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A novel, high-yielding approach to a chiral inducer: (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol

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ABSTRACT

A new method for preparing (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol in high yield based on selective 2,3-spiroboration of (2*R*,3*R*)-1,1,4,4-tetraphenylbutanetetraol has been developed. It avoids traditional oxidation and reduction steps, and provides a simplified, more straightforward, and high-yielding synthesis of the title compound.

1. Introduction

Chiral diols with a C_2-symmetry axis,[1] such as enantiopure 1,1′-bi-2-naphthols (BINOLs[2]) and α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanols (TADDOLs[3]), usually provide high levels of absolute stereochemical control. Thus the synthesis of C_2 chiral diols is of interest to synthetic chemists. (2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol **1**, which is a C_2 symmetrical chiral diol derived from dialkyl (2*R*,3*R*)-tartrate, has attracted considerable attention due to its wide applications as a chiral inducer in asymmetric synthesis.[4] Recently, Pietruszka reviewed the preparation and applications of (2*R*,3*R*)-**1**.[5]

Compound (2*R*,3*R*)-**1** was firstly prepared by Nakayama and Rainier as early 1990.[6] As shown in Scheme 1, the secondary hydroxyls at the 2- and 3-positions of the (2*R*,3*R*)-tartrate ester were first protected by *p*-methoxybenzaldehyde (step 1), then phenyl groups were introduced via Grignard reaction (step 2), after which the freshly generated tertiary hydroxyls were methylated with MeI and NaH in dimethylsulfoxide (step 3). In the next reaction step, the *p*-methoxybenzyl group was removed by oxidation with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) to give the hydroxyester (step 4), which was subsequently treated with $LiAlH_4$ to give the expected product. Pietruszka et al. reported on an improved procedure[7] for the synthesis of (2*R*,3*R*)-**1**. As shown in Scheme 1, the reaction solvents in steps 2 and 3 were changed to tetrahydrofuran (THF), while in step 4, toxic and expensive DDQ was replaced by inexpensive inorganic salts, although $LiAlH_4$ was still required.

(2*R*,3*R*)-1,1,4,4-Tetraphenylbutanetetraol **2**, which is a parent compound of the TADDOLs, could be conveniently synthesized via a one step reaction of (2*R*,3*R*)-tartrate diester and phenylmagnesium bromide according to our earlier published procedure.[8] Over the course of studying 1,1,4,4-tetrasubstituted butanetetraol chemistry,[9] we found that (2*R*,3*R*)-**2** could undergo selective 2,3-spiroboration with $B(OH)_3$ or $NaBH_4$. The secondary hydroxyl groups at the 2- and 3-positions of (2*R*,3*R*)-**2** were selectively protected and functional transformation of the tertiary hydroxyl groups at the 1- and 4-positions could be conveniently carried out. Herein we report a novel approach to (2*R*,3*R*)-**1** based on selective 2,3-spiroboration of (2*R*,3*R*)-**2** without the utilization of toxic and expensive DDQ and $LiAlH_4$ (Scheme 2).

2. Results and discussion

During previous studies, it was found that (2*R*,3*R*)-**2** could undergo highly regioselective 1,3-cycloboronation with alkylboronic acid to give chiral bicyclo[4.4.0]diboronate.[9d] Considering polytropism of boron chemistry, the reaction of (2*R*,3*R*)-**2** and $B(OH)_3$ was examined. A THF solution of (2*R*,3*R*)-**2** was allowed to mix with a concentrated aqueous solution of $B(OH)_3$ and KOH to give a homogeneous solution. The solution was refluxed for several hours until (2*R*,3*R*)-**2** was completely reacted (detected by TLC). The THF was removed, and water was added to the residue with stirring to precipitate a white solid, which was pure enough for ^1H NMR analysis after washed with ethanol. The ^1H NMR spectra show that there are two sets of aromatic proton resonances at 7.0 (m) and 6.76 (s) ppm and two sets of nonaromatic proton resonances at 4.45 (s) and 4.18 (s) ppm (the latter disappeared after the addition of D_2O) with an intensity ratio of 16:4:1:1, meaning that the two hydroxyl groups of (2*R*,3*R*)-**2** had undergone boration. Furthermore, the ^{13}C NMR

