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Synthesis of novel prostaglandins containing a boronate in the α chain

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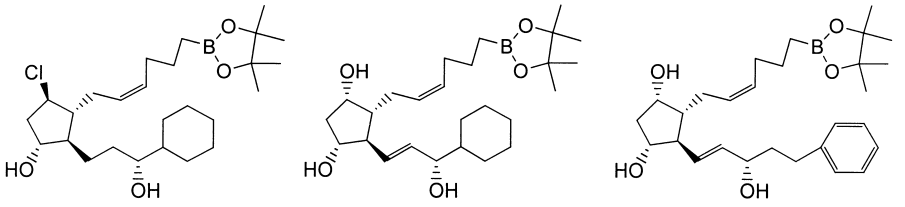
Abstract

A novel class of prostaglandins containing a boronate in the α chain have been synthesized. The key steps in the synthesis were the preparation of the ylide containing the boronate and the subsequent Wittig reaction using the ylide.

Many prostaglandin derivatives have been synthesized in an attempt to develop therapeutic agents during the past decades. Recently, much of this effort has centered on the identification of prostaglandin derivatives as ocular hypotensives for the use in the treatment of glaucoma.[1] In this paper, we report the successful synthesis of a novel class of prostaglandin in which the carboxylic acid is replaced by boronic acid ester (Scheme 1).



Scheme 1.

The strategy was to synthesize the ylide precursor **8** containing a boronate moiety and to treat **8** with the intermediate **14** under the conditions of the Wittig reaction.[2] Compounds **2** and **3** were obtained by an analogous synthetic sequence.

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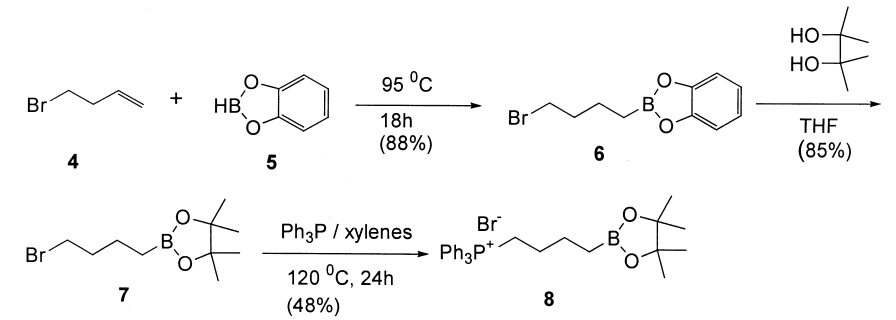
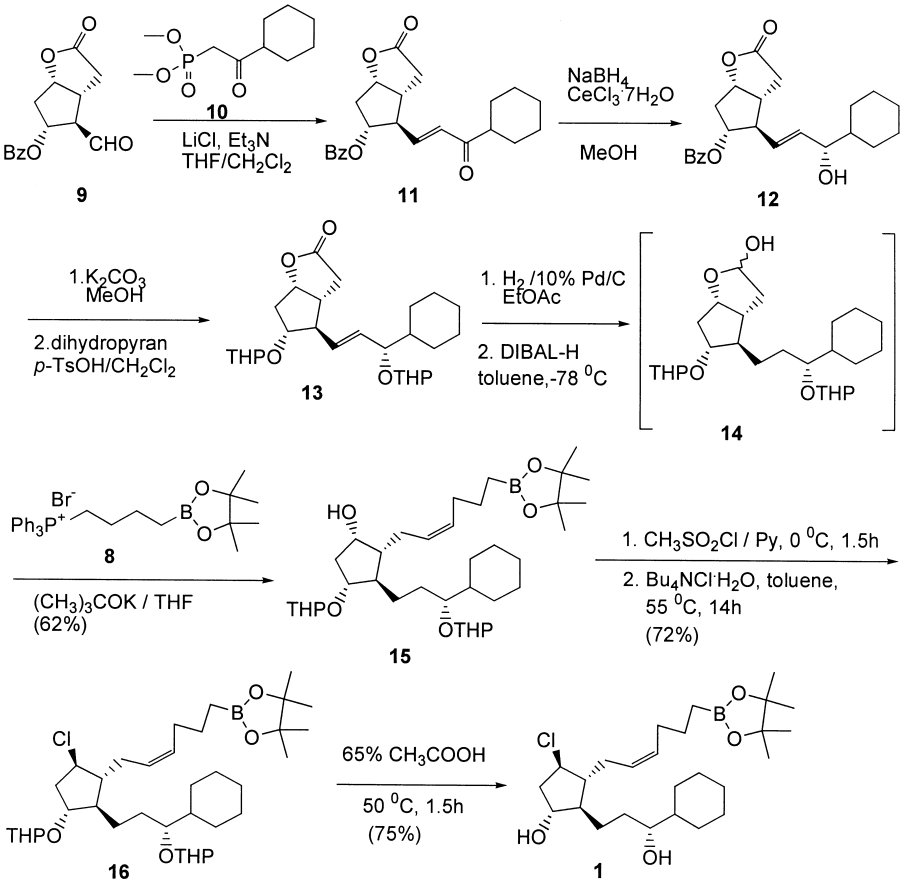
The first intermediate, catechol-4-bromo-butylboronate **6**, was obtained by hydroboration[3] of 4-bromo-butene **4** with catecholborane **5** at 95°C for 18 h (Scheme 2). Distillation gave boronate **6**, which was then transesterified[4] with pinacol in THF to give pinacol-4-bromo-butylboronate **7**. The boronate was heated with triphenylphosphine in xylene at 120°C for 24 h to provide the ylide precursor **8**,[10] which was recrystallized from diethyl ether and was stable if stored in a refrigerator. This type of boronate has not been reported previously.



Scheme 2.



