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Syntheses with organoboranes. XIII. Synthesis of ω-(4-bromophenyl)alkanoic acids and their borylation

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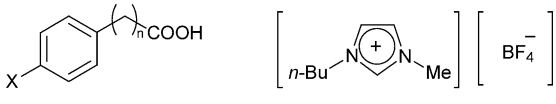
Abstract

ω-(4-Bromophenyl)alkanoic acids **2c**–**e** were obtained from 1-bromo-4-alkenylbenzenes **5c**–**e** by hydroboration–thermal isomerization–oxidation. Their esters **11c**–**e** were transformed in good yields into the corresponding boronates **12c**–**e** by the cross-coupling reaction with 4,4,5,5,4′,4′,5′,5′-octamethyl[2,2′]bi[[1,3,2]dioxaborolanyl] (**10**) in an ionic liquid, [bmim][BF_4]. The use of pinacolborane for the coupling reaction in the ionic liquid gave debromination products, and low yields of **12c**–**e**. Ethyl 3-(4-bromophenyl)propanoate (**7c**) was transformed into ethyl 3-(4-[1,3,2]dioxaborolanyl)propanoate (**9c**) by the cross-coupling with [2,2′]bi[[1,3,2]dioxaborinanyl].

Keywords: Organoboranes; Boronic acids; Cross-coupling reaction; Ionic liquid

1. Introduction

Arylboronic acids and esters (boronates) are important synthetic intermediates [1,2], and certain acids show biological activity [3,4]. For our work in the latter direction, ω-(4-dihydroxyborylphenyl)alkanoic acids were required. The first two acids of the homologous series, 4-dihydroxyborylbenzoic acid (**1a**) and 4-dihydroxyborylphenylacetic acid (**1b**), are known. The acid **1a** was prepared by oxidation of tolylboronic acid [5], and **1b** was synthesized by the conversion of 4-bromomethylphenylboronic acid into 4-cyanomethylphenylboronic acid, and hydrolysis of the nitrile [6]. In both syntheses the dihydroxyboryl group was introduced by the classical transmetalation of the corresponding arylmagnesium halide with trialkyl borates, and then the carboxylic group was elaborated. Unfortunately, this approach is not convenient for the synthesis of higher homologs since the elaboration of carboxylic group becomes less direct. For example, initially we attempted the synthesis of **1c** from 4-(3-butenyl)bromobenzene. Treatment of the corresponding Grignard derivative with tri-*n*-butyl borate gave 4-(but-3-en-1-yl)phenylboronic acid. Oxidation of the acid with aqueous potassium permanganate gave **1c** in low yield, and other products. The reverse approach involving the introduction of dihydroxyboryl group in the final step is possible by the palladium-catalyzed cross-coupling reaction of tetraalkoxydiborons with appropriate aryl halides [7]. Recently, a procedure employing pinacolborane, as dihydroxyboryl equivalent, was described [8]. This approach requires ω-(4-halophenyl)alkanoic acids for the cross-coupling reaction. However, no general synthesis of these acids is known. Consequently, we decided to investigate the preparation of ω-(4-bromophenyl)alkanoic acids **2c**–**e** using thermal isomerization of the corresponding organoboranes as the key step. An ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), was used as the reaction medium for the cross-coupling of their esters with tetraalkoxydiborons, to test its influence on the reaction time, temperature, and yields of the coupling products.



X = $B(OH)_2$: **1a** n = 0; **1b** n = 1; **1c** n = 2

X = Br: **2c** n = 2; **2d** n = 3; **2e** n = 4

[bmim][BF_4]

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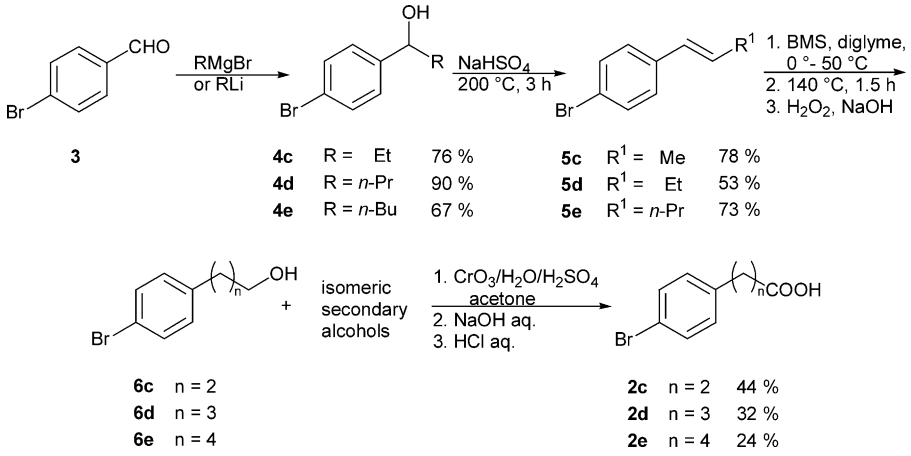
2. Results and discussion