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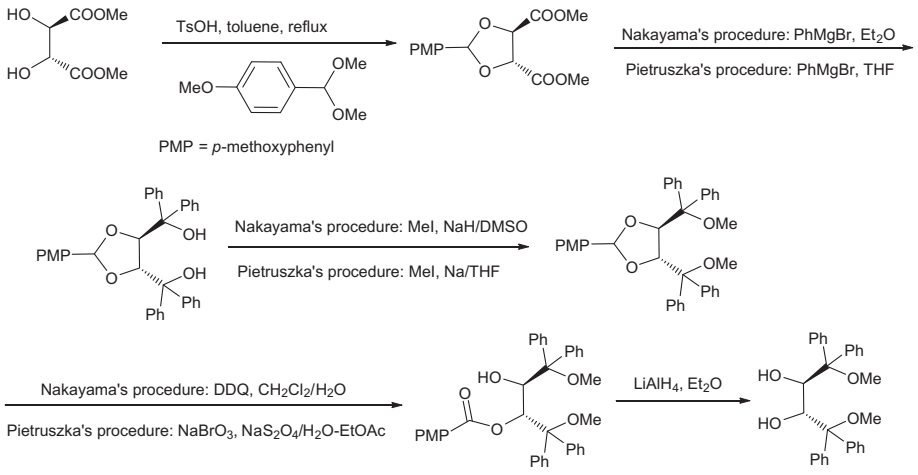
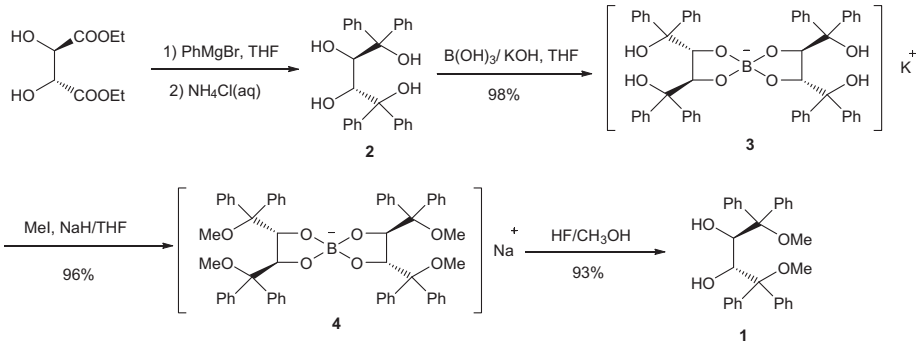


Scheme 1. Synthesis of (2*R*,3*R*)-**1** according to Nakayama's and Pietruszka's procedures.



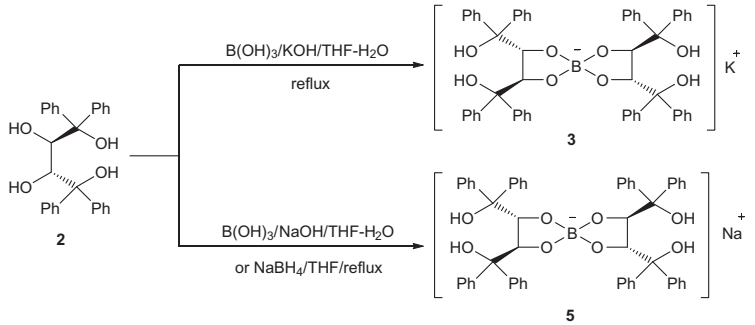
Scheme 2. Synthesis of (2*R*,3*R*)-**1** based on selective 2,3-spiroboration of (2*R*,3*R*)-**2**.

spectra exhibit two types of aliphatic carbon at 85.6 and 83.0 ppm. These spectroscopic characteristics reveal that the product has a symmetric molecular structure, but is different to that of the known bicyclo[4.4.0]diboronate.[9d] In order to confirm the structure of the novel compound, the white solid was dissolved in hot methanol and cooled slowly to room temperature, to give colorless crystals suitable for X-ray diffraction analysis. The crystallographic data[10] revealed that the novel compound was potassium (2*R*,3*R*,7*R*,8*R*)-2,3,7,8-tetrakis(hydroxydiphenylmethyl)-1,4,6,9-tetraoxa-5-boraspiro[4.4]nonan-5-uide **3**.

Obviously, selective 2,3-spiroboration rather than 1,3-cycloboronation took place when (2*R*,3*R*)-**2** was allowed to react with $B(OH)_3$ in the presence of KOH. In fact, other bases such as NaOH, or amines, also promoted selective 2,3-spiroboration of (2*R*,3*R*)-**2** with $B(OH)_3$. In the case of NaOH, sodium spiroborate **5** [sodium (2*R*,3*R*,7*R*,8*R*)-2,3,7,8-tetrakis(hydroxydiphenylmethyl)-1,4,6,9-tetraoxa-5-boraspiro[4.4]nonan-5-uide] was afforded (Scheme 3).

