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Desymmetrization of C₂-symmetric bis(boronic esters) by Zweifel olefinations

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Abstract: Anti-configured 1,3-dimethyl deoxypropionate motifs are important sub-structures in natural products. Herein, we describe a bidirectional approach for the rapid construction of natural products featuring such motifs using C_2 -symmetrical 1,3-bis(boronic esters). As for its application in convergent syntheses it was important to establish a selective mono-Zweifel olefination we describe the scope and limitations using different 1,3-bis(boronic esters) and nucleophiles. This protocol takes advantage of the combination of the Hoppe–Matteson–Zweifel chemistry which was elegantly put into practice by Aggarwal. In order to show its applicability the total syntheses of two natural products, serricornin and (+)-invictolide, were performed.

In the context of our program to establish synthetic access to various natural products^[1] we focused on those featuring the 1,3-(poly)deoxypropionate motif. Polyketides and polyketide-peptide hybrides featuring this motif like sambutoxin (1), borrelidin (2), (+)-kalkitoxin (3) and (+)-invictolide (4) are challenging to synthesize without functional group inter-conversions using established aldol chemistry (Figure 1).^[2]



Figure 1. Natural products containing the 1,3-deoxypropionate motif.

On the other hand, an elegant and rapid concept for the synthesis of those polydeoxypropionates is the so called assembly line synthesis developed by Aggarwal and coworkers

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using boronic esters.^[3] This method was applied to the total synthesis of (+)-hydroxyphthioceranic acid, (+)-kalkitoxin (3)[2c] and many more natural products.^[6] One advantage of this strategy, namely the individual control of each chiral center, is also a drawback as it requires a linear work flow and an iterative introduction of every single methyl or ethyl group.^[2c, 4] Based on this state of development and the fact that a large variety of natural products feature anti-configured 1,3-dimethyl deoxypropionate motifs, we envisioned to use C2-symmetrical 1,3bis(boronic esters) for the sequential Zweifel olefination with different nucleophiles. The synthesis of such a precursor was already described by the group of Aggarwal^[5] and recently, Aggarwal and coworkers subjected this 1,3-bis(boronic ester) to a double-sided vinylidene homologation.^[6] However, our goal was to use this C2-symmetrical 1,3-bis(boronic esters) in desymmetrizing mono-Zweifel olefinations (Scheme 1).^[7]



 $\label{eq:scheme1} \begin{array}{l} \mbox{Scheme 1}. \mbox{ Desymmetrization of C_2-symmetric 1,3-bis(boronic esters) by mono-Zweifel olefination.} \end{array}$

At the outset of our investigation we started by optimizing the reaction conditions for the addition of simple vinyl metal species to 1,3-bis(boronic ester) 5a^[5] (Scheme 2). First transformations with vinyl lithium^[8] generated yields around 35%, but during the upscaling process the yield dropped drastically to 10% or less (Scheme 2). Subsequently, vinyImagnesium bromide was used as the nucleophile^[9] and the yields were around 25%. We then further optimized the mono-Zweifel olefination by adding iodine as a solid^[10] and not as a methanolic solution. The subsequent methanol addition was done with a very slow addition rate of 0.15 mL/min. This variation gave satisfactory and reliable yields around 48% and 94% based on recovered starting material and works equally well for small and large scale reactions (for details see SI). It should be pointed out that separation of the starting material and the olefination product was easily achievable upon standard column chromatography.

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Scheme 2. Optimized conditions for the mono-Zweifel olefination. Standard reaction conditions: **5a** (1.0 eq.), vinyl compound (1.1 to 2.0 eq.), THF, 30 min at -78 °C, then 30 min at t, I_2 (elem., 4.0 eq.), MeOH (0.15 mL/min) 30 min at -78 °C, then NaOMe (8.0 eq.) in MeOH (0.50 mL/min) at -78 °C, 30 min, then rt o/n. [b] yield dropped to 10% during upscaling. [c] I_2 addition as a methanolic solution. [d] Ate-complex formation and I_2 addition at -95 °C. [e] Ate-complex formation from -78 °C to 0 °C. a) LDA, Et₂O, THF, -78 °C to 0 °C, 1.5 h, 73%. **6a**, **7a**, **7b** and **7c** were obtained as single diastereoisomers.

