Synthesis of (2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol

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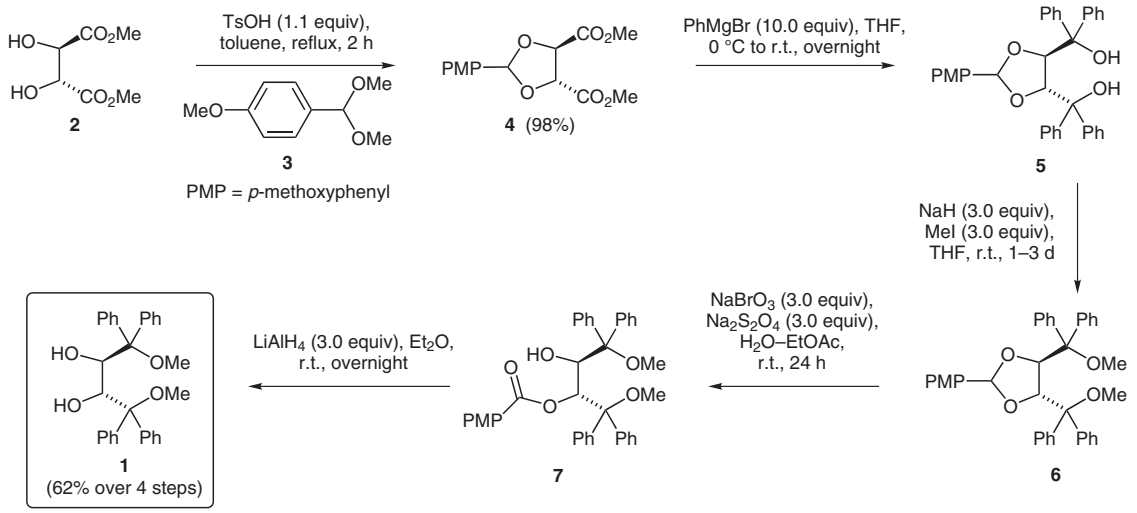
Abstract: (2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol proved to be an excellent auxiliary and stable protective group for boronic acids. Herein we report an improved practical procedure for its synthesis.

Key words: tartrate-derived auxiliary, boron, protective group, asymmetric synthesis



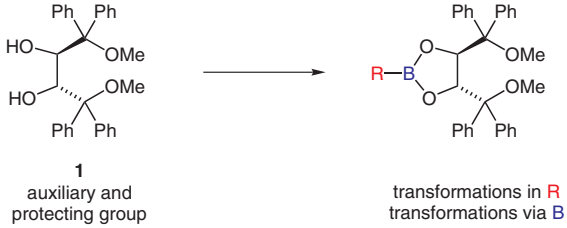
Scheme 1 Synthesis of diol **1**

Introduction

The synthesis of C_2-symmetric diols is of considerable interest due to their applications as chiral inducers.[1,2] Tartrate-based diols are especially popular. Contrary to the well-documented TADDOLs,[3] the corresponding 1,2-diols are less regularly applied. The first synthesis of diol **1** was put forward by Nakayama and Rainier.[4] In the present paper, we wish to report in detail an improved synthesis (Scheme 1) of the sterically hindered, conformationally rigid, chiral auxiliary and efficient protective group **1** for boronic acids (Scheme 2). In contrast to common boronic esters, boronic acids are considerably stable after esterification with auxiliary **1** allowing many functional group transformations in the side-chain.[5]

Synthetic Applications

A literature survey showed several applications of diol **1** in asymmetric synthesis. It is interesting to note that Nakayama and Rainier reported a preliminary result on a potential application in boron chemistry. An allyl addition was achieved albeit in moderate selectivity.[4] Despite the fact that later Zhang et al. successfully used the auxiliary **1** as best chiral inducer for the titanium-mediated asymmetric synthesis of α,α-disubstituted amino acids,[6] the focus remained on utilizing boronic acids.



Scheme 2 Diol **1** as auxiliary and protecting group for boronic acids

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The potential of **1** for cyclopropane chemistry was first described in 1997.[7] In the meantime the scope was demonstrated: Not only *cis*-[8] and *trans*-disubstituted[5,9] cyclopropanes were synthesized, but also 1,2,3-tri-[10] and 1,2,3,3-tetrasubstituted[10b] derivatives. Furthermore, numerous transformations via boron, as well as via the side-chain, were established.[11]

Boronic esters derived from diol **1** were also utilized as remote activating group. While the level of 1,8-stereoinduction observed for Diels–Alder reactions was low,[12] additions to furyl aldehyde bearing a chiral boronate in the C-3 position were highly selective.[13] The approach was extended to the corresponding furyl sulfonylamides.[14]