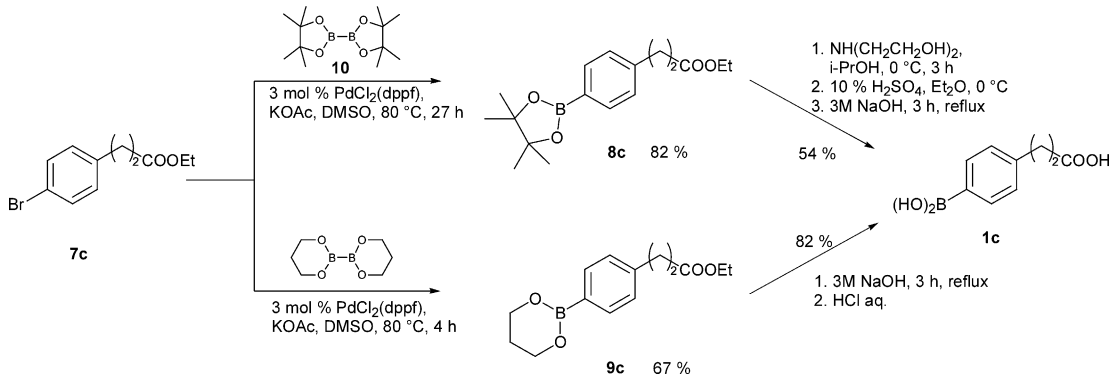
The synthesis of **2c**–**e** from 4-bromobenzaldehyde (**3**) is shown in Scheme 1. Treatment of **3** with an appropriate alkylmagnesium bromide or alkyllithium afforded the alcohols **4c**–**e** in good yields. It should be noted that the use of alkylmagnesium iodides results in lower yields of the alcohols, and formation of side products. For example, the reaction of **3** with ethylmagnesium iodide produced 1-(4-bromophenyl)propan-1-ol (**4c**), (4-bromophenyl)methanol, and 1-bromo-4-propenylbenzene (**5c**).Variation of the reaction conditions (temperature, time, concentration) affected the ratio of the products, however, the formation of the undesired (4-bromophenyl)methanol could not be avoided. Dehydration of **4c**–**e** by heating in the presence of sodium hydrogensulfate and *tert*-butylcatechol afforded the corresponding olefins **5c**–**e**, predominantly containing the *E* isomers. Hydroboration of **5c**–**e** with borane–dimethyl sulfide (BMS) produced the corresponding organoboranes, which were thermally isomerized at 140 °C in diglyme. The isomerization was monitored in time by oxidation of aliquots with alkaline hydrogen peroxide, and GC analysis of the product alcohols. The equilibrium composition of the organoboranes was reached in 1.5–2 h. In contrast to organoboranes derived from simple alkenes, the migration of boron to the terminal position was not complete. The amount of organoboranes with boron at the terminal position decreased with increasing chain length of **5c**–**e**, which is not observed for trialkylboranes, even with long chain alkyl groups, e.g. triacontyl [9]. Apparently, 4-bromophenyl group influences distribution of the product organoboranes at the equilibrium, similarly to phenyl group [10]. Mixed trialkylboranes derived from alkenes and sterically demanding dialkylboranes, e.g. dicyclohexylborane or di(2,5-dimethylcyclohexyl)borane, undergo thermal isomerization at a much higher rate as compared to simple tri-*sec*-alkylboranes [11]. The hydroboration of **5c**–**e** with these dialkylboranes afforded the corresponding organoboranes as indicated by ^{11}B-NMR analysis ($\delta \approx 83$, characteristic for trialkylboranes). However, the time required for reaching the thermal isomerization equilibrium was comparable to that observed for the hydroboration products of **5c**–**e** with BMS. Cyclohexanol or 2,5-dimethylcyclohexanol formed as the oxidation products in a mixture with the product alcohols **6c**–**e**, made their isolation difficult. Consequently, hydroboration with BMS, followed by thermal isomerization and oxidation, was used for the synthesis of **2c**–**e**. The mixture of product alcohols was oxidized with Jones' reagent, and the acids **2c**–**e** were separated from ketones, formed as side products, by simple extraction with an aqueous base. The decreasing yields, **2c** > **2d** > **2e**, reflect the amount of the corresponding organoboranes with boron at the terminal position.

The palladium-catalyzed cross-coupling reaction of 4,4,5,5,4′,4′,5′,5′ - octamethyl[2,2′]bi[[1,3,2]dioxaborolanyl] (**10**) with ethyl 3-(4-bromophenyl)propanoate (**7c**) carried out at 80 °C for 27 h, gave the coupling product **8c** which was hydrolyzed to **1c**, isolated in 44% overall yield (Scheme 2). The yield of **1c** was increased to 55% and the reaction time was shortened to 4 h, by using for the coupling the less sterically hindered [2,2′]bi[[1,3,2]-dioxaborinanyl], instead of **10**.