After having successfully accomplished the addition of vinylmagnesium bromide we turned our attention to other olefins that could be useful intermediates in total synthesis (Scheme 2). For this we used but-1-en-2-ylmagnesium bromide[11] and obtained using the previously optimized conditions the corresponding product 7a. As we will describe below, this product can be easily converted to its corresponding ethyl ketone. We also investigated the addition of different lithiated enolethers^[8b, 9, 12], however only the lithiated vinyl carbamate led to the desired Zweifel olefination 7c. In the beginning we obtained the double-olefination product in favor of the mono-olefination but we overcame this problem by reducing the equivalents of the vinyl species to only 1.1 eq. and obtained the desired mono-Zweifel product 7c in 73% yield. Beyond that, lithiated vinyl bromide was used as nucleophile giving us the versatile boronic ester 7b in 46% yield. Interestingly, all of these nucleophiles were more reactive than vinylmagnesium bromide, because unreacted starting material could not be reisolated. To show the utility of these products, mono-Zweifel product 7c was subjected to an elimination under basic conditions affording alkyne 8. In our case higher yields were observed when LDA (73%) was used instead of tBuLi (41%, Scheme 2). In both cases no epimerization was observed.[12] Alkyne 8 could be a powerful intermediate in total synthesis after hydrometalation, cross-coupling or even additional hydroboration.

After examination of different nucleophiles we investigated structural variations of the 1,3-bis(boronic esters, Scheme 3).

Scheme 3. Substrate scope of the mono-Zweifel olefination. All reactions were run using the optimized conditions of Scheme 2. Yields refer to isolated yield after flash column chromatography. The *dr* was determined by ¹H-NMR.

The sterically demanding *iso*butyl and cyclohexyl residues were well tolerated by the mono-Zweifel olefination, which is quite remarkable due to the steric hindrance next to the reaction center.^[7, 8b] Boronic esters containing terminal double bonds (**6g-6h**) could also be prepared in good yields. Due to their additional functionalities they could be valuable building blocks in total synthesis. Compounds **6i** and **6j** could also be synthesized using the mono-Zweifel olefination, but partial epimerization was observed. In the case of boronic ester **6k** we observed traces of the double olefination product.

With a reliable method in hand, we applied building block 6a to the total synthesis of (+)-invictolide (4) and serricornin (20).[2d-f, ^{13]} (-)-Invictolide is one of the lactons used for the queen recognition of the red fire ant Solenopsis invicta (Buren).[13] With its three methyl groups and the 1,3-anti-deoxypropionate motif (+)-invictolide (4) matches perfectly our synthetic strategy. In our retrosynthetic analysis (Scheme 4) we envisioned lactolformation and oxidation as the last steps, whereby the doublebond of Zweifel olefination functions as precursor for the carbonyl moiety. The required secondary alcohol in linear precursor 9 should be installed by lithiation-borylation chemistry from mono-Zweifel product 6a and TIB ester 10. The corresponding alcohol could either be derived from 1-propylboronic acid pinacol ester (17) by assembly line synthesis or by Myers alkylation using auxiliary 14. We on purpose performed both routes in order to compare steps and yields and by doing so obtaining an assessment of both strategies.

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Scheme 4. Retrosynthetic analysis of (+)-invictolide (4).

Our synthesis started with gram-scale preparation of C₂symmetric 1,3-bis(boronic ester) $5a^{[5]}$ using a slightly modified protocol of the Aggarwal group (see SI). The described mono-Zweifel olefination gave us boronic ester **6a** in an overall yield of $45\%^{[14]}$ (Scheme 5).



Scheme 5. Synthesis of boronic ester 6a. a) bromoethane, nBu_4NHSO_4 , NaOH, CHCl₃, H₂O, rt, o/n, \geq 95%; b) sBuLi, (+)-sparteine, Et₂O, -78 °C, 5 h, then Me₃SnCl, Et₂O, -78 °C to rt, 1.5 h, 70%, er 99:1; c) nBuLi, Et₂O, -78 °C, 1.5 h, then pinBCH₂Bpin, Et₂O, -78 °C to rt, o/n, 82%, dr \geq 95:5; d) vinylMgBr, THF, 30 min at -78 °C, then 30 min at rt, then l₂, MeOH 30 min at -78 °C, then NaOMe, MeOH, 30 min at -78 °C, then rt o/n, 35%, 81% brsm.

Alcohol **15** was synthesized via two different routes: Myers alkylation and assembly line synthesis (Scheme 6). The first step in the Myers alkylation route was the preparation of the auxiliary **14** from (-)-pseudoephedrine (**13**).^[15] Afterwards, alkylation using 1-propyliodide (**16**) and subsequent reduction finished the synthesis of alcohol **15**.^[15b, 16] The assembly line route started with the synthesis of 1-propylboronic acid pinacol ester (**17**) from 1-propyliodide (**16**).^[4b] Subsequently, a three-step sequence consisting of lithiation-borylation, Matteson-homologation and oxidation led to alcohol **15**.^[2c] This alcohol was then subjected to a Mitsunobu reaction^[17] using TIBOH (**11**) to afford TIB ester **10** in 92% yield.



