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Convenient and versatile synthesis of formyl-substituted benzoxaboroles

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ABSTRACT

Despite of the medicinal significance of benzoxaboroles, with the newly discovered clinical compound AN2690 as an example, the synthetic method for rapid diversification of this novel scaffold is lacking. To this end, a versatile and scalable synthesis of formyl-substituted benzoxaboroles is described here. A key step is the mono-oxidation of the two hydroxyls in compound **4** by taking advantage of the stable oxaborole ring in non-coordinating solvents, which was devised based on the study of the intramolecular coordination and exchange properties.

1. Introduction

Boron, neighbouring carbon in the periodic table, has been a largely under-utilized element in modern medicinal chemistry research. Although boronic acids have been investigated as enzyme inhibitors of proteases, proteasome, arginase, nitric oxide synthase, esterase and transpeptidase during the past two decades,[1] none of them had become a clinically usable drug until bortezomib (Fig. 1), a peptidyl boronic acid that inhibits 20S proteasome, was approved by US FDA in 2003 for the treatment of multiple myeloma,[2] which inspired enthusiasm in boron-containing molecules as a novel druggable chemical class. As an extension of boron's new role in drug discovery, AN2690 (Fig. 1), a small benzoxaborole, was discovered to inhibit leucyl-tRNA synthetase (LeuRS) by taking advantage of its readily sp^2–sp^3 inter-convertible boron atom to form a tetrahedral covalent adduct with the *cis*-diol on tRNA, which results in trapping of tRNA in the enzyme's editing domain.[3] As a treatment against onychomycosis, AN2690 is currently under clinical trials.[4] Despite of the surging medicinal significance of benzoxaboroles, the study of their synthesis and properties has been very limited[4–7] and the synthetic method for rapid diversification of this novel structure is highly desired. Thus, we undertook the task to devise a convenient and versatile synthetic method for the rapid diversification of the benzoxaborole scaffold in order to expand its utilization in drug discovery.

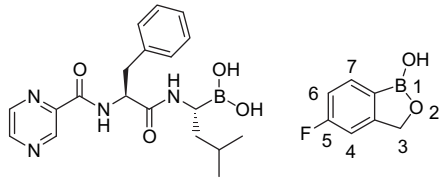

Figure 1. Structures of bortezomib and AN2690.

In this report, we describe the development of a practically scalable synthesis of formyl-substituted benzoxaboroles as highly versatile and medicinally useful scaffolds and their derivatization. First, 2,6-diformylbromobenzene (**3**), which is also a useful building block in supramolecular chemistry, was obtained using a mild and readily scalable method (Scheme 2). The intramolecular coordination phenomenon of compounds **14** and **15** (Figs. 2 and 3), and the effect of solvents on exchange rate was investigated. The empty p-orbital possessed by the boron atom offered a unique protective group for its neighbouring hydroxyl group, thus made possible the quantitative mono-oxidation of the two equivalent hydroxyl groups in non-coordinating solvent. We thus developed a mild and scalable synthesis of 7-formylbenzoxaborole (**1**) with 47.3% overall yield over six steps from the commercially available 2,6-dimethylbromobenzene (**6**). Furthermore, this synthetic route can be readily applied to any substitution position (4-, 5-, 6-, or 7-) on the benzoxaborole's aromatic ring, which for the first time provided access to the systematic modification of the benzoxaborole scaffold. Combined with the chemical versatility of the formyl group, we thus established a valuable synthetic tool for the study of benzoxaboroles as potential drug candidates. The subsequent derivatization reactions were investigated and proved to be compatible with the benzoxaborole functionality.

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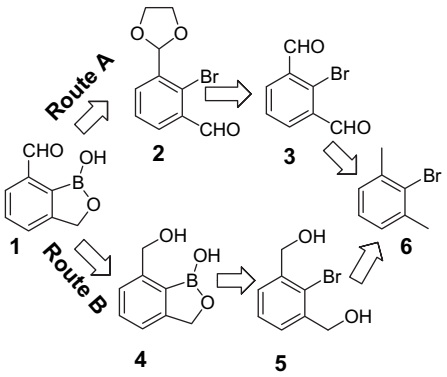
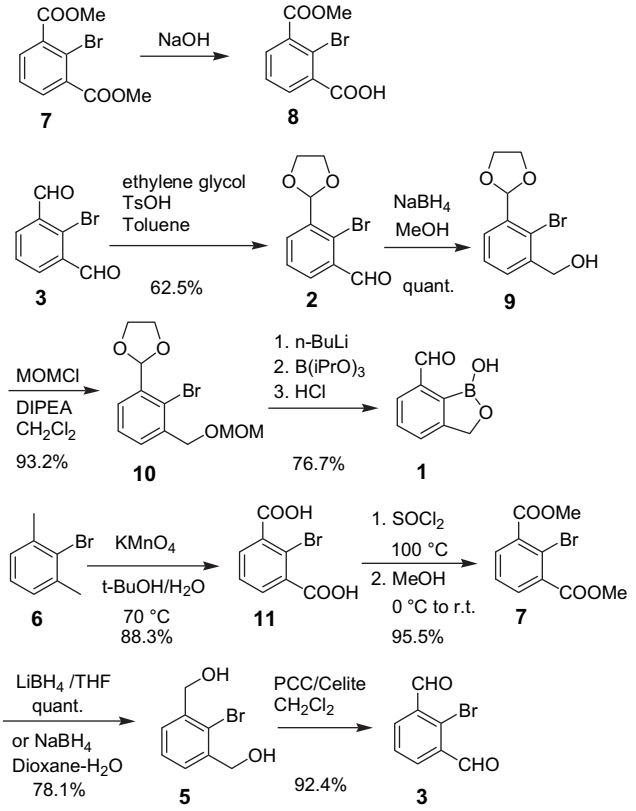


Scheme 1. Retrosynthetic route A and B towards **1**.

