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Chiral 6-phenyl-2,3-bismethylenemethoxycarbonyl-[1,4]-dioxane as a designer synthon for an efficient and short synthesis of optically pure 2,6-dioxabicyclo[3.3.0]octane-3,7-dione

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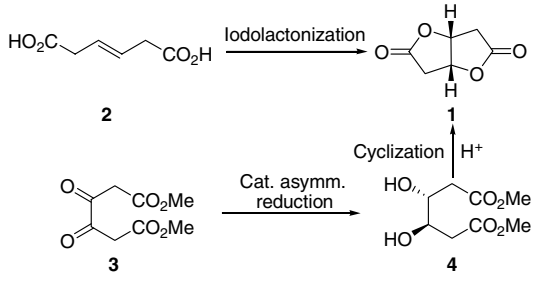
Abstract—Chiral 6-phenyl-2,3-bismethylenemethoxycarbonyl-[1,4]-dioxane, synthesized by the PET cyclization of **8**, has been used as a designer synthon for an efficient and short synthesis of optically pure 2,6-dioxabicyclo[3.3.0]octane-3,7-dione.

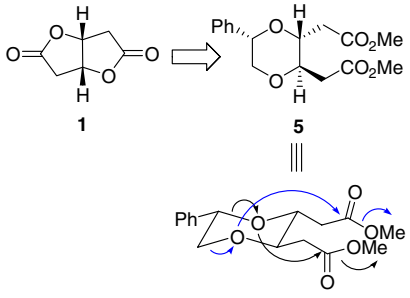
2,6-Dioxabicyclo[3.3.0]octane-3,7-dione (bis-lactone, **1**) has been shown to be a useful intermediate in the synthesis of some important biologically active compounds such as eldanolide,[1] the Geisman–Weiss lactone,[2] prostaglandin analogs,[3] *trans*-lauradiols,[4] 8,9-epoxyeicosatrienoic acid[5] and enantiomerically pure butenolides.[6] However, in spite of the significant utility of **1**, it was surprising to note that only two strategies exist for its synthesis. Hizuka et al.,[1] have synthesized **1** in racemic form by the iodo lactonization of *trans*-3-hexenedioic acid (**2**) and its synthesis in the optically pure form was achieved by catalytic asymmetric reduction,[6] using $RuCl_2$[(*S*)-BINAP](*p*-cymene) as the catalyst, of 3,4-dioxohexanedioate (**3**) to give **4** followed by cyclization.

However, the yield of **1** in the latter approach is poor due to the formation of other un-utilizable diastereoisomers of **4** (Scheme 1). Considering the importance of **1** in the synthesis of several important classes of compounds, we envisaged optically pure 6-phenyl-2,3-bismethylenemethoxycarbonyl-[1,4]-dioxane (**5**) as a possible precursor for its synthesis. The design of **5** was based on its stable but equally labile 1,4-dioxane moiety, which is suitable for an easy transformation to **1** with the aid of a Lewis acid as shown in Scheme 2.

We envisioned the synthesis of **1** utilizing a novel *trans*-1,2-stereoselective carbon–carbon bond formation strategy, developed in our group[7,8] between two activated olefins through a photoinduced electron transfer (PET) cycle as shown in Figure 1.



Scheme 1.



Scheme 2.

In this letter, we report our success in synthesizing diastereomerically pure **5** and its conversion to optically active **1**.

Keywords: Chiral dioxan; Bis-lactone; Photoinduced electron transfer.
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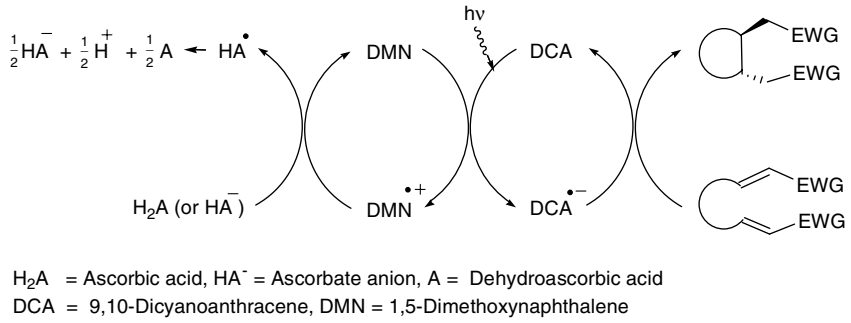
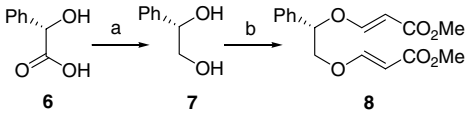