Scheme 3.

The intermediate **14** was synthesized starting from commercially available Corey lactone[5] **9** and dimethyl(2-cyclohexyl-2-oxo)ethylphosphonate **10**, which was synthesized from dimethyl methylphosphonate and methyl cyclohexanecarboxylate (Scheme 3). The phosphonate **10** was treated with lithium chloride and triethylamine in THF followed by Horner–Emmons reaction with the Corey lactone aldehyde **9** to give the corresponding enone **11**.[6] Reduction of the carbonyl group of **11** with sodium borohydride and cerium(III) chloride in methanol afforded a mixture (1:1) of the two diastereomeric allyl alcohols, which were separated by HPLC.[7] Cleavage of the benzoate ester of the alcohol **12** followed by protection of the resulting diol afforded the THP-ether diol **13**. Reduction of the lactone **13** with diisobutylaluminum hydride (DIBAL-H) in toluene and treatment of the resulting lactol **14** with the ylide precursor **8** in potassium *tert*-butoxide in THF gave the boronate **15**. Treatment of boronate **15** with methanesulfonyl chloride in pyridine and then with tetrabutylammonium chloride in toluene provided the chloride **16**.[8] The cleavage of the THP-ethers under mildly acidic conditions gave the final product **1**,[10] which was purified by HPLC. Compounds **2**[10] and **3**[10] were synthesized using a similar method.

Compounds **1** and **2** showed the DP receptor binding affinities[9] of 61 and 55 μM respectively. Compound **3** exhibited FP receptor binding affinity[9] of 8.7 μM. Further biological studies are in progress.

Acknowledgements

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10. All compounds were fully characterized by ^{1}H and ^{13}C NMR (600 MHz) and mass spectroscopy. Characteristic data for final compounds and a key intermediate are given as follows. Compound **1**: ^{1}H NMR ($CDCl_3$) δ 5.51–5.49 (m, 1H), 5.41–5.39 (m, 1H), 4.09 (s, 1H), 4.04 (s, 1H), 2.30–2.28 (m, 2H), 2.15–2.12 (m, 2 H), 2.09–2.05 (m, 3H), 1.81–1.47 (m, 15H), 1.34–1.30 (m, 1H), 1.24 (s, 12H), 1.21–1.01 (m, 5H), 0.81–0.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 132.14 (CH), 125.97 (CH), 82.94 (C), 76.34 (CH), 76.07 (CH), 60.84 (CH), 54.36 (CH), 51.77 (CH), 44.56 (CH_2), 43.48 (CH), 31.83 (CH_2), 30.0 (CH_2), 29.88 (CH_2), 29.23 (CH_2), 27.98 (CH_2), 26.49 (CH_2), 26.28 (CH_2), 26.12 (CH_2), 24.81 (CH_3), 24.07 (CH_2); ESMS 469 ($M+H^+$), HR-FABMS calcd for $M+H^+$ $C_{26}H_{47}ClBO_4$ 469.3260, found 469.3260. Compound **2**: ^{1}H NMR ($CDCl_3$) δ 5.55–5.41 (m, 4H), 4.20–4.13 (m, 1H), 3.81–3.80 (s,

1H), 3.79–3.77 (s, 1H), 2.44–2.07 (m, 7H), 1.87–1.38 (m, 13 H), 2.09–2.05 (m, 2H), 1.24–1.21 (m, 12H), 1.14–1.13 (m, 2H), 0.98–0.94 (m, 2H), 0.80–0.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 133.68 (CH), 133.50 (CH), 130.95 (CH), 128.09 (CH), 83.01 (C), 78.12 (CH), 72.98 (CH), 56.08 (CH), 50.48 (CH), 43.55 (CH), 42.72 (CH_2), 29.76 (CH_2), 28.84 (CH_2), 26.53 (CH_2), 26.10 (CH_2), 26.03 (CH_2), 25.63 (CH_2), 24.80 (CH_3), 24.05 (CH_2); ESMS 466 $(M+NH_4)^+$; HR-FABMS calcd for (M–H) $C_{26}H_{44}BO_5$ 447.3282, found 447.3282. Compound **3**: ^{1}H NMR ($CDCl_3$) δ 7.30–7.18 (m, 5H), 5.64–5.61 (m, 1H), 5.54–5.50 (m, 1H,), 5.43–5.40 (m, 2H), 4.20 (s, 1H), 4.12–4.11 (m, 1H), 3.94 (s, 1H), 2.72–2.70 (m, 2H), 2.34–1.77 (m, 13H), 1.54–1.46 (m, 2H), 1.24–1.22 (m, 12H), 0.81–0.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 141.84 (CH), 134.52 (CH), 132.77 (CH), 128.42 (CH), 128.04 (C), 125.82 (CH), 83.04 (C), 73.23 (CH), 72.08 (CH), 56.05 (CH), 50.63 (CH_2), 42.75 (CH_2), 38.83 (CH_2), 31.80 (CH_2), 29.79 (CH_2), 25.70 (CH_2), 24.79 (CH_3), 24.04 (CH_2); ESMS 488 $(M+NH_4)^+$; HR-FABMS calcd for (M–H) $C_{26}H_{42}BO_5$ 469.3126, found 469.3126. Compound **8**: ^{1}H NMR (CD_3OD) δ 7.78–7.62 (m, 15H), 3.42–3.25 (m, 2H), 1.60–1.59 (m, 4H), 1.14–1.10 (m, 12H), 0.82–0.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 136.22 (CH), 134.85 (CH), 134.65 (CH), 131.58 (CH), 131.33 (CH), 120.92 (C), 119.21 (C), 26.28 (CH_2), 25.85 (CH_2), 24.71 (CH_3), 23.23 (CH_2), 22.22 (CH_2); ESMS 445 (M^+).