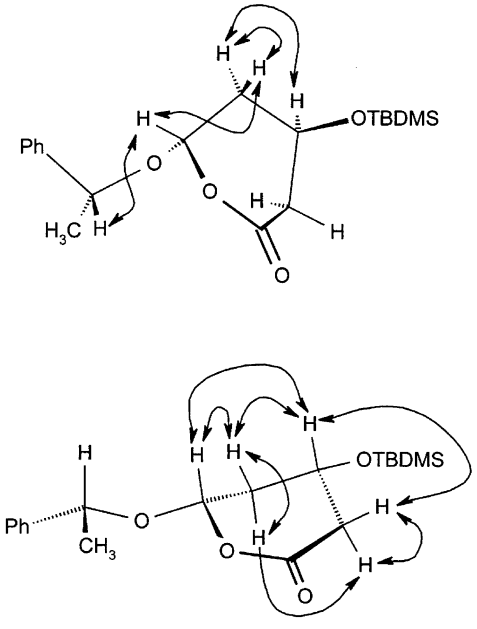


Figure 2. Selected NOE for compounds **10** (upper) and **11** (lower).

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11. Leaving the reaction for longer times led to no increase in conversion, but the diastereoisomeric ratios on the isolated products are lower.
12. **Desymmetrisation of 3-(*t*-butyldimethylsilyloxy)pentandial (2)/PCC oxidation procedure. (3*R*,5*S*,1′*R*)-3-(*t*-Butyldimethylsilyloxy)-5-hydroxy-5-(1′-phenylethoxy) pentanoic acid lactone (10), (3*S*,5*S*,1′*R*)-3-(*t*-butyl dimethylsilyloxy)-5-hydroxy-5-(1′-phenylethoxy)pentanoic acid lactone (11)**. 1-Phenyl-ethanol (325 mg) was added to a suspension of dial **2** (576 mg) and 4 Å powdered molecular sieves (2.5 g) in dry THF (10 mL). The slurry was refluxed for 24 h, filtered through Celite® and the THF was removed under reduced pressure to yield 757 mg of crude product. This oil was dissolved in DCM (12 mL) and then added dropwise to a suspension of PCC (2.0 g) and powdered 4 Å molecular sieves (3.0 g) in DCM (15 mL) at room temperature. The reaction was stirred vigorously at room temperature for 18 h, diethyl ether was then added and the mixture was stirred for a further 1 h. The suspension was filtered over a pad of silica gel, and washed through with further ether. The ether was removed under reduced pressure to give a crude mixture of lactones. Further purification by column chromatography yielded **10** (79 mg, 9%) and **11** (9 mg, 1%).
13. Data for compound **10**: $[\alpha]_D^{25}$ +157 ($c=1.02$, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.03 (3H, s, $SiC\underline{H}_3$), 0.02 (3H, s, $SiC\underline{H}_3$), 0.76 (9H, s, $SiC(C\underline{H}_3)_3$), 1.46 (3H, d, J 6.8, $CHC\underline{H}_3$), 1.85 (1H, ddd, J 3.6, 6.8, 13.8, H-4β), 1.94 (1H, ddd, J 3.6, 5.6, 13.8, H-4α), 2.47 (1H, dd, J 5.6, 17.2, H-2), 2.76 (1H, dd, J 4.8, 17.2, H-2′), 4.33 (1H, m, H-3α), 4.99 (1H, q, J 6.4, H-1′), 5.25 (1H, dd, J 3.6, 5.6, H-5β), 7.36–7.27 (5H, $C_6\underline{H}_5$); selected NOE H-3α↔H-4α (4%), H-4α↔H-4β (23%), H-4β↔H-5β (7%), H-5β↔H-1′ (7%); δ_C (100 MHz; $CDCl_3$) −4.79, −4.93, 17.87 23.92, 25.57, 37.05, 39.95, 62.51, 75.78, 97.92, 126.46, 127.97, 128.56, 141.79, 169.64.
Data for compound **11**: $[\alpha]_D^{25}$+144 ($c=0.37$, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.03 (6H, s, $Si(C\underline{H}_3)_2$), 0.86 (9H, s, $SiC(C\underline{H}_3)_3$), 1.47 (3H, d, J 6.6, $CHC\underline{H}_3$), 1.82 (1H, ddd, J 7.7, 9.2, 14.0, H-4α), 2.22 (1H, dddd, J 1.8, 4.4, 5.4, 14.0, H-4β), 2.51 (1H, dd, J 9.2, 16.8, H-2α), 2.69 (1H, ddd, J 1.8, 5.4, 16.8, H-2β), 3.98 (1H, tt, J 5.4, 9.2, H-3β), 5.08 (1H, q, J 6.6, H-1′), 5.04 (1H, dd, J 4.4, 7.7, H-5β), 7.28–7.38 (5H, $C_6\underline{H}_5$); selected NOE H-3β↔H-2β (4%), H-3β↔H-5β (5%), H-3β↔H-4β (5%), H-2β↔H-2α (18%), H-4β↔H-4α (23%), H-4α→H-2α (3%), H-4β↔H-5β (10%); δ_C (100 MHz; $CDCl_3$) −4.81, −4.75, 17.89 24.04, 25.61, 38.69, 40.13, 62.62, 75.81, 97.86, 126.56, 128.06, 128.70, 141.98, 169.53.
14. $[\alpha]_D^{25}$ −9.6 ($c=1.2$, $CHCl_3$), Ref. 2b; $[\alpha]_D^{25}$ −9.83 ($c=5.38$, $CHCl_3$), Ref. 5.
15. **(−)-(*R*) Methyl (*t*-butyldimethylsilyl) mevaldate (*R*)-(1).** Sodium methoxide (18 mg) was added to a solution of lactone **8** (23 mg) in dry MeOH (3 mL) at −35°C. The reaction was stirred at −35°C for 24 h, then quenched with saturated NH_4Cl (3.5 mL). The reaction was then warmed to room temperature and diethyl ether (10 mL) and brine (2 mL) were added. The layers were separated and the aqueous layer was then extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (2×5 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a crude reaction product (25 mg), which was purified by column chromatography to give (*R*)-**1** (13 mg, 76%) and (*R*)-2-phenylethanol (5 mg, 64%).
16. Data for compound **1**: (*R*)-(**1**) $[\alpha]_D^{25}$ −10.5 ($c=1.5$, $CHCl_3$), lit.;[2b] (*S*)–(**1**) $[\alpha]_D^{25}$ +10.7 ($c=0.475$, $CHCl_3$); δ_H (200 MHz; $CDCl_3$) 0.01 (6H, s, $Si(C\underline{H}_3)_2$), 0.86 (9H, s, $SiC(C\underline{H}_3)_3$), 2.49 (2H, dd, J 1.6, 5.9, H-2, H-2′), 2.58 (1H, m, H-4, H-4′), 3.61 (3H, s, $COOC\underline{H}_3$), 4.56 (1H, q, J 5.9, H-3), 9.73 (1H, t, J 1.9, $C\underline{H}O$); δ_C (50 MHz; $CDCl_3$) −4.48, −4.40, 17.81 25.56, 42.30, 50.84, 51.37, 64.99, 170.95, 200.35.
17. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 168527 and 168528. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).