Auxiliary **1** also enabled [3,3]-sigmatropic rearrangements of boron-containing allyl alcohols leading to enantio- and diastereomerically pure allylboronic esters with a stereogenic centre in the α-position to the boron moiety.[15] Highly selective allyl additions led to homoallylic alcohols with a *Z*-double bond. The versatility was recently demonstrated in a natural product synthesis.[16]

Synthesis of Auxiliary 1

The first two steps were conventionally performed as previously reported (Scheme 1).[3,9a] L-(+)-Dimethyl tartrate (**2**) was protected with anisaldehyde dimethylacetal (**3**)[17] under acidic conditions furnishing diester **4** in 98% yield after recrystallization. For the addition of phenylmagnesium bromide, minimum amounts of solvent were used, yet the formation of biphenyl could not be prevented. The side-product caused no problems in the following sequence, purification was not essential at this stage. However, complete conversion into diol **5** (omitting the contamination of the product with the intermediate monoester) was important to facilitate the ultimate workup procedure, hence the use of excess of Grignard reagent. The next step was previously the least reliable and most cumbersome to work up. Sequential methylation with dimsyl anion/MeI was replaced by directly using excess NaH in THF (instead of DMSO) followed by MeI. The intermediate **6** was thus obtained in higher purity. The cleavage of the PMP-group required two steps, an oxidation leading to ester **7** and a final reduction to furnish the desired diol **1**. For the first transformation we replaced the toxic and expensive 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with commercially available cheap sodium bromate and sodium dithionite.[18,19] The final release of auxiliary **1** was accomplished by reduction with $LiAlH_4$; purification was achieved by flash column chromatography (the packed column was reused several times after flushing with EtOAc). The yield over 4 steps was 62%. A typical scale is 100 mmol, but regular scaling up to 50 g of product was also successfully achieved without loss of yield.

The reactions were carried out by using standard Schlenk techniques under dry N_2 with magnetic stirring. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use; THF was freshly distilled from sodium/benzophenone. Common solvents for chromatography (PE, EtOAc) were distilled prior to use; PE refers to a fraction with a boiling point between 40–60 °C. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm (230–400 mesh). TLC (monitoring the course of the reactions) was performed on precoated plastic sheets (Polygram® SIL G/UV_{254}, MachereyNagel) with detection by UV (254 nm) or by coloration with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), H_2O (940 mL)]. ^1H and ^{13}C NMR spectra were recorded at 20 °C in $CDCl_3$ on a Bruker ARX 300/500 spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard (^1H) or relative to the resonance of the solvent (^{13}C: $CDCl_3$ = 77.0 ppm); coupling constants *J* are given in Hz. Higher order δ and *J* values are not corrected. Microanalyses were performed at the Institut für Organische Chemie, Stuttgart. Melting points or softening ranges (Büchi 510) are not corrected. Specific rotations were measured at 20 °C. IR spectra were obtained on a Perkin-Elmer 283 spectrometer.

(4*R*,5*R*)-Dimethyl 2-(4-Methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate (4)

A 250 mL round-bottomed flask fitted with a magnetic stir bar and a Claisen condenser with a drying tube was charged with anisaldehyde dimethylacetal[17] (**3**; 35.6 g, 195 mmol), L-(+)-dimethyl tartrate (**2**; 32.9 g, 185 mmol), *p*-toluenesulfonic acid (43 mg, 0.12 mol%), and toluene (165 mL). MeOH–toluene was continuously removed from the stirred solution by distillation. The crude product was dissolved in CH_2Cl_2 (150 mL) and neutralized with K_2CO_3. The mixture was filtered through a pad of Celite and the resulting solution concentrated under reduced pressure to furnish a yellow oil, which was recrystallized from PE to yield 53.8 g (98%) of **4** as a pale yellow solid; mp 71 °C; R_f = 0.07 (PE–EtOAc, 85:15); $[\alpha]_D^{20}$ –21 (*c* = 1.6, $CHCl_3$).

IR (KBr): 3080, 2950, 1650, 1494, 1446, 1422, 1370, 1304, 1264, 1193, 1147, 1076, 1033, 1015, 964, 760, 738, 703, 648, 637 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, $ArOCH_3$), 4.84 (d, ^3J = 4.1 Hz, 1 H, 4-H or 5-H), 4.95 (d, ^3J = 4.1 Hz, 1 H, 4-H or 5-H), 6.09 (s, 1 H, 2-H), 6.91 (m_c, 2 H_{arom}), 7.51 (m_c, 2 H_{arom}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 52.79, 52.81 (CO_2CH_3), 55.3 ($ArOCH_3$), 77.3 (C-4 and C-5), 106.7 (C-2), 113.8 (CH_{arom}), 127.4 (C_{arom}), 128.8 (CH_{arom}), 161.0 (C_{arom}), 169.5, 170.2 (CO_2CH_3).

Anal. Calcd for $C_{14}H_{16}O_7$ (296.3): C, 56.76; H, 5.44. Found: C, 56.52; H, 5.44.