In another study on the synthesis of boronic acids we obtained high yields of coupling products from aryl iodides and bromides with the readily available pinacolborane, carrying the reaction in an ionic liquid, [bmim][BF_4]. Recently, palladium cross-coupling reactions were reported to occur with great efficiency in ionic liquids [12–14]. However, application of this method to the synthesis of **12c**–**e** by coupling methyl esters **11c**–**e** with pinacolborane gave mainly the debromination products, and only low yields of the coupling products. Fortunately, the reaction of **10** with **11c**–**e** in [bmim][BF_4] gave the coupling products cleanly in 86–89% yield (Scheme 3). The ionic liquid as the



Scheme 1.



Scheme 2.

reaction medium provides the following advantages. The reaction is much faster as compared to coupling in DMSO. The yields are higher, isolation of products is very simple, and they are obtained in good purity directly from the reaction. The catalyst remains in the ionic liquid, and the solution can be used again for the coupling reaction. It was recycled three times in the reaction of **10** with **11c**, and no decrease of the catalytic activity was observed.

3. Conclusion

ω-(4-Bromophenyl)alkanoic acids **2c**–**e** were prepared by the hydroboration–thermal isomerization–oxidation sequence. The acids were transformed into the corresponding boronates **12c**–**e** in good yields by the palladium-catalyzed cross-coupling reaction of **11c**–**e** with **10** in an ionic liquid, [bmim][BF_4]. The use of an ionic liquid as the reaction medium for the cross-coupling reaction was highly advantageous. The coupling products were formed cleanly, their isolation was simple, and the solution of the catalyst in the ionic liquid could be recycled.

4. Experimental

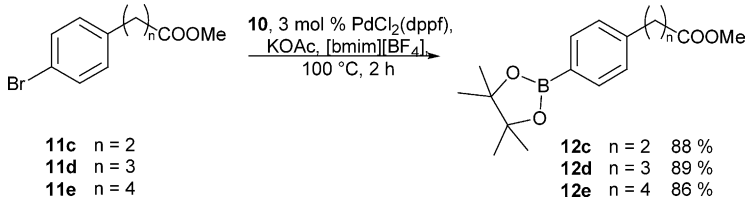
^{1}H-, ^{13}C- and ^{11}B-NMR spectra were recorded on Varian Gemini 200 MHz, and Bruker AMX 300 MHz spectrometers. GC analyses were performed on a Hewlett–Packard 5890 chromatograph equipped with a HP-1 column (5 m × 0.53 mm).

4.1. Materials

4,4,5,5,4′,4′,5′,5′-Octamethyl[2,2′]bi[[1,3,2]dioxaborolanyl] (**10**) [15], tetrakis-bis-(dimethylaminodiboron) [15], ethyl 3-(4-bromophenyl)propanoate (**7c**) [16], pinacolborane [17] and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) [18], were prepared according to the literature. [Bmim][BF_4] was dried at 100 °C for 4 h under 0.1 mmHg, the water content was 0.45% (Karl Fisher titration). Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl prior to use. Et_2O and diglyme were distilled from lithium aluminum hydride.

4.2. [2,2′]Bi[[1,3,2]dioxaborinanyl]

A 250 cm^3, three-necked flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser connected to a nitrogen source and a bubbler, was flushed with nitrogen. To the flask were added, tetrakis-bis-(dimethylamino)diboron (5.00 g, 25.5 mmol), toluene (50 cm^3), and a solution of propane-1,3-diol (3.90 g, 51 mmol) in toluene (30 cm^3). The flask was immersed in an ice-water bath, and ethereal solution of hydrogen chloride (17 cm^3, 102 mmol) was added. As soon as the addition started, a white precipitate of dimethylamine hydrochloride appeared. The slurry was stirred at room temperature (r.t.) for an additional 4 h. The precipitate was filtered off under nitrogen. The filtrate was evaporated to dryness under vacuum, and a white solid was obtained. It was taken in pentane (80 cm^3), and the remaining solid was removed by filtration. The solvent was evaporated, and the product, a white solid, was kept



Scheme 3.

under vacuum for 12 h, 3.12 g, 72%, m.p. 157–160 °C; ^{1}H-NMR, $CDCl_3$, δ 1.92 (quintet, $J = 5.2$ Hz, CH_2, 4H), 3.93 (t, $J = 5.4$ Hz, CH_2, 8H); ^{13}C-NMR, $CDCl_3$, δ 27.58 (CH_2), 61.14 (O–CH_2); ^{11}B-NMR, $CDCl_3$, δ 24.09. Lit. [19], m.p. 158–162 °C.

