Desymmetrization of $C_2$-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 by 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 by 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 et al. 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 hybrids featuring this motif like sambutoxin (1), borrelinid (2), (+)-kalkitoxin (3), and (+)-invictolide (4) are challenging to synthesize without functional group interconversions by using established aldol chemistry (Figure 1).[2]

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 co-workers by 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 workflow 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 $C_2$-symmetrical 1,3-bis(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 co-workers subjected this 1,3-bis(boronic ester) to a double-sided vinylidene homologation.[6] However, our goal was to use this $C_2$-symmetrical 1,3-bis(boronic esters) in desymmetrizing mono-Zweifel olefinations (Scheme 1).[7]

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At the outset of our investigation we started by optimizing the reaction conditions for the addition of simple vinyl metal species to the 1,3-bis(boronic ester) \(5a\)\(^{[5]}\) (Scheme 2). First transformations with vinyl lithium\(^{[6]}\) generated yields around 35\%, but during the upscaling process the yield dropped drastically to 10\% or less (Scheme 2). Subsequently, vinylmagnesium 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\(^{-1}\). 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 the Supporting Information). It should be pointed out that separation of the starting material and the olefination product was easily achievable upon standard column chromatography.

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, by 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 enol ethers,\(^{[8b, 9, 12]}\) however, only the lithiated vinyl carbamate led to the desired Zweifel olefination product \(7c\). 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 equivalents 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 re-isolated. 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). The sterically demanding isobutyl 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.\(^{[14a, b]}\) 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 by 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 \((20)\).\(^{[8d–f, 13]}\) (++)-Invictolide is one of the lactones used for the queen recognition of the red fire ant \textit{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 lactol formation and oxidation as the last steps, whereby the double bond of the Zweifel olefination functions as precursor for the carbonyl moiety. The required secondary alcohol in the linear precursor \(9\) should be installed by lithiation–borylation chemistry from the mono-Zweifel product \(6a\) and the TIB ester \(10\). The corresponding alcohol could either be derived from 1-propylboronic acid pinacol ester \((17)\) by assembly line synthesis or by Myers alklylation by 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.

Our synthesis started with the gram-scale preparation of the \(C_3\)-symmetric 1,3-bis(boronic ester) \(5a\)\(^{[5]}\) by using a slightly modified protocol of the Aggarwal group (see the Supporting Information). The described mono-Zweifel olefination gave us boronic ester \(6a\) in an overall yield of 45\%\(^{[14]}\) (Scheme 5).

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

Comparison of the two different routes showed that the stereoselectivity was excellent (e.r. 99:1) in both approaches. One step less is needed in the Myers route (three vs. four) whereby the yields are within the same range. However, 1-propylboronic acid pinacol ester (17) is also commercially available but

In summary, we developed a bidirectional approach to polyketides or polyketide fragments featuring the 1,3-deoxypropionate motif. The key step in this approach is a desymmetrization by 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.

**Acknowledgements**

In terms of preparation of the manuscript we thank Daniel Lücke, Lucas Millbrodt, Christoph Etting, and Alina Eggert. We thank Dr. J. Fohrer, M. Rettsadt, and D. Körtje for detailed 2D NMR analysis and A. Schulz and R. Reichel for mass spectra. A generous gift of Bpin₃ from Allychem is also appreciated. Furthermore we thank Prof. Dr. V.K. Aggarwal and his group for helpful discussions on Zweifel olefinations.

**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** C₂-symmetry · desymmetrization · lithiation–borylation chemistry · mono-Zweifel olefination · natural product synthesis

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