2. Results and discussion

In order to explore benzoxaboroles as a medicinally useful scaffold, we embarked on the task to device a convenient and scalable synthesis of formylbenzoxaboroles that can be converted to a variety of different functionalized benzoxaboroles. We aimed to develop a one-fit-all method that can be easily applied to any of the four positions on the aromatic ring, namely 4-, 5-, 6- or 7- position (Fig. 1). At the same time, we were urged to explore a route that is amenable to rapid scale-up with mild conditions and facile purifications.

Using 7-formylbenzoxaborole as an example, the retrosynthetic analysis is shown (Scheme 1). Dimethylbromobenzenes have all four possible dimethyl substitution patterns (2,6-, 2,5-, 2,4- and 2,3-) commercially available and were chosen as the starting materials. The key was to break down the equivalency of the two methyl groups, rendering one into hydroxymethyl to close the oxaborole ring while the other into formyl oxidation state with satisfactory yields.



Scheme 2. Synthesis of compound **1** and **3**.

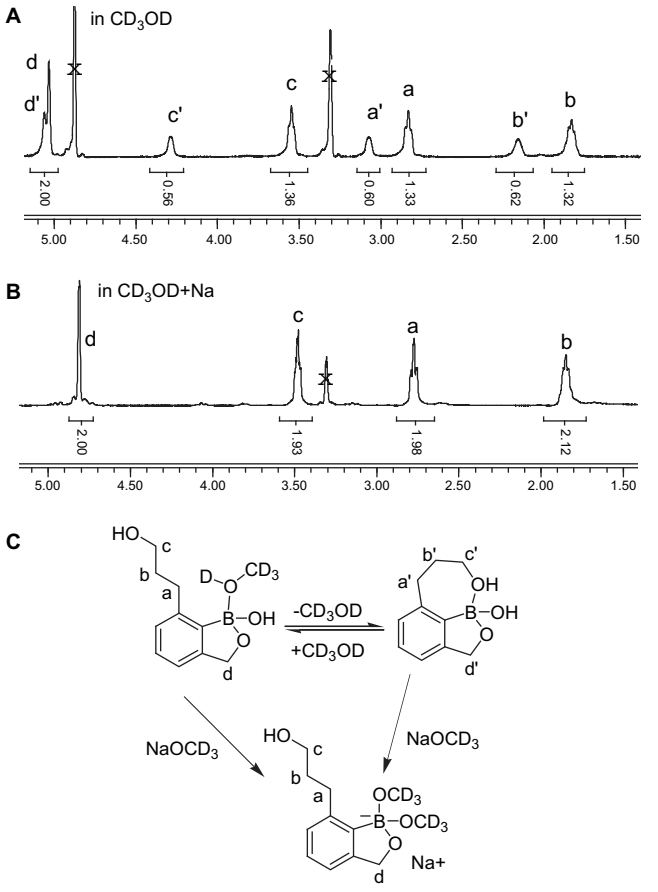


Figure 2. Top: (A) Compound **14** in CD_3OD existed as two components. H_a, H_b and H_c from free propoxyl; $H_{a'}$, $H_{b'}$ and $H_{c'}$ from boron-coordinated propoxyl. (B) Addition of sodium gave a single component. H_a, H_b and H_c from free propoxyl. (C) Proposed equilibrium of compound **14** in CD_3OD and single component after addition of sodium.

We tried to differentiate the two methyl groups in their carboxylate or formyl oxidation states with moderate success, and they were not applicable to large scale synthesis due to low yields and requirement of column chromatography in purification. For example, treatment of diester **7** with NaOH gave the mono-acid **8** in 79% yield (Scheme 2). Selective reduction of either carboxylic acid or ester in compound **8** was attempted. Reduction of ester with $LiBH_4$ was only successful when a THF solution of **8** and ethanol were added to $LiBH_4$ giving 90% yield. Reduction of carboxylic acid with BH_3/THF failed, while BH_3/Me_2S gave 70% yield. We abandoned this route due to its inefficiency and necessity of using expensive palladium catalyst for subsequent boronylation. Although multi-step masking of acid or ester groups would allow the use of more economical butyl lithium/borate method, the lengthened route would be unfavourable for scale-up. We continued to explore the possibility of resolving the two methyl groups in their formyl oxidation state following Route A (Scheme 1). Slow addition of ethylene glycol to the diformyl compound **3** with azeotropic removal of water gave mono-protected compound **2** in 62.5% yield (Scheme 2). Subsequent reduction of the formyl group and protection of the hydroxyl group allowed the use of butyl lithium/borate method to install boronic acid and the acidic removal of acetal protection was done in one pot to give 7-formylbenzoxaborole (**1**) in 44.7% yield over four steps from the diformylbromobenzene (**3**) (Scheme 2). The ethylene glycol monoprotection step gave unsatisfactory yield and required column chromatography, which burdened the large scale synthesis. Furthermore, this synthetic route for 7-formylbenzoxaborole (**1**) was not applicable to 6-, 5-, or 4-formylbezoxaboroles because ethylene