4.2.1. 1-(4-Bromophenyl)propan-1-ol (**4c**). Typical procedure

A solution of bromoethane (17.43 g, 160 mmol) in Et_2O (135 cm^3) was added dropwise, keeping gentle reflux, to magnesium turnings (3.89 g, 160 mmol) suspended in Et_2O (25 cm^3), and the mixture was refluxed for 30 min. The solution of ethylmagnesium bromide thus obtained was cooled to −5 °C and a solution of **3** (20.00 g, 110 mmol) in Et_2O (50 cm^3) was added. The mixture was stirred for 1 h at r.t., poured on ice, and acidified with 6 M HCl. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×50 cm^3). The organic solutions were combined, washed with 10% $NaHCO_3$ solution (50 cm^3), water (50 cm^3), brine (50 cm^3), and dried over magnesium sulfate. The product was isolated by distillation, 26.38 g, 76%, b.p. 84–89 °C/0.1 mmHg; ^{1}H-NMR, $CDCl_3$, δ 0.9 (t, $J = 7.4$ Hz, CH_3, 3H), 1.63–1.83 (m, CH_2, 2H), 1.93 (s, OH, 1H), 4.58 (t, $J = 6.6$ Hz, CH, 1H), 7.21 (d, $J = 8.6$ Hz, CH, 2H), 7.47 (d, $J = 8.6$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 10.02 (CH_3), 31.90 (CH_2), 75.27 (CH–O), 121.18 (C_{Ar}), 127.79 (CH_{Ar}), 131.46 (CH_{Ar}), 143.59 (C_{Ar}). Lit. [20], b.p. 138–139 °C/11 mmHg.

4.2.2. 1-(4-Bromophenyl)butan-1-ol (**4d**)

Prepared from **3** and butyl magnesium bromide following the procedure described above. Yield 90%, b.p. 95–98 °C/0.1 mmHg; ^{1}H-NMR, $CDCl_3$, δ 0.91 (t, $J = 7.2$ Hz, CH_3, 3H), 1.16–1.47 (m, CH_2, 2H), 1.54–1.82 (m, CH_2, 2H), 2.28 (s, OH, 1H), 4.59 (t, $J = 6.6$ Hz, CH, 1H), 7.18 (d, $J = 8.2$ Hz, CH, 2H), 7.44 (d, $J = 8.2$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 13.83 (CH_3), 18.81 (CH_2), 41.15 (CH_2),73.63 (CH–O), 121.07 (C_{Ar}), 127.59 (CH_{Ar}), 131.41 (CH_{Ar}), 143.86 (C_{Ar}). Lit. [21], b.p. 147 °C/11 mmHg.

4.2.3. 1-(4-Bromophenyl)pentan-1-ol (**4e**)

A 2.5 M solution of *n*-BuLi (50 cm^3, 125 mmol) was added to a solution of **3** (23.12 g, 125 mmol) in Et_2O (50 cm^3) at −70 °C. The mixture was stirred for 15 min at −70 °C, and then for 2 h at r.t. It was washed with water (3×10 cm^3) and dried over magnesium sulfate. The product was isolated by distillation, 24.58 g, 67%, b.p. 105 °C/0.2 mmHg; ^{1}H-NMR, $CDCl_3$, δ 0.88 (t, $J = 6.8$ Hz, CH_3, 3H), 1.18–1.44 (m, CH_2, 4H), 1.60–1.82 (m, CH_2, 2H), 1.87 (s, OH, 1H), 4.62 (t, $J = 6.8$ Hz, CH, 1H), 7.21 (d, $J = 6.7$ Hz, CH, 2H), 7.48 (d, $J = 6.7$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 13.96 (CH_3), 22.56 (CH_2), 27.83 (CH_2), 28.84 (CH_2), 74.00 (CH–O), 121.17 (C_{Ar}), 127.70 (CH_{Ar}), 131.50 (CH_{Ar}), 143.97 (C_{Ar}). Lit. [22], b.p. 122–127 °C/1 mmHg.

4.2.4. 4-(Prop-1-en-1-yl)bromobenzene (**5c**). Typical procedure

A mixture of **4c** (9.62 g, 45 mmol), sodium hydrogensulfate (1.62 g, 13 mmol), *p*-hydroquinone (1.5 g) and 4-*tert*-butylcatechol (1.5 g), was heated under nitrogen at 200 °C for 3 h. Et_2O (150 cm^3) was added, the organic layer was separated, washed with 10% $NaHCO_3$ (3×20 cm^3), water (3×20 cm^3), and dried with magnesium sulfate. The product was isolated by distillation, 6.85 g, 78%, b.p. 102 °C/0.2 mmHg; (*E* isomer, 97% GC); ^{1}H-NMR, $CDCl_3$, δ 1.87 (dd, $J_1 = 1.2$ Hz, $J_2 = 6.0$ Hz, CH_3, 3H), 6.25 (dq, $J_1 = 13.8$ Hz, $J_2 = 6.0$ Hz, CH, 1H), 6.35 (d, $J = 13.8$ Hz, CH, 1H), 7.18 (d, $J = 8.5$ Hz, CH, 2H), 7.39 (d, $J = 8.5$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 18.56 (CH_3), 120.42 (C_{Ar}), 126.67 (CH=), 127.45 (CH_{Ar}), 130.02 (CH=), 131.60 (CH_{Ar}), 136.93 (C_{Ar}). Lit. [20], b.p. 108–110 °C/11 mmHg.