It should be pointed out that (2*R*,3*R*)-**2** can also undergo selective 2,3-spiroboration with $NaBH_4$ in refluxing THF. As shown in Scheme 3, sodium spiroborate salt **5** was obtained by the reaction of (2*R*,3*R*)-**2** with $NaBH_4$ in the absence of strong bases. While the reactivity of $NaBH_4$ is higher than that of $B(OH)_3$, it is more economical and practical to use $B(OH)_3$ as a protective agent for the secondary hydroxyl groups of (2*R*,3*R*)-**2**.

The secondary hydroxyl groups of (2*R*,3*R*)-**2** were protected by selective 2,3-spiroboration to generate a chiral spiroborate salt, in



Scheme 3. Formation of chiral 2,3-spiroborate salts via the reaction of (2*R*,3*R*)-**2** with $B(OH)_3$ or $NaBH_4$.

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which the tertiary hydroxyl groups were free. Sequential methylation of the tertiary hydroxyl groups could conventionally be performed by using excess NaH and MeI in THF, and the methylation could nearly quantitatively provide spiroborate salt, sodium (2*R*,3*R*,7*R*,8*R*)-2,3,7,8-tetrakis(methoxydiphenylmethyl)-1,4,6,9-tetraoxa-5-boraspiro[4.4]nonan-5-uide **4**, which was hydrolyzed by HF in methanol to give (2*R*,3*R*)-**1** in excellent yield.

3. Conclusion

In conclusion, a high-yielding approach to chiral diol (2*R*,3*R*)-**1** based on a highly selective 2,3-spiroboration of (2*R*,3*R*)-**2** has been discovered. Compound (2*R*,3*R*)-**1** could undergo quantitatively a selective 2,3-spiroboration reaction with $B(OH)_3$ in the presence of bases or with $NaBH_4$ in refluxing THF to give the corresponding spiroborate salt **3** or **5**. The tertiary hydroxyl groups of the spiroborate salt were methylated by using excess NaH and MeI, and then hydrolyzed by HF in methanol to give (2*R*,3*R*)-**1** in excellent yield. This preparation avoids traditional oxidation and reduction steps, and does not utilize the toxic and expensive DDQ and $LiAlH_4$, and is a simplified and high-yielding synthesis.

4. Experimental

4.1. General

Diethyl (2*R*,3*R*)-tartrate was prepared from (2*R*,3*R*)-tartaric acid and ethanol. (2*R*,3*R*)-**2** was synthesized from diethyl (2*R*,3*R*)-tartrate and PhMgBr in THF using a conventional Grignard reaction procedure. $B(OH)_3$ and $NaBH_4$ were purchased and used directly. Commercially available starting materials were used without further purification if not specified.

IR spectra were recorded on a Nicolet 170 SX FT-IR spectrophotometer, in KBr, in cm^{-1}. NMR spectra were recorded at 300 MHz for ^1H, and 75 MHz for ^{13}C on a Varian Mercury VS 300 (ppm, relative to TMS). Optical rotations were measured on a Perkin-Elmer 341 Mc polarimeter. Mp: VEB Wagetechnik Rapio PHMK 05; uncorrected.

4.2. Preparation of potassium (2*R*,3*R*,7*R*,8*R*)-2,3,7,8-tetrakis (hydroxydiphenylmethyl)-1,4,6,9-tetraoxa-5-boraspiro[4.4] nonan-5-uide 3

To a round-bottomed flask fitted with a magnetic stirrer bar, 12.8 g (30 mmol) of (2*R*,3*R*)-1,1,4,4-tetraphenylbutanetetraol and 100 mL of THF were added and stirred to give a transparent solution. To this solution 0.93 g (15 mmol) of $B(OH)_3$ and approximately 10 ml of saturated KOH solution were added and refluxed for 4 h. The solvent was then removed, and to the residue was added water after which it was stirred for 0.5 h and filtered to give a white solid, which was washed with ethanol to give 13.2 g of **3** with mp >300 °C, 98% yield. $[\alpha]_D^{25} = +169.7$ (*c* 0.13, MeOH), ^1H NMR (300 MHz, DMSO-d_6): δ 7.06–6.95 (m, 32H, Ph-H), 6.76 (s, 8H), 4.46 (s, 4H, OC-H), 4.18 (s, 4H, O-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.1, 145.1, 128.4, 127.9, 127.5, 126.7, 126.1, 81.1, 78.8. IR (KBr): 3416, 1618, 1384 cm^{-1}.