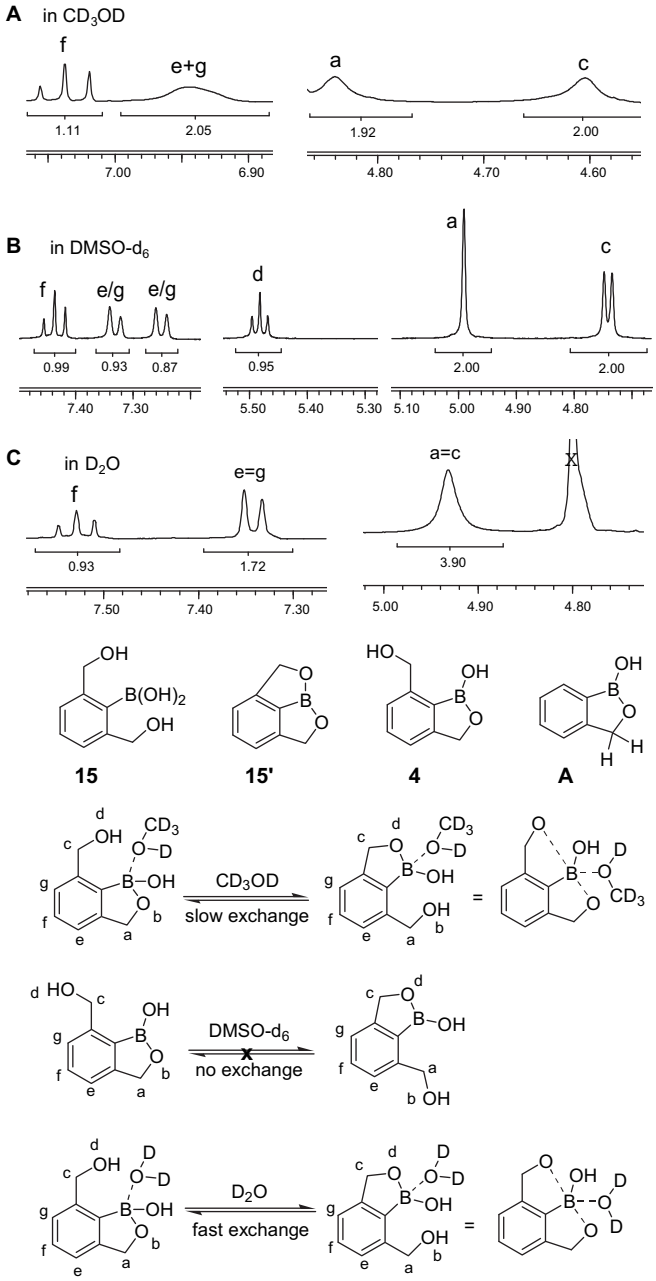


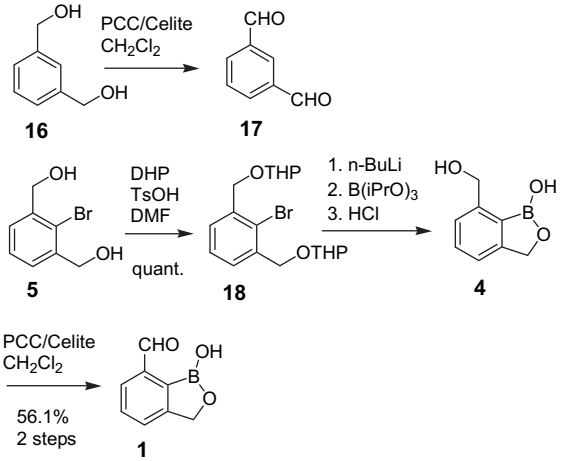
Figure 3. NMR of compound **15** in CD_3OD, DMSO-d_6 and D_2O, respectively, and the proposed structures.

glycol protection would give mixtures of regioisomers due to their lack of structural symmetry.