4.2.5. 4-(But-1-en-1-yl)bromobenzene (**5d**)

Prepared from **4d** following the procedure described above. Yield, 53%, b.p. 87 °C/0.6 mmHg; (*E* isomer, 93% GC); ^{1}H-NMR, $CDCl_3$, δ 1.13 (t, $J = 7.4$ Hz, CH_3, 3H), 2.19–2.32 (m, CH_2, 2H), 6.32 (m, CH=CH, 2H), 7.26 (d, $J = 8.4$ Hz, CH, 2H), 7.43 (d, $J = 8.4$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 13.43 (CH_3), 25.97 (CH_2), 120.27 (C_{Ar}), 127,38 (CH=), 127.62 (CH_{Ar}), 131.42 (CH_{Ar}), 133.35 (CH=), 136.76 (C_{Ar}). Lit. [23], b.p. 98 °C/0.2 mmHg.

4.2.6. 4-(Pent-1-en-1-yl)bromobenzene (**5e**)

Prepared from **4e** following the procedure described above. Yield, 73%, b.p. 64 °C/0.4 mmHg; (*E* isomer, 97% GC); ^{1}H-NMR, $CDCl_3$, δ 0,95 (t, $J = 7.5$ Hz, CH_3, 3H), 1,49 (m, CH_2, 2H), 2.22 (q, $J = 7.5$ Hz, CH_2, 2H), 6.24 (dt, $J_1 = 15.6$ Hz, $J_2 = 7.5$ Hz, CH, 1H), 6.32 (d, $J = 15.6$ Hz, CH, 1H), 7.20 (d, $J = 8.6$ Hz, CH, 2H), 7.40 (d, $J = 8.6$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 13.66 (CH_3), 22.37 (CH_2), 35.02 (CH_2), 120.32 (C_{Ar}), 127.42 (CH_{Ar}), 128.76 (CH=), 131.44 (CH_{Ar}), 131.74 (CH=), 136.84 (C_{Ar}). Lit. [23], b.p. 105 °C/0.05 mmHg.

4.2.7. 3-(4-Bromophenyl)propanoic acid (**2c**). Typical procedure

A solution of **5c** (21.68, 110 mmol) in diglyme (50 cm^3) was added to a solution of BMS (5.5 cm^3, 55 mmol) in diglyme (50 cm^3) at 0 °C. After 1 h at 0 °C, the mixture was kept at 50 °C for another hour, and then at 140 °C for 1.5 h. The mixture was cooled, 3 M NaOH (18 cm^3, 55 mmol) was added, followed by 30% H_2O_2 (14 cm^3, 132 mmol). The mixture was stirred at 25 °C for 1 h, and at 50 °C for 2 h. Et_2O (150 cm^3) was added, and the aqueous layer was saturated with anhydrous

potassium carbonate. The organic layer was washed with water (3×50 cm^3), and brine (2×50 cm^3). The organic solution was dried over magnesium sulfate. The solvent was evaporated to give the crude **6c**, which was dissolved in acetone (60 cm^3). Jones reagent (16.5 g CrO_3, 17 cm^3 conc. H_2SO_4, 100 cm^3 H_2O) was added dropwise, at r.t., to the vigorously stirred acetone solution, and stirring was continued for 30 min. Acetone was removed, and the remaining mixture was extracted with EtOAc (3×50 cm^3). The organic layer was separated, washed with water (3×50 cm^3), and extracted with 3 M NaOH (3×50 cm^3). The alkaline solution was acidified with concentrated HCl to precipitate the product, 11.1 g, 44%, m.p. 129–133 °C; ^{1}H-NMR, $CDCl_3$, δ 2.67 (t, $J = 7.2$ Hz, CH_2, 2H), 2.92 (t, $J = 7.2$, CH_2, 2H), 7.09 (d, $J = 8.4$ Hz, CH, 2H), 7.42 (d, $J = 8.4$ Hz, CH, 2H), 10.20–10.80 (s, OH, 1H); ^{13}C-NMR, $CDCl_3$, δ 29.73 (CH_2), 35.14 (CH_2), 120.30 (C_{Ar}), 129.87 (CH_{Ar}), 131.44 (CH_{Ar}), 138.86 (C_{Ar}), 178.73 (COOH). Lit. [16], m.p. 132–135 °C.