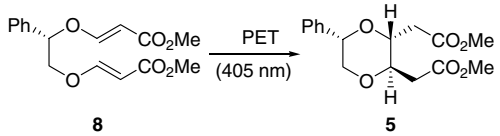
Figure 1.



Scheme 3. Reagents and conditions: (a) LAH, dry THF, reflux, 8 h, 86%; (b) methyl propiolate, NMM, dry DCM, rt, 6 h, 78%.

We began the synthesis of optically pure (*S*)-**5** by synthesizing precursor **8** in 78% yield by the reaction of **7** with methyl propiolate in the presence of *N*-methylmorpholine (NMM).[9] Compound **7** was obtained in 86% yield by the LAH reduction of commercially available (*S*)-(+)-mandelic acid (Scheme 3).

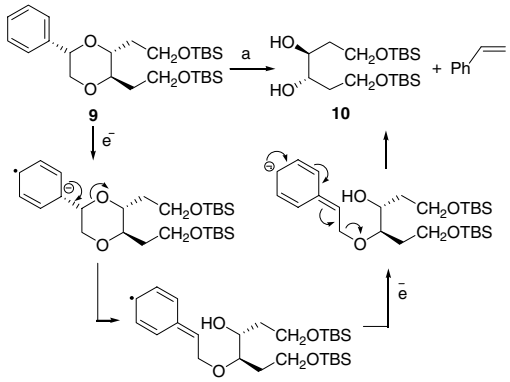
PET activation of **8** involved irradiation ($\lambda = 405$ nm) of a solution of **8** (1.96 mmol) containing DMN (0.29 mmol), DCA (0.59 mmol) and ascorbic acid (5.09 mmol) in 700 mL of solvent [DMF/*i*-PrOH/H_2O (88:10:2)] in a specially designed photoreactor consisting of three chambers. The first and outermost chamber contained the irradiation solution and the second one was charged with $CuSO_4{\cdot}5H_2O/NH_3$ filter solution.[10] A 450 W Hanovia medium pressure mercury lamp was housed in a water-cooled jacketed chamber, which was immersed into the second chamber. The whole photoreactor was constructed of Pyrex glass. The *i*-PrOH functioned as the hydrogen donor. All the light ($\lambda = 405$ nm) under this experimental set up was absorbed by DCA only. Before irradiation, the solution was deoxygenated by bubbling argon for 2 h and a slow stream of argon was continued throughout the entire duration of the irradiation. After acceptable consumption of the starting material (92%, monitored by GC), irradiation was discontinued. Work-up and purification of the crude photolysate through silica gel column chromatography gave **5** ($[\alpha]_D^{22}$ EtOH, +60.83, *c* 2.05, $CHCl_3$) in 88% yield (Scheme 4).



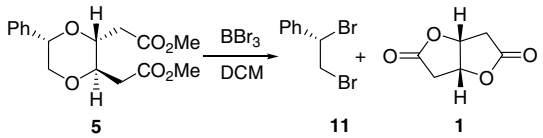
Scheme 4.