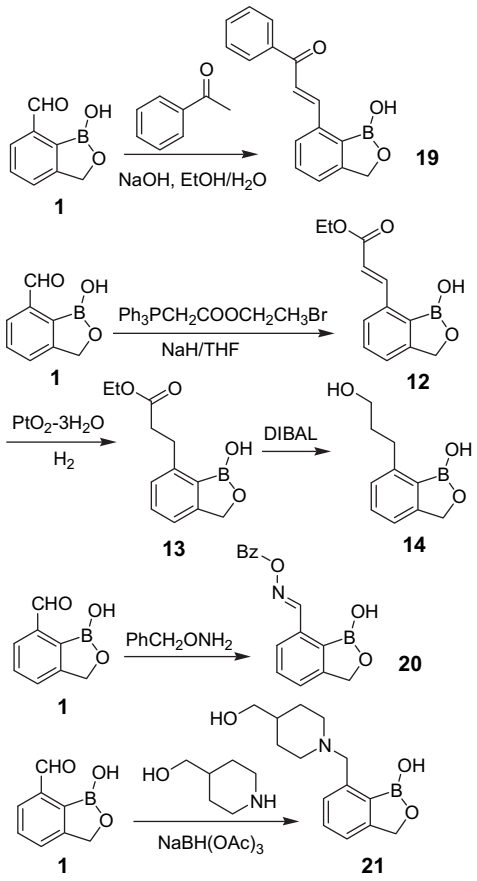
It is noteworthy that 2,6-diformylbromobenzene (**3**) is a widely utilized building block in the construction of various supramolecular structures and organometallic catalysts.[8–10] Previously, it was synthesized from 2,6-dimethylbromobenzene by photochemical tetra-bromination followed by hydrolysis.[11] This method involved vigorous and hard-to-control photochemical reaction, which was unfavourable for large scale preparation. Another method used strong oxidants such as Ac_2O/CrO_3 to convert 2,6-dimethylbromobenzene (**6**) to 2,6-bis(diacetoxylmethyl)bromobenzene followed by acidic hydrolysis to obtain the dialdehyde **3**.[8,12] It proved problematic in our attempt to scale it up due to the highly explosive nature of the oxidant and the low yields in hydrolysis. This prompted us to explore a new route to circumvent these practical issues. We developed a milder oxidation–reduction sequence and established a scalable synthetic route with 78% yield over four steps from 2,6-dimethylbromobenzene (**6**) (Scheme 2). The reactions were mild and easy-to-control, and high yields allowed rapid purification without any need of column chromatography, which made large scale preparation possible. First, 2,6-dimethylbromobenzene (**6**) was converted to the dicarboxyl compound **11** using $KMnO_4$ in *t*-BuOH/H_2O. The yield was as low as 16% under previously reported reflux condition. We investigated the effects of temperatures and found that overnight heating at 70 °C gave improved yield (88%) compared to 110 °C (16%), 100 °C (60%) or 85 °C (77%). At the same time, slow addition of $KMnO_4$ in portions was essential for satisfactory yield. To minimize over-oxidation, 2.5 equiv of $KMnO_4$ was first added slowly and heated for 2 h, then another 2.5 equiv was added after cooling and followed by heating at 70 °C overnight. The two carboxyl groups were converted to methyl esters using $SOCl_2$ and CH_3OH/Et_3N, reduced to hydroxymethyls with $LiBH_4$, then oxidized to dialdehyde **3** with PCC. All three steps gave near quantitative yields that resulted in an overall 78% yield. We also investigated alternative reducing agents to replace relatively costly $LiBH_4$. Addition of $LiAlH_4$ gave de-brominated product even at temperatures as low as −78 °C. Use of DIBAL gave 81.6% yield. Reduction with $NaBH_4$ in dioxane/water at 0 °C to room temperature gave 78.1% yield while reaction of $NaBH_4$ with addition of LiCl or $ZnCl_2$ failed to produce the desired product. Thus, $NaBH_4$ (dixoane/water) may be used as an alternative reducing agent with its reasonable yield and much lower cost.

During our study of the ^1H NMR of 7-(3′-hydroxypropyl)benzoxaborole (**14**, Fig. 2), we observed an interesting intramolecular coordination phenomenon that led to our further investigation and the development of the final key mono-oxidation step that yielded an improved synthesis of 7-formylbenzoxaborole (**1**) (Scheme 3). This new route is also readily applicable to the synthesis of 6-, 5- and 4-formylbenzoxaboroles. Compound **14** was synthesized during the derivatization of compound **1** (Scheme 4). Wittig reaction converted compound **1** to the acrylic acid ethyl ester **12**, which underwent hydrogenation using PtO_2 to give propionate **13**. Reduction of the ester with DIBAL gave the hydroxypropyl compound **14** used in the following study.

As shown in the ^1H NMR of compound **14** in CD_3OD, the three methylene groups give rise to six peaks that can be grouped into two sets of signals (H_a, H_b, H_c and $H_{a'}$, $H_{b'}$, $H_{c'}$), which indicates the existence of the hydroxypropyl chain in two distinct states (Fig. 2A). With an empty p-orbital, the trigonal boron can accept a lone electron pair from heteroatoms X (X=O, N or F). The B–X bonds can be strong covalent bonds such as in the boronic acid-based sugar receptors with an adjacent amine group[13] and the bis-methanol adduct of diazaborine[14] where boron has a tetrahedral geometry. It can



Scheme 3. Improved synthesis of compound **1**.



Scheme 4. Representative reactions of compound **1**.

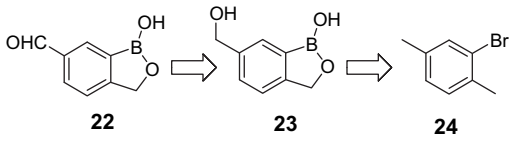
also be an intermediate B–X interaction that is weaker than covalent bond but has detectable electron effects resulting in a more shielded boron such as in the bis(boronate-amide) receptor.[15] Thus, we deduced two coordination states as shown in Figure 2C to account for the two sets of methylene signals. Protons H_a, H_b and H_c are from the free hydroxypropyl chain while protons $H_{a'}$, $H_{b'}$ and $H_{c'}$, with downfield shifts, result from the coordination of the terminal hydroxyl to boron. The flow of electron from hydroxyl oxygen to boron resulted in the more de-shielded $H_{a'}$, $H_{b'}$ and $H_{c'}$. Furthermore, we added metallic sodium to replace the terminal hydroxyl group with high affinity CD_3O^- anion. Indeed, only a single component was observed that corresponded to a free hydroxypropyl chain (Fig. 2B). This is the first time an intramolecular reversible coordination in benzoxaborole is reported. The five-membered oxaborole ring is stable and spontaneously formed.[4–7] Although there were two terminal hydroxyls in compound **14**, only the hydroxypropyl–OH was in reversible coordination with boron while the hydroxymethyl–OH was locked by the stable oxaborole ring. Benzoxaborole, as a cyclic boronic ester, has properties rather different from acyclic aromatic boronic ester. In compound **A** (Fig. 3), the five-membered oxaborole ring is rather stable and stays closed in DMSO, methanol and water as indicated by the constant chemical shifts (~5.0 ppm) of the methylene protons. We were intrigued to ask what would happen if there were two equivalent hydroxymethyl groups adjacent to boronic acid as illustrated by compound **15** (Fig. 3).