4.2.8. 4-(4-Bromophenyl)butanoic acid (**2d**)

Prepared from **5d** following the procedure described above. Yield, 32%, m.p. 82–84 °C; ^{1}H-NMR, D_2O, δ 1.64 (m, CH_2, 2H), 1.99 (t, $J = 7.3$ Hz, CH_2, 2H), 2.40 (t, $J = 7.3$, CH_2, 2H), 6.99 (d, $J = 8.4$ Hz, CH, 2H), 7.29 (d, $J = 8.2$ Hz, CH, 2H); ^{13}C-NMR, D_2O, δ 28.47 (CH_2), 35.32 (CH_2), 38.02 (CH_2), 119.96 (C_{Ar}), 131.36 (CH_{Ar}), 132.20 (CH_{Ar}), 142.43 (C_{Ar}), 184.13 (COOH). Lit. [24], m.p. 83–86 °C.

4.2.9. 5-(4-Bromophenyl)pentanoic acid (**2e**)

Pprepared from **5e** following the procedure described above. Yield, 24%, m.p. 90–92 °C; ^{1}H-NMR, $CDCl_3$, δ 1.65 (m, CH_2, 4H), 2.38 (t, $J = 7.3$ Hz, CH_2, 2H), 2.60 (t, $J = 7.1$, CH_2, 2H), 7.04 (d, $J = 8.4$ Hz, CH, 2H), 7.39 (d, $J = 8.4$ Hz, CH, 2H), 9.40–10–20 (s, OH, 1H); ^{13}C-NMR, $CDCl_3$, δ 24.05 (CH_2), 30.47 (CH_2), 33.72 (CH_2), 34.84 (CH_2), 119.47 (C_{Ar}), 130.06 (CH_{Ar}), 131.31 (CH_{Ar}), 140.81 (C_{Ar}), 179.65 (COOH). Lit. [25], m.p. 91–92 °C.

4.3. Ethyl 3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]propanoate (**8c**)

Ethyl 3-(4-bromophenyl)propanoate (**7c**) (2.57 g, 10 mmol) was added to a mixture of $PdCl_2$(dppf) (0.24 g, 0.3 mmol), **10** (2.64 g, 10.5 mmol), and potassium acetate (2.94 g, 30 mmol) in DMSO (60 cm^3). The mixture was stirred at 80 °C for 27 h, cooled, and diluted with benzene (150 cm^3). The benzene solution was washed with water (3×100 cm^3), dried over magnesium sulfate and filtered through a silica pad. The solvent was evaporated to give the product, a yellow oil, 2.5 g, 82%; ^{1}H-NMR, $CDCl_3$, δ 1.22 (t, $J = 7.1$ Hz, CH_3, 3H), 1.35 (s, CH_3, 12H), 2.60 (t, $J = 7.1$ Hz, CH_2, 2H), 2.95 (t, $J = 7.4$ Hz, CH_2, 2H), 4.12 (q, $J = 7.1$ Hz, CH_2, 2H), 7.20 (d, $J = 8.4$ Hz, CH, 2H), 7.75 (d, $J = 8.4$ Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 14.05 (CH_3), 24.69 (CH_3), 30.98 (CH_2), 35.55 (CH_2), 60.21 (O–CH_2) 83.48 (O–C), 129.94 (C_{Ar}), 131.35 (CH_{Ar}), 134.88 (CH_{Ar}), 143.75 (C_{Ar}), 172.53 (C=O); ^{11}B-NMR, $CDCl_3$, δ 30.62; A sample was purified by column chromatography on silica gel (hexane–AcOEt, 90/10). Anal. Calc. for $C_{17}H_{25}BO_4$: C, 67.12; H, 8.28. Found: C, 66.78; H, 8.26%.

4.4. Ethyl 3-(4-[1,3,2]dioxaborinan-2-yl-phenyl)propanoate (**9c**)

Ethyl 3-(4-bromophenyl)propanoate (**7c**) (1.71 g, 6.7 mmol) was added to the mixture of $PdCl_2$(dppf) (0.164 g, 0.2 mmol), [2,2′]bi[[1,3,2]dioxaborinanyl] (1.75 g, 10.4 mmol), and potassium acetate (2.0 g, 20 mmol) in DMSO (40 cm^3). The mixture was stirred at 80 °C for 4 h, cooled, and diluted with benzene (150 cm^3). The benzene solution was washed with water (3×100 cm^3), dried over magnesium sulfate, and filtered through a silica pad. The solvent was evaporated to give the product as a yellow oil, 1.17 g, 67%; ^{1}H-NMR, $CDCl_3$, δ 1.23 (t, $J = 7.2$ Hz, CH_3, 3H), 2.04 (quintet, $J = 5.4$ Hz, CH_2, 2H), 2,61 (t, $J = 7.8$ Hz, CH_2, 2H), 2.95 (t, $J = 8.2$ Hz, CH_2, 2H), 4.10–4.18 (m, CH_2, 6H) 7.18 (d, $J = 8.0$ Hz, CH, 2H), 7.82 (d, $J = 8.0$ Hz, CH, 2H). A sample was purified by column chromatography on silica gel (hexane–AcOEt, 90/10). Anal. Calc. for $C_{14}H_{19}BO_4$: C, 64.15; H, 7.31. Found: C, 63.89; H, 8.28%.