4.3. X-ray crystal structure analysis of 3

A single crystal suitable for X-ray structural analysis was obtained by slowly cooling a hot methanol solution of potassium salt **3** to room temperature. A colorless crystal of dimensions 0.32 mm × 0.28 mm × 0.27 mm was mounted on a glass fiber. X-ray diffraction intensity data collection and cell refinement were performed on Bruker P4 four-circle diffractometer equipped with a graphite monochromator. A total of 8584 unique reflections were collected using Mok$_\alpha$ (λ = 0.71073 Å) radiation by fine-focus sealed tube at 273(2) K, of which 6130 reflections had $I > 2\sigma(I)$ and were used in the structure solution and refinements. The corrections for *Lp* factors and empirical absorption were applied to the intensity data. All calculations were performed on Enraf-Nonius Molen/VAX Software using the program SHELXL-97. The structure was solved by direct methods and refined on F^2 using a full-matrix least-squares technique. The non-hydrogen atoms were also refined by a full-matrix least-squares technique, anisotropically, and hydrogen atoms were included but not refined. Cell dimensions were obtained by the least-squares refinement of well centered 289 reflections in the range of $2.21 < \theta < 25.50°$. Convergence with unweighted and weighted agreement factors was achieved at $R = 0.0502$ and $R_w = 0.1043$ $(w = 1/[\backslash s^2(Fo^2) + (0.0450P)^2 + 1.2659P]$ where $P = (Fo^2 + 2Fc^2)/3$, $S = 0.00065(16)$ and $Fc^* = kFc[1 + 0.001 \times Fc^2 \backslash l^3 / \sin(2 \backslash q)]^{-1/4}$). The maximum and minimum peaks on the final difference Fourier map correspond to 0.415 and −0.458 *e* Å^{-3}.

Crystal data for potassium salt **1**: empirical formula, C56 H48 B K O8; formula weight, 898.85; calculated density, 1.296 g/cm^3; volume (V), 4605.4(12) Å^3; crystal system, Orthorhombic; space group, P2(1)2(1)2(1); $Z = 4$; unit cell dimensions, a = 13.088(2), b = 16.158(2), c = 21.778(3), $\alpha = 90°$ $\beta = 90°$, $\gamma = 90°$; absorption coefficient (μ), 0.173 mm^{-1}; index ranges $-15 \leqslant h \leqslant 15$, $-14 \leqslant k \leqslant 19$, $-26 \leqslant l \leqslant 23$; F(000), 1888; GOF, 0.997.

4.4. Preparation of sodium (2*R*,3*R*,7*R*,8*R*)-2,3,7,8-2,3,7,8-tetrakis (methoxydiphenylmethyl)-1,4,6,9-tetraoxa-5-boraspiro[4.4] nonan-5-uide 4

Under an argon stream, a dried two-neck round-bottomed flask fitted with a magnetic stirrer bar was charged with 13.2 g (14.7 mmol) of potassium salt **1** from the previous step and 160 mL of dried THF. The flask was then placed in ice bath, after which 1.9 g of NaH (95%, 73.5 mmol) were added and then the solution was stirred for 1 h at room temperature, followed by adding 4.6 ml of MeI (73.5 mmol), and stirred for 5 h at room temperature. A white precipitate appeared, which was filtered and stirred with 120 mL water for 1 h. The undissolved white solid (13.2 g) in water was filtered, dried, and used directly in the next step without further purification. Yield: 96%, mp: 140–142 °C, $[\alpha]_D^{25} = +16.7$ (*c* 0.8, DMSO). ^1H NMR (300 Hz, DMSO-d_6): δ 6.74–7.31 (m, 40H, Ar-H), 4.3 (s, 4H, CH), 2.4 (s, 12H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.2, 143.6, 128.3, 128.1, 127.3, 126.9, 126.7, 88.6, 84.5, 59.7. ES-MS (ES$^+$): 961.

4.5. Preparation of (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl butane-2,3-diol 1

In a 250 mL plastic bottle fitted with a magnetic stirrer bar was charged with 13.2 g (14.1 mmol) of sodium salt **4** from the previous step and 165 mL of methanol and stirred. The resulting solution was placed in an ice bath, and 2.9 mL (58.4 mmol) 40% HF was added slowly. The mixture was stirred for 3 h and quenched with a saturated $NaHCO_3$ solution. The solution was extracted by Et_2O and the organic phase was dried over anhydrous Na_2SO_4. After concentration and purification by flash column chromatography on silica gel, 11.9 g of the desired product (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol were obtained in 93% yield, mp: 78–80 °C, $[\alpha]_D^{15} = +59.6$ (*c* 0.08, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.44 (m, 20H, Ph-H), 4.71 (d, J = 3.3 Hz, 2H, CH), 3.16 (s, 6H, OCH_3), 2.74 (br, 2H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 141.5, 129.0, 128.3, 128.1, 128.0, 127.5, 127.7, 85.4, 71.3, 53.7. ESI: 477 [M+23].

Acknowledgments

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10. Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-970282. Data can be obtained free of charge, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk; web: http://www.ccdc.cam.ac.uk).