Compound **15** was obtained by reduction of compound **1** with $NaBH_4$ for the subsequent study. The ^1H NMR of compound **15** in CD_3OD showed a slow exchange as indicated by the broadened signal of two aromatic protons at 6.91–6.97 ppm (Fig. 3A). We assigned it to H_e and H_g and the merging of the two protons can be accounted for by the slow exchange of O_b or O_d coordinating to boron (Fig. 3). Interestingly, in DMSO-d_6 the sharply resolved signals indicated no exchange (Fig. 3B). One of the two hydroxyls coordinated to the boron while the other existed in its free form with the characteristic OH proton as a triplet at 5.48 ppm (Fig. 3B and D). Proton H_a was downfield shifted to 4.99 ppm, which was characteristic of the well-formed oxaborole ring structure. So compound **15** existed as a well-defined structure of compound **4** in DMSO. This observation suggested that although both OH groups are positioned to coordinate to the boron, the bis-coordinated compound **15′** was not formed due to unfavourable constrains of the tricyclic system. In DMSO-d_6, once the stable oxaborole ring was closed, the other OH group was unable to break it open by exchanging. However, CD_3OD rendered the opening and re-closing of the oxaborole ring feasible. It has been known that tetrahedral boron forms weaker B–O bond than trigonal boron due to the loss of conjugation between the boron p-orbital and the oxygen.[16,17] The exchange induced by CD_3OD was likely triggered by coordination of a CD_3OD molecule to the empty p-orbital of boron. This interaction served to induce a distortion from the trigonal geometry and weaken the B–O bond that held the oxaborole ring. In D_2O, fast exchange was observed as indicated by the complete merging and sharpening of the aromatic signals H_e and H_g as a doublet (Fig. 3C). The two hydroxymethyl signals H_a and H_c also completely merged into a singlet at 4.93 ppm. The chemical shift of the merged H_a and H_c in D_2O is in between the coordinated H_a (4.99 ppm) and the free H_c (4.74 ppm) in DMSO-d_6 but closer to the coordinated H_a, which suggests that in the fast exchange process in D_2O, the averaged structure has both hydroxyls coordinated to boron to a significant extent (Fig. 3).

The above intramolecular coordination properties indicated that compound **15** existed as a well-defined structure of compound **4** in DMSO, but had slow to fast exchange in coordinating solvent CD_3OD or D_2O. This observation suggested that in non-coordinating solvents, one of the two hydroxyls could be protected by forming a strong intramolecular B–O bond while leaving the other hydroxyl to be manipulated by chemical modifications. We tested the assumption by carrying out the oxidation of compound **4** with excess PCC in methylene chloride and obtained mono-oxidized compound **1** in quantitative yield (Scheme 3). On the contrary, 1,3-bis(hydroxymethyl)benzene **16**, which lacks the boronic acid gave 1,3-diformylbenzene **17** as the main product under the same condition, which is consistent with previous reports where dialdehyde was the major product with even 1 equiv of oxidant[18] and where low yield (68%) was obtained with insufficient amount of PCC.[19] This efficient mono-oxidation allowed us to shorten the synthesis of compound **1** (Scheme 3). Compound **5** was converted to THP protected compound **18** in quantitative yield. Boronic acid was installed using *n*-BuLi and B(*i*-PrO)$_3$, and HCl was added subsequently to remove THP groups, producing compound **4**. Due to its high water solubility thus postulated problem in purification, crude compound **4** was directly oxidized with PCC to compound **1**. The final product was purified by taking advantage of the Lewis acidity of the boronic ester group. At basic pH, with the coordination of two hydroxide ions the boron was negatively charged thus remained in aqueous phase, which allowed the removal of impurities into organic phase. Subsequently, it was acidified to neutral form and extracted into ethyl acetate to give 56.1% yield over two steps with satisfactory purity. This improved route gave the desired 7-formylbenzoxaborole (**1**) in 47.3% overall yield over six steps from commercially available 2,6-dimethylbromobenzene (**6**). More importantly, it was proved to be amenable to large scale synthesis with its high yields, easy-to-control reaction conditions, robust reproducibility and facile purification without any need of column chromatography.

It is noteworthy that this new route is readily applicable to the synthesis of 6-, 5- or 4-formylbenzoxaboroles as further demonstrated in the synthesis of 6-formylbenzoxaborole (**22**) from

2,5-dimethylbromobenzene (**24**) (Scheme 5). This, for the first time, provided an opportunity to rapidly diversify the under-explored benzoxaboroles as medicinally important molecules. We demonstrated the derivatization of these formylbenzoxaboroles under conditions compatible with the stability of the oxaborole ring by the representative synthesis of α,β-unsaturated ketone (**19**) by aldol condensation, α,β-unsaturated ester (**12**) by Wittig reaction, *O*-alkyloxime (**20**) by condensation with *O*-alkyl hydroxylamine, amine (**21**) by reductive amination (Scheme 4). The benzoxaborole moiety, known to be unstable under certain oxidative or alkaline conditions due to C–B bond cleavage, proved to be intact in these reactions.



