



Fiorito, D., Keskin, S., Bateman, J. M., George, M., Noble, A., & Aggarwal, V. K. (2022). Stereocontrolled Total Synthesis of Bastimolide B Using Iterative Homologation of Boronic Esters. *Journal of the American Chemical Society*, 144(18), 7995–8001.
<https://doi.org/10.1021/jacs.2c03192>

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
[10.1021/jacs.2c03192](https://doi.org/10.1021/jacs.2c03192)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via American Chemical Society at <https://doi.org/10.1021/jacs.2c03192>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Stereocontrolled Total Synthesis of Bastimolide B Using Iterative Homologation of Boronic Esters

Daniele Fiorito, Selbi Keskin, Joseph M. Bateman, Malcolm George, Adam Noble, and Varinder K. Aggarwal*



Cite This: *J. Am. Chem. Soc.* 2022, 144, 7995–8001



Read Online

ACCESS |



Metrics & More



Article Recommendations



Supporting Information

ABSTRACT: Bastimolide B is a polyhydroxy macrolide isolated from marine cyanobacteria displaying antimalarial activity. It features a dense array of hydroxylated stereogenic centers with 1,5-relationships along a hydrocarbon chain. These 1,5-polyols represent a particularly challenging motif for synthesis, as the remote position of the stereocenters hampers stereocontrol. Herein, we present a strategy for 1,5-polyol stereocontrolled synthesis based on iterative boronic ester homologation with enantiopure magnesium carbenoids. By merging boronic ester homologation and transition-metal-catalyzed alkene hydroboration and diboration, the acyclic backbone of bastimolide B was rapidly assembled from readily available building blocks with full control over the remote stereocenters, enabling the total synthesis to be completed in 16 steps (LLS).

Polyketides are arguably the most important class of natural products, having been extensively mined, studied, and exploited as therapeutic agents for the promotion of human health.¹ Their complex structures coupled with their significant biological activity have fueled intense interest in their synthesis.² Indeed, the stereoselective synthesis of polypropionates/polyacetates represents one of the crowning achievements of synthesis in the 20th century.^{3–10} Despite the advances in polyketide synthesis, several challenges still remain, such as the stereoselective construction of 1,5-stereogenic centers.¹¹ Of particular interest is the construction of 1,5-polyols, as they occur in many polyketides.¹² The current state-of-the-art technology to access 1,5-diols is through a three-step sequence comprising stereoselective aldehyde allylation, cross-metathesis with acrolein, and alcohol protection (Figure 1A).¹³ This method, like numerous others,^{4,14–18} is attractive because it can be iterated to access 1,5-polyols.

Iterative methods are ideal in the synthesis of molecules bearing common repeat motifs as they simplify not only synthesis but also analysis (retrosynthesis) because they allow disconnections around the common repeating building blocks.¹⁹ Indeed, by use of a comprehensive knowledge base of individual reactions, iterative methods can also now be recognized by computer algorithms in the construction of complex molecules.¹⁸ We recently reported the iterative synthesis of 1,3-polyols through a sequence of asymmetric alkene diboration and selective homologation of the resulting primary boronic ester with a metalated butenyl TIB ester A (Figure 1B, M = Li, MgCl, TIB = 2,4,6-triisopropylbenzoyl).²⁰ We reasoned that performing anti-Markovnikov hydroboration, instead of diboration, followed by homologation with the same metalated butenyl TIB ester A could provide an iterative strategy for the construction of 1,5-polyols in just two steps per iteration rather than three (Figure 1C).

In this paper we describe the success of this approach and its application to the first total synthesis of bastimolide B (1,

Scheme 1), one of the most complex polyketides, featuring 10 hydroxylated stereocenters, six of which feature 1,5-relationships.

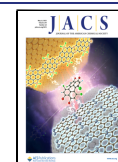
Bastimolide B (1) is a 24-membered macrolide whose structure and stereochemistry were assigned by analogy to its 40-membered ring analogue bastimolide A (C1–C39 lactone formation), which was characterized by X-ray analysis.^{21,22} The interest in bastimolides A and B stems from their potent antimalarial activity against multidrug-resistant strains of *P. falciparum*.²³ Although synthetic studies toward these natural products have been reported, there have been no total syntheses to date.²⁴ Interestingly, a recent report described the use of a computer algorithm to propose a plausible route to bastimolide A in 43 steps [longest linear sequence (LLS)] by using the most efficient iterative homologation reactions currently available.¹⁸ Herein, we describe a novel stereocontrolled approach to 1,5-polyols based on iterative boronic ester homologations and its application to the total synthesis of 1 in just 16 steps LLS.

In our retrosynthetic analysis of 1, we envisioned constructing the macrocycle from terminal alkene-containing polyol 2 using (*Z*)-iodocrotonic acid (3) as a synthetic linchpin, which could undergo esterification followed by a stereoretentive C(sp³)–C(sp²) Suzuki cross-coupling macrocyclization (Scheme 1).

Polyol 2 could be obtained in a convergent manner by a late-stage lithiation–borylation reaction between two equally complex fragments A (4, C24–C39) and B (5, C4–C23).

Received: March 27, 2022

Published: May 2, 2022



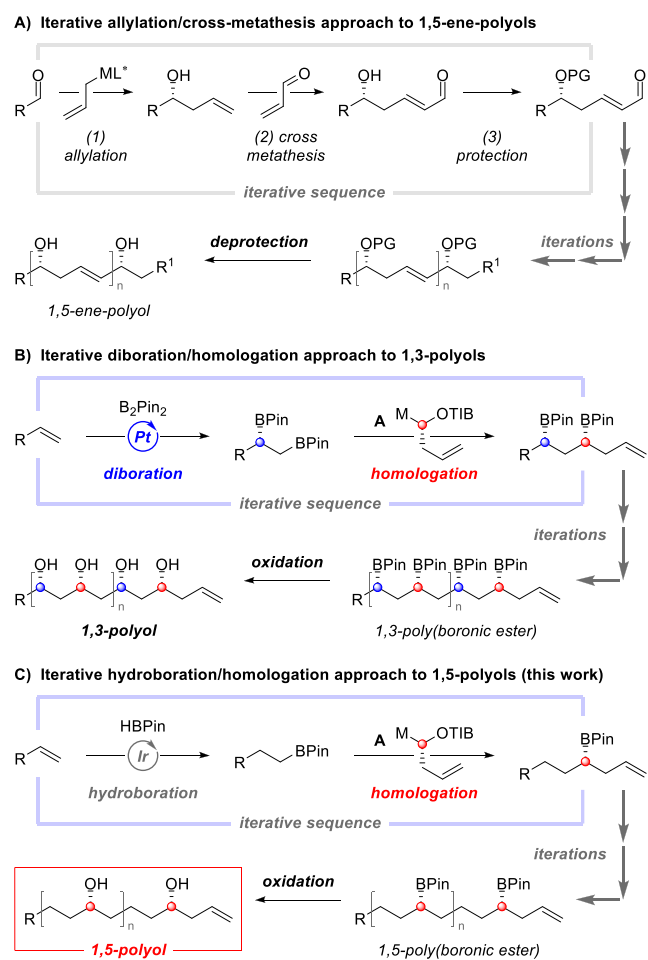