Bis(diphenylmethanol) 5

A flame dried 2 L three-necked, round-bottomed flask equipped with a magnetic stir bar, 250 mL pressure-equalizing addition funnel, reflux condenser and a N_2 inlet was charged with Mg turnings (24.3 g, 1 mol), a small crystal of I_2, and THF (280 mL). Bromobenzene (105 mL, 157 g, 1 mol) was then added dropwise so that THF was gently refluxing. The suspension was refluxed for an additional 1 h. The mixture was cooled to 0 °C and a solution of the acetal **4** (29.6 g, 100 mmol) in THF (180 mL) was slowly added. The stirring was continued overnight at r.t. After dilution with Et_2O (500 mL), the reaction was quenched with aq NH_4Cl (1 L, 50%) and the ethereal layer was separated. The aqueous layer was extracted with Et_2O (3 × 200 mL); the combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), and the solvents were removed under reduced pressure to yield 60.0 g of the crude product **5** as a yellow foam, which was used in the next step without further purification; R_f = 0.17 (PE–EtOAc, 85:15).

Dimethyl Ether 6

A flame dried 1 L Schlenk flask equipped with a magnetic stir bar and a silicone septum was charged with the crude bis(diphenylmethanol) **5** (60.0 g) from the previous step and THF (220 mL). NaH (95%; 7.58 g, 300 mmol) was added at 0 °C. The solution was stirred for 30 min at r.t. before MeI (18.7 mL, 300 mmol) was added and then stirred overnight at r.t. The reaction was followed by TLC, and if needed, one or two more portions of NaH and MeI were added. The mixture was diluted with Et_2O (250 mL) and hydrolyzed with H_2O (250 mL). The aqueous layer was extracted with Et_2O (3 × 250 mL), and the combined organic layers were washed with H_2O (5 × 200 mL) and brine (200 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 58.9 g of crude dimethyl ether **6** as a yellow foam, which was used in the next step without further purification; R_f = 0.40 (PE–EtOAc, 85:15).

4-Methoxybenzoate 7

A 1 L two-necked, round-bottomed flask equipped with a magnetic stir bar and a 250 mL pressure-equalizing addition funnel was charged with crude dimethyl ether **6** (58.9 g) in EtOAc (200 mL). A solution of $NaBrO_3$ (45.3 g, 300 mmol in 150 mL H_2O) was added over a period of 15 min. To the vigorously stirred two-phase mixture was added dropwise a solution of $Na_2S_2O_4$ (52.2 g, 300 mmol in 150 mL H_2O) while cooling the reaction vessel with an ice-bath. After stirring for 24 h at r.t., the mixture was diluted with EtOAc (200 mL) and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with aq 2 M $Na_2S_2O_3$ solution (8 × 200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude product **7** as a yellow foam. The ester **7** was further purified by dissolving and refluxing it in CH_2Cl_2 (400 mL) with charcoal (4 g) for 1 h. The mixture was brought to r.t. and filtered through a pad of Celite. The solvent was removed under reduced pressure to yield 4-methoxybenzoate **7** as a yellow foam, which was used in the next step without further purification; R_f = 0.24 (PE–EtOAc, 85:15).

(2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol (1)

A flame-dried 500 mL Schlenk flask equipped with a magnetic stir bar and a silicone septum was charged with 4-methoxybenzoate **7** and Et_2O (350 mL). $LiAlH_4$ (11.4 g, 300 mmol) was added at 0 °C and the mixture was stirred overnight at r. t. After dilution with Et_2O (100 mL) and hydrolysis by the addition of H_2O (11 mL), aq 15% NaOH (11 mL), and H_2O (11 mL), a yellowish precipitate was formed, which was filtered through a pad of Celite. The filter cake was thoroughly washed with Et_2O. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude title compound **1** as a yellow foam. The product was purified by flash column chromatography on silica gel with PE–EtOAc (93:7) as eluent; yield: 28 g (62% over 4 steps); colorless solid; mp 76–79 °C; R_f = 0.44 (PE–EtOAc, 85:15); $[\alpha]_D^{20}$ +59.7 (*c* = 1.0, $CHCl_3$).

IR (film): 3422, 1493, 1445, 1175, 1069, 757, 695 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 2.66 (br, 2 H, OH), 3.08 (s, 6 H, OCH_3), 4.64 (d, ^3J = 3.7 Hz, 2 H, 2-H and 3-H), 7.13–7.37 (m, 20 H_{arom}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 53.4 (OCH_3), 71.1 (C-2 and C-3), 85.1 (C-1 and C-4), 127.1, 127.2, 127.7, 127.8, 128.0, 128.7 (CH_{arom}), 141.2, 142.5 (C_{arom}).

Anal. Calcd for $C_{30}H_{30}O_4$ (454.6): C, 79.27; H, 6.65. Found: C, 79.16; H, 6.71.

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