Scheme 5. Synthesis of 6-formyl benzoxaborole.

3. Conclusions

Benzoxaborole AN2690 (Fig. 1) was recently identified as a novel aminoacyl tRNA synthetase inhibitor[3] and is currently under clinical trials as a treatment of onychomycosis.[4] However, synthetic method for rapid structural diversification of benzoxaborole scaffold is largely under-explored despite of their medicinal significance. We developed a practically scalable synthesis of the versatile 7-formylbenzoxaborole (**1**) that will allow rapid derivatization and exploration of their medicinal value in depth. We obtained a 47.3% overall yield over six steps from the commercially available 2,6-dimethylbromobenzene (**6**). Furthermore, this method is readily applicable to the synthesis of all three other regioisomers, 4-, 5- and 6-formylbenzoxaboroles. The application to the synthesis of 6-formylbenzoxaborole was also carried out and the derivatization reactions were demonstrated to be compatible with the benzoxaborole stability. The key mono-oxidation step was developed based on the observation that the strength of the intramolecular B–O interaction relies on ring size and coordinating ability of the solvent. We also developed a mild and scalable synthesis of the intermediate 1,3-diformylbromobenzene (**3**), which has wide use in supramolecular and organometallic chemistry. Owing to the recently highlighted significance of benzoxaboroles in drug discovery and the rarity of a systematic synthesis and modification strategy, we believe this method will find wide application in the field of drug discovery and biological mechanistic studies.

4. Experimental

4.1. Preparation of 2-bromo-1,3-benzenedicarboxylic acid (11)

To a solution of compound **6** (60 g, 324.3 mmol) in *t*-BuOH (250 mL) and H_2O (250 mL) was added $KMnO_4$ (128 g, 0.81 mol) in portions while stirring at room temperature. The mixture was stirred at 70 °C for 2 h before it was cooled to room temperature. A second batch of $KMnO_4$ (128 g, 0.81 mol) was added as before. After stirring at 70 C for 10 h, the hot reaction mixture was filtered and the residue was washed with water (3×300 mL). After concentration to 300 mL, the filtrate was acidified in ice-bath to pH=2 with concd HCl to get white precipitate. After extraction with EtOAc (4×500 mL), the organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain 70.2 g of compound **11** (88.3%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.58 (s, 2H), 7.68 (m, 2H), 7.50 (q, J_1=8 Hz, J_2=7.2 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.1, 137.1, 131.1, 128.2, 116.6; HRMS-EI: $C_8H_5BrO_4$ calcd 243.9371, found 243.9372; mp: 218–221 °C.

4.2. Preparation of 2-bromo-isophthalic acid dimethyl ester (7)

Compound **11** (44.20 g, 180.4 mmol) in $SOCl_2$ (300 mL) was gradually heated to 100 °C for a period of 5 h and stirred at 100 °C for another 4 h. After $SOCl_2$ was evaporated in vacuo and the flask was cooled to 0 °C, methanol (200 mL) and triethylamine (100 mL) were added slowly while stirring. The reaction mixture was stirred at room temperature for 2 h and was concentrated in vacuo. The residue was extracted with EtOAc, dried over $MgSO_4$ and concentrated in vacuo to obtain 47.05 g of compound **7** (95.5%) as viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (m, 2H), 7.40 (t, 1H), 3.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 134.8, 132.0, 126.9, 117.9, 52.5; HRMS-EI: $C_{10}H_9BrO_4$ calcd 241.9684, found 241.9683.

4.3. Preparation of 2,6-bis(hydroxymethyl) bromobenzene (5)

To a solution of compound **7** (30.50 g, 112 mmol) in ethyl ether (300 mL) was added $LiBH_4$ (5.42 g, 245.8 mmol) in THF (100 mL) slowly at 0 °C. The reaction mixture was stirred at room temperature overnight, quenched with 0.4 M HCl to pH=6∼7 and extracted with ethyl acetate to obtain 24.51 g of compound **5** (quantitative).

Alternative method: compound **7** (13.65 g, 50.0 mmol) was dissolved in 250 mL 1,4-dioxane/H_2O (3:2, 250 mL) and cooled to 0 °C. To this mixture was added $NaBH_4$ (18.90 g, 0.50 mol) and stirred at room temperature for 2 d before it was quenched with 6 M HCl in ice-bath, extracted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo to obtain 8.50 g of compound **5** (78.1%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (m, 3H), 5.39 (t, J=5.6 Hz, 2H), 4.52 (d, J=5.6 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.0, 127.0, 126.3, 120.4, 62.9; HRMS-EI: $C_8H_9BrO_2$ calcd 215.9786, found 215.9783; mp: 167–169 °C.

4.4. Preparation of 2-bromobenzene-1,3-dicarbaldehyde (3)

A mixture of compound **5** (12.0 g, 55.3 mmol), PCC (35.7 g, 165.9 mmol) and Celite (53.6 g) in CH_2Cl_2 (500 mL) was stirred at room temperature overnight. The reaction mixture was filtered through Celite and silica gel pad and the filtrate was evaporated in vacuo to obtain 10.90 g of compound **3** (92.4%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 2H), 8.08 (m, 2H) and 7.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 135.3, 134.4, 130.9, 128.3; HRMS-EI $C_8H_5BrO_2$ calcd 211.9473, found 211.9472; mp: 137–141 °C.