4.5. 3-(4-Dihydroxyborylphenyl)propanoic acid (**1c**)

4.5.1. Hydrolysis of **8c**

A solution of diethanolamine (1.05 g, 10 mmol) in 2-propanol (2 cm^3) was added to **8c** (2.5 g, 8.2 mmol) at 0 °C, and the mixture was stirred for 3 h. Cold Et_2O (20 cm^3) was added, a white precipitate which was formed was filtered off (1.61 g), and added to a mixture of 10% sulfuric acid (2 cm^3) and Et_2O (20 cm^3). The mixture was stirred until the precipitate dissolved. The ethereal solution was separated, washed with water, and dried over magnesium sulfate. The solvent was evaporated to dryness, and a white solid was obtained, 0.93 g, 76%, m.p. 38–40 °C.

The solid was refluxed with 3 M NaOH (20 cm^3) for 3 h. The solution was cooled to 0 °C and acidified with conc. HCl. The precipitate which was formed was filtered off, washed with water, and dried. The product was a white solid, 0.63 g, 72%, m.p. 172–173 °C. ^{1}H-NMR, DMSO-d_6, δ 2.50 (t, $J = 7.4$ Hz, CH_2, 2H), 2.80 (t, $J = 7.2$ Hz, CH_2, 2H), 7.16 (d, $J = 7.4$ Hz, CH, 2H), 7.68 (d, $J = 7.4$ Hz, CH, 2H), 7.92 (s, OH, 2H), 12.10 (s, –OH, 1H); D_2O exchange 7.92 and 12.10; ^{13}C-NMR,

DMSO-d_6, δ 30.31 (CH_2), 34.95 (CH_2), 127.04 (CH_{Ar}), 133.99 (CH_{Ar}), 142.58 (C_{Ar}), 172.38 (COOH); ^{11}B-NMR, DMSO-d_6, δ 30.38; Anal. Calc. for $C_9H_{11}BO_4$: C, 55.72; H, 5.72. Found: C, 55.46; H, 5.71%.

4.5.2. Hydrolysis of **9c**

Ethyl 3-(4-[1,3,2]dioxaborinan-2-yl-phenyl)propanoate (1.17 g, 4.5 mmol) was refluxed with 3 M NaOH (20 cm^3) for 3 h. The solution was cooled to 0 °C and acidified with conc. HCl. The product, a white solid which, precipitated was filtered off, washed with water, and dried, 0.71 g, 82%, m.p. 168–170 °C. Spectroscopic data identical as above.

4.5.3. Methyl 3-(4-bromophenyl)propanoate (**11c**). Typical procedure

Methanol (10 cm^3) was added carefully to thionyl chloride (10.71 g, 90 mmol) at 0 °C, followed by **2c** (15 mmol). The mixture was refluxed for 2 h, the solvent and excess thionyl chloride were evaporated and the remaining oil was dissolved in Et_2O (100 cm^3). The organic solution was washed with water (3×20 cm^3), and dried over magnesium sulfate. The solvent was removed, and product was isolated by distillation, 2.9 g, 80%, 92 °C/0.4 mmHg; ^{1}H-NMR, $CDCl_3$, δ 2.60 (t, J = 7.8 Hz, CH_2, 2H), 2.90 (t, J = 7.8, CH_2, 2H), 3.66 (s, CH_3, 3H), 7.06 (d, J = 8.1 Hz, CH, 2H), 7.39 (d, J = 8.1 Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 30.06 (CH_2), 35.21 (CH_2), 51.48 (CH_3), 119.91 (C_{Ar}), 129.92 (CH_{Ar}), 131.54 (CH_{Ar}), 139.31 (C_{Ar}), 172.80 (C=O). Lit. [26], b.p. 154–155 °C/16 mmHg.

4.5.4. Methyl 4-(4-bromophenyl)butanoate (**11d**)

Prepared from **2d** following the procedure described above. Yield, 83%, b.p. 110 °C/0.4 mmHg; ^{1}H-NMR, $CDCl_3$, δ 1.92 (m, CH_2, 2H), 2.32 (t, J = 7.6 Hz, CH_2, 2H), 2.60 (t, J = 7.4, CH_2, 2H), 3.66 (s, CH_3, 3H), 7.04 (d, J = 8.4 Hz, CH, 2H), 7.39 (d, J = 8.4 Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 26.22 (CH_2), 33.17 (CH_2), 34.43 (CH_2), 51.48 (CH_3), 119.70 (C_{Ar}), 130.17 (CH_{Ar}), 131.40 (CH_{Ar}), 140.26 (C_{Ar}), 173.72 (C=O). Lit. [24], b.p. 90 °C/0.05 mmHg.