Scheme 6. Synthesis of TIB ester 10 via Myers alkylation and assembly line synthesis. a) LDA, LiCl, THF, -78 °C to rt, 1.5 h, then 1-propyliodide (16), THF, 0 °C to rt, o/n; b) LDA, BH₃*NH₃, THF, -78 °C to rt, 5 h, 53% o2s, er 99:1; c) *t*BuLi, pinBO/Pr, Et₂O, -105 °C, 10 min, 88%; d) *n*BuLi, 12, Et₂O, -78 °C to rt, o/n; e) BrCH₂Cl, *n*BuLi, Et₂O, -78 °C to rt, o/n; f) 2 \leq NaOH, H₂O₂, THF, -20 °C to rt, 2 h, 45% o3s, er 99:1; g) TIBOH (11), PPh₃, DIAD, THF, 0 °C to rt, o/n, 92%.

Comparison of the two different routes showed that the stereoselectivity was excellent (*er* 99:1) in both approaches. One step less is needed in the Myers route (three vs. four) while the

yields are within the same range. However, 1-propylboronic acid pinacol ester (17) is also commercially available but quite expensive. However, in the case 17 is purchased three steps would be needed in both approaches. One drawback of the Myers route is the use of an auxiliary and the related low atom economy. Another difference is the number of purification steps, with the Myers route requiring three and the assembly line approach requiring two. A practical disadvantage of the assembly line approach is the required very slow addition rate (20 μ L/min) of *n*BuLi during the Matteson-homologation.

However, with both fragments in hand, the fragment coupling using lithiation-borylation chemistry was the next step. The obtained boronic ester was directly subjected to an oxidation giving us secondary alcohol **9** in good yield and high diastereoselectivity.^[18] The subsequent two-step sequence consisting of ozonolysis^[19] and Ley-Griffith-oxidation^[20] of the intermediately formed lactol finished the - to the best of our knowledge - shortest total synthesis of (+)-invictolide (**4**, Scheme 7).



Scheme 7. Fragment coupling and endgame in the total synthesis of (+)-invictolide (4). a) sBuLi, (-)-sparteine, Et₂O, -78 °C, 5 h, then **6a**, THF, -78 °C to 40 °C, o/n; b) 2 M NaOH, H₂O₂, THF, -20 °C to rt, 2 h, 62% o2s, $dr \ge 95:5$; c) O₃, PPh₃, CH₂Cl₂, -78 °C to rt, o/n, 87%; d) TPAP, NMO, 4 Å MS, CH₂Cl₂, rt, 2.5 h, 80%.

By using the same strategy we also accomplished the synthesis of serricornin (**20**), the female sex pheromone of the cigarette beetle *Lasioderma serricorne*.^[21] TIB ester **18** was prepared by using the established phase transfer conditions.^[5, 22] Lithiation-borylation chemistry of boronic ester **7a** with TIB ester **18**^[5, 22] and subsequent oxidation gave us secondary alcohol **19** in 70% yield over two steps in a 10:1 diastereomeric ratio. Finally, ozonolysis^[19] provided serricornin (**20**) as a mixture of its open chain and hemiketal form (Scheme 8).^[11]



Scheme 8. Total synthesis of serricornin (**20**). a) NaOH, 1-bromopropane, *n*Bu_ANHSO₄, H₂O, CHCl₃, rt, o/n, ≥ 95%; b) sBuLi, (+)-sparteine, Et₂O, -78 °C, 5 h, then **7a**, THF, -78 °C to 40 °C, o/n; c) 2 м NaOH, H₂O₂, THF, -20 °C to rt, 2.5 h, 70% o2s, *dr* 10:1; d) O₃, PPh₃, CH₂Cl₂, -78 °C to rt, o/n, 74%, *dr* 18:1 hemiketal form.

In summary, we developed a bidirectional approach to polyketides or polyketide fragments featuring the 1,3-deoxy-

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propionate motif. The key step in this approach is a desymmetrization using the mono-Zweifel olefination. We could show the value of key intermediates **6a** and **7a** in the syntheses of (+)-invictolide (**4**) and serricornin (**20**). Furthermore, a detailed substrate scope showed the general applicability of the developed methodology. Finally, the use of different nucleophiles enables synthetic access to a variety of valuable building blocks.

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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It's a crab! By combining the Hoppe-, Matteson-, Aggarwal- and Zweifelchemistry, a bidirectional access to polyketides featuring the challenging 1,3-deoxypropionate motif is presented. The desymmetrization of various 1,3-bis(boronic esters) led to synthetically interesting building blocks. With this reliable method the pheromones invictolide and serricornin were synthesized.



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