4.5. Preparation of 2-(2′-bromo-3′-((tetrahydro-pyran-2″-yloxy)methyl)benzyloxy)-tetrahydro-pyran (18)

Compound **5** (18.0 g, 82.9 mmol) and *p*-toluenesulfonic acid monohydrate (0.78 g, 4.1 mmol) were dissolved in DMF (200 mL), and DHP (34.8 mL, 331.7 mmol) was added. The reaction mixture was stirred at room temperature for 1 d and was quenched with saturated $NaHCO_3$, extracted with ethyl ether, washed with brine, dried over Na_2SO_4 and evaporated in vacuo to obtain 34.15 g of compound **18** (quantitative) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.32 (m, 1H), 4.86 (m, 2H), 4.72 (dd, J_1=33.2 Hz, J_2=13.2 Hz, 2H), 3.89 (m, 2H), 3.53 (m, 2H), 1.94 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 127.6, 126.9, 122.6, 98.1, 68.5, 61.8, 30.3, 25.2, 19.1; HRMS-EI: $C_{18}H_{25}BrO_4$ calcd 384.0936, found 384.0935.

4.6. Preparation of 7-formyl-1-hydroxy-1,3-dihydro-2,1-benzoxaborole (1)

Compound **18** (14.0 g, 36.3 mmol) was dissolved in THF (200 mL) and *n*-BuLi (1.6 M in hexane, 25 mL, 40 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 20 min and triisopropyl borate (9.2 mL, 40 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight before it was quenched with 6 M HCl (100 mL), stirred at room temperature for 6 h and concentrated in vacuo. The crude compound **4** was directly dissolved in CH_2Cl_2 (150 mL), and PCC (15.7 g, 72.6 mmol) and Celite (23.5 g) were added. The mixture was stirred at room temperature overnight and was filtered through a Celite and silica pad and the filtrate was washed with 1 M HCl and extracted with 1 M NaOH. The aqueous phase was acidified with concd HCl to pH=2 and extracted with ethyl acetate. The resulting organic phase was washed with brine, dried with Na_2SO_4 and evaporated in vacuo to obtain 3.30 g of compound **1** (56.1% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ10.39 (s, 1H), 9.22 (s, 1H), 7.87 (m, 1H), 7.72 (m, 2H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 155.1, 142.9, 132.2, 131.9, 125.2, 122.4, 104.0, 72.0; HRMS-EI $C_8H_7BO_3$ calcd 162.0488, found 162.0490; mp: 146–148 °C. Compound **4**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.9 (s, 1H), 7.44 (t, J=7.2 Hz, 1H), 7.33 (d, J=7.2 Hz, 1H), 7.25 (d, J=7.2 Hz, 1H), 5.48 (t, J=5.6 Hz, 1H), 4.99 (s, 2H) and 4.74 (d, J=5.6 Hz, 2H); ^{13}C NMR (75 MHz, D_2O): δ 131.8, 123.1 (br), 66.7 (br); ^{13}C NMR (100 MHz, D_2O+NaOH): δ 148.1, 141.2, 127.2, 124.6, 120.2, 67.5, 64.1; HRMS-EI: $C_8H_9BO_3$ calcd 164.0645, found 164.0650; mp: 290–291 °C.

4.7. Preparation of (*E*)-[3-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-1-phenyl]propenone (19)

To a mixture of acetophenone (0.22 mL, 1.85 mmol), ethanol (5 mL) and water (8 mL) was added NaOH (296 mg, 7.41 mmol). After stirring for 5 min compound **1** (300 mg, 1.85 mmol) was added and the reaction mixture was stirred at room temperature overnight before quenched with 6 M HCl to pH=2 in ice-bath. The mixture was evaporated, extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The residue after rotary evaporation was purified by column chromatography and re-crystallization (hexane/ethyl acetate) to obtain 240 mg of compound **19** (49.1%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.39 (s, 1H), 8.14 (m, 5H), 7.68 (t, J=7.4 Hz, 1H), 7.58 (t, J=8 Hz, 3H), 7.48 (m, 1H) and 5.05 (s, 2H); ^{13}C NMR (300 MHz, CD_3OD) δ 192.8, 156.2, 145.3, 139.6, 139.4, 134.2, 132.4, 129.7, 127.4, 124.8, 123.9, 71.9; HRMS-EI $C_{16}H_{13}BO_3$ calcd 264.0958, found 264.0964; mp: 136–137 °C.

4.8. Preparation of (*E*)-[3-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)]acrylic acid ethyl ester (12)

To a solution of compound **1** (400 mg, 2.47 mmol) and (ethyloxycarbonylmethyl)triphenylphosphonium bromide (1.06 g, 2.47 mmol) in THF (25 mL) was added under stirring NaH (60% in oil, 99 mg, 2.47 mmol) at −5 °C. The reaction mixture was stirred at room temperature for 12 h, added another portion of NaH (50 mg, 1.24 mmol) at 0 °C and stirred at room temperature for 8 h. The reaction was quenched with water, acidified to pH=2 ~ 3, extracted with ethyl acetate and dried over Na_2SO_4. The residue after rotary evaporation was purified by column chromatography and re-crystallization (hexane/ethyl acetate) to obtain 200 mg of compound **12** (34.9% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.10 (d, J=16.2 Hz, 1H), 7.82 (d, J=10 Hz, 1H), 7.52 (t, J=7.5 Hz, 1H), 7.44 (m, 1H), 6.81 (d, J=16.2 Hz, 1H), 5.02 (s, 2H), 4.19 (q, J=7.1 Hz, 2H) and 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR (300 MHz, CD_3OD): δ 168.8, 155.9, 144.9, 138.9, 132.3, 125.9, 123.7, 120.1, 71.9, 61.5, 14.6; HRMS-EI: $C_{12}H_{13}BO_4$ calcd 232.0907, found 232.0909; mp: 151–152 °C.