Compound **5** was characterized by ^1H NMR, ^{13}C NMR and mass spectrometry.[11] Since, H-2, H-3 and one of the H-4 protons appeared together between δ 3.80 and 4.10 (3H, multiplets) in the ^1H NMR spectrum, the stereochemical assignment of this compound by 2D NMR spectroscopy proved difficult. Furthermore, our attempt to obtain single crystals for X-ray diffraction of the corresponding diacid also failed due to its poor crystalline nature (crystals were found twinned). Therefore, we decided to establish the absolute stereochemistry by transforming **5** to a known compound and comparing its optical rotation values. In this context, **5** was first transformed to **9** by LAH reduction followed by protection of the primary alcohols as –OTBS ethers. Subjecting **9** to Na/liq. NH_3 reduction gave **10** ($[\alpha]_D^{22}$ −24.5, *c* 0.24, MeOH) in quantitative yield along with the formation of styrene (Scheme 5). Comparison of the optical rotation value of **10** with the same substrate prepared from L-(−)-tartaric acid confirmed the absolute stereochemistry of **5** as 6(*S*)-phenyl-2,3-(*R*,*R*)-bismethylene-methoxycarbonyl-[1,4]-dioxane.

Although, the use of **5** for the synthesis of a C_2 symmetric 1,2-disubstituted 1,2-diol was not projected originally, this result indicated that the above strategy could also be used for the synthesis of enantiomerically pure C_2 symmetric 1,2-disubstituted 1,2-diols as this structural unit is part of various biologically active natural products[12] and useful auxiliaries for asymmetric synthesis.[13] Therefore, the development of a stereoselec-



Scheme 5. Reagents and conditions: (a) Na, liq. NH_3, dry THF, −78 °C, 20 min, quantitative.



Scheme 6.

tive synthesis of C_2 symmetric 1,2-disubstituted 1,2-diols has been an important subject in organic chemistry. These compounds have been prepared by the stereoselective addition of a nucleophile to a carbonyl functionality bearing a chiral α-alkoxy group,[14] nucleophilic opening of a chiral epoxide[15] and by asymmetric dihydroxylation[16] of *trans*-olefins. However, the enantiomeric excess recorded has ranged from poor to good.

Since both forms of optically active **6** are cheaply available, we also synthesized (*R*)-**5** and transformed it to the corresponding D-(+)-**10** ($[\alpha]_D^{22}$ +23.8, *c* 0.24, MeOH) by following similar sequences from (*R*)-**6** as described earlier for (*S*)-**6**.

Next, we examined the cleavage of **5** in order to obtain **1** in optically pure form. Towards this end, substrate **5** (0.33 mmol) dissolved in dry dichloromethane (5 mL) was cooled to −78 °C and treated with BBr_3 (0.79 mmol). After 30 min, the temperature was raised to −20 °C and the reaction was allowed to stir for 1 h. After additional stirring for 2 h at 0 °C, the solution was poured into a beaker containing ice-cold water. Extraction with DCM followed by concentration produced a gummy residue. Washing of the residue with petroleum ether several times removed all of the by-product **11** and crystallization of the remaining residue with acetone–petroleum ether mixture produced **1** [yield, 98%, mp 132–133 °C, $[\alpha]_D^{22}$ +124.48 (*c* 0.21, H_2O), literature[6] mp 132 °C, $[\alpha]_D^{19}$ +143 (*c* 1.0, H_2O)] (Scheme 6).

In summary, we have shown the utility of designer synthon **5** in the synthesis of optically active bis-lactone **1** and C_2 symmetric 1,2-disubstituted 1,2-diols. Further application of **5** in the synthesis of a prostaglandin precursor is in progress and will be reported in due course.

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11. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.66 (4H, m), 3.59 (6H, s), 3.62 (2H, m) 4.01–3.80 (2H, m), 4.65 (1H, dd, $J = 1.53$, 3.80 Hz), 7.45–7.30 (5H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 37.2, 37.5, 52.1, 72.5, 75.5, 76.0, 77.6, 126.2, 128.0, 128.5, 138.0, 170.6. MS *m/z*: 308 (M^+, 1), 246 ($M^+-C_2H_6O_2$, 1), 235 ($M^+-C_3H_5O_2$, 1), 203 (3), 188 (8), 156 (15), 140 (8), 129 (16), 104 (100), 91 (18), 77 (21), 59 (35).
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