4.5.5. Methyl 5-(4-bromophenyl)pentanoate (**11e**)

Prepared from **2e** following the procedure described above. Yield, 73%, 115 °C/0.2 mmHg; ^{1}H-NMR, $CDCl_3$, δ 1.61 (m, CH_2, 4H), 2.35 (t, J = 7.2 Hz, CH_2, 2H), 2.59 (t, J = 7.2, CH_2, 2H), 3.63 (s, CH_3, 3H), 7.05 (d, J = 8.3 Hz, CH, 2H), 7.40 (d, J = 8.3 Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 24.39 (CH_2), 30.64 (CH_2), 33.77 (CH_2), 34.85 (CH_2), 51.47 (CH_3), 119.44 (C_{Ar}), 130.12 (CH_{Ar}), 131.30 (CH_{Ar}), 140.99 (C_{Ar}), 173.87 (C=O).

4.5.6. Methyl 3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]propanoate (**12c**). Typical procedure

The ester **11c** (0.73 g, 3 mmol) was added to a suspension of $PdCl_2$(dppf) (73 mg, 0.09 mmol) in degassed [bmim][BF_4] (3 cm^3), under argon atmosphere, and the mixture was heated to 100 °C with vigorous stirring. The deep-red solution was cooled to ambient temperature, potassium acetate (0.89 g, 9 mmol), and **10** (0.84, 3.3 mmol), were added. The mixture was heated with vigorous stirring at 100 °C for 2 h. It was cooled and extracted with petroleum ether (5×15 cm^3). The combined extracts were washed with water (2×15 cm^3), and dried over magnesium sulfate. Evaporation of the solvent afforded an oily product, 0.77 g, 88%; ^{1}H-NMR, $CDCl_3$, δ 1.33 (s, CH_3, 12H), 2.63 (t, J = 7.2 Hz, CH_2, 2H), 2.96 (t, J = 8.2 Hz, CH_2, 2H), 3.66 (s, CH_3, 3H), 7.21 (d, J = 8.2 Hz, CH, 2H), 7.73 (d, J = 8.2 Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 24.82 (CH_3), 31.09 (CH_2), 35.47 (CH_2), 51.55 (O–CH_3), 83.66 (O–C), 127.67 (CH_{Ar}), 135.03 (CH_{Ar}), 143.80 (C_{Ar}), 172.18 (C=O); ^{11}B-NMR, $CDCl_3$, δ 31.87; A sample was purified by column chromatography on silica gel (hexane–CH_2Cl_2–AcOEt, 70/20/10). Anal. Calc. for $C_{16}H_{23}BO_4$: C, 66.23; H, 7.99. Found: C, 65.98; H, 7.95%.

4.5.7. Methyl 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]butanoate (**12d**)

Prepared from **11d** following the procedure described above, oil, 0.81 g, 89%; ^{1}H-NMR, $CDCl_3$, δ 1.33 (s, CH_3, 12H), 1.95 (m, CH_2, 2H), 2.32 (t, J = 7.6 Hz, CH_2, 2H), 2.66 (t, J = 7.8 Hz, CH_2, 2H), 3.66 (s, CH_3, 3H), 7.19 (d, J = 8.2 Hz, CH, 2H), 7.74 (d, J = 8.2 Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 24.78 (CH_3), 26.23 (CH_2), 33.25 (CH_2), 35.22 (CH_2), 51.39 (O–CH_3) 83.57 (O–C), 127.86 (CH_{Ar}), 134.88 (CH_{Ar}), 144.69 (C_{Ar}), 173.76 (C = O); ^{11}B-NMR, $CDCl_3$, δ 31.21; A sample was purified by column chromatography on silica gel (hexane/CH_2Cl_2/AcOEt, 70/20/10). Anal. Calc. For $C_{17}H_{25}BO_4$ C 67.12, H 8.28. Found: C 66.80, H 8.27.

4.5.8. Methyl 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]pentanoate (**12e**)

Prepared from **11e** following the procedure described above, oil, 0.82 g, 86%; ^{1}H-NMR, $CDCl_3$, δ 1.33 (s, CH_3, 12H), 2.31 (m, CH_2, 4H), 2.63 (m, CH_2, 4H), 3.65 (s, CH_3, 3H), 7.17 (d, J = 8.2 Hz, CH, 2H), 7.71 (d, J = 8.2 Hz, CH, 2H); ^{13}C-NMR, $CDCl_3$, δ 24.48 (CH_2), 24.78 (CH_3), 30.60 (CH_2), 33.84 (CH_2), 35.66 (CH_2), 51.37 (O–CH_3), 83.42 (O–C), 127.78 (CH_{Ar}), 134.82 (CH_{Ar}), 145.46 (C_{Ar}), 173.94 (C=O); ^{11}B-NMR, $CDCl_3$, δ 31.50; A sample was purified by column chromatography on silica gel (hexane–CH_2Cl_2–AcOEt, 70/20/10). Anal. Calc. for $C_{18}H_{27}BO_4$: C, 67.94; H, 8.55. Found: C, 67.61; H, 8.54%.

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