4.9. Preparation of [3-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)]propionic acid ethyl ester (13)

To a solution of compound **12** (1.20 g, 5.17 mmol) in methanol (10 mL) was added $PtO_2 \cdot 3H_2O$ (73 mg, 0.26 mmol) and the reaction mixture was vacuumed and filled with hydrogen and stirred overnight at room temperature. The reaction mixture was filtered and evaporated in vacuo to obtain 1.16 g of compound **13** (96%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.34 (t, J=7.6 Hz, 1H), 7.18 (d, J=7.6 Hz, 1H), 7.11 (d, J=7.2 Hz, 1H), 5.02 (s, 2H), 4.06 (q, J=7.2 Hz, 2H), 3.05 (t, J=7.6 Hz, 2H), 2.61 (t, J=7.6 Hz, 2H) and 1.19 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 174.9, 132.2, 128.2, 120.1, 72.1, 61.4, 37.1, 30.9, 14.5; HRMS-EI: $C_{12}H_{15}BO_4$ calcd 234.1063, found 234.1060; mp: 93–95 °C.

4.10. Preparation of 7-(3′-hydroxypropyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (14)

To a solution of compound **13** (500 mg, 2.15 mmol) in THF (20 mL) was added dropwise DIBAL (1.0 M in hexane, 12.9 mL, 12.9 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature and quenched with 1 M HCl at 0 °C. The mixture was extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. After rotary evaporation, the residue was purified by column chromatography to obtain 270 mg of compound **14** (65.5%). ^{1}H NMR (400 MHz, CD_3OD, Na added): δ 7.03 (m, 1H), 6.91 (m, 1H), 6.83 (m, 1H), 4.81 (s, 2H), 3.48 (m, 2H), 2.77 (m, 2H) and 1.84 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 155.5, 147.9, 132.5, 132.1, 128.1, 127.1, 119.6, 72.8, 72.1, 70.5, 62.5, 37.0, 35.9, 32.0, 31.8; HRMS-EI $C_{10}H_{13}BO_3$ calcd $[M-1]^-$ 191.0879, found 191.0882; mp: 91–93 °C.

4.11. Preparation of (*E*)-(1,3-dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*O*-benzyl oxime (20)

To a mixture of compound **1** (200 mg, 1.24 mmol), *O*-benzylhydroxylamine hydrochloride (240 mg, 1.50 mmol) and sodium formate (0.48 g, 7.1 mmol) was added 88% formic acid (1.9 mL). The mixture was heated at 85 °C overnight, quenched with water (10 mL) and extracted with ethyl acetate (20 mL×3). The residue after rotary evaporation was purified by column chromatography to obtain 222 mg of compound **20** (59.3%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.06 (s, 1H), 8.58 (s, 1H), 7.67 (d, J=5.4 Hz, 1H), 7.51 (t, J=5.4 Hz, 1H), 7.39 (m, 6H), 5.19 (s, 2H) and 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 152.6, 136.3, 133.7, 131.3, 130.1, 128.8, 128.7, 128.6, 123.3, 76.9, 71.5; HRMS-EI $C_{15}H_{14}BNO_3$ calcd 267.1067, found 267.1069; mp 56–58 °C.

4.12. Preparation of 7-{[4-(hydroxymethyl)piperidin-1-yl]methyl}-1-hydroxy-1,3-dihydro-2,1-benzoxaborole (21)

To a solution of compound **1** (320 mg, 1.98 mmol) and (piperidin-4-yl) methanol (227 mg, 1.98 mmol) in 1,2-dichoroethane (10 mL) in ice-bath was added $NaBH(OAc)_3$ (587.5 mg, 2.77 mmol). The reaction mixture was stirred at room temperature overnight, quenched with saturated $NaHCO_3$ and washed with ethyl acetate. The aqueous phase was concentrated and purified by reversed phase column chromatography to obtain 173 mg of compound **21** (173 mg, 33.7%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.27 (m, 2H), 7.17 (m, 1H), 4.83 (s, 2H), 4.29 (s, 2H), 3.48 (m, 4H), 2.93 (m, 2H), 1.96 (m, 1H), 1.82 (m, 2H) and 1.38 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 150.8, 132.4, 128.3, 128.0, 122.7, 71.1, 66.5, 62.7, 52.8, 37.6, 27.7; HRMS-EI $C_{14}H_{20}BNO_3$ calcd $[M-1]^-$ 260.1458, found 260.1461; mp: 109–113 °C.

4.13. Preparation of 6-formyl-1-hydroxy-1,3-dihydro-2,1-benzoxaborole (22)

Procedure similar to that of compound **1**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.06 (s, 1H), 9.44 (s, 1H), 8.28 (s, 1H), 8.01 (m, 1H), 7.63 (m, 1H) and 5.09 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 194.1, 133.6, 132.5, 130.6, 129.6, 123.2, 122.1, 72.2; HRMS-EI: $C_8H_7BO_3$ calcd 162.0488, found 162.0494; mp: 133–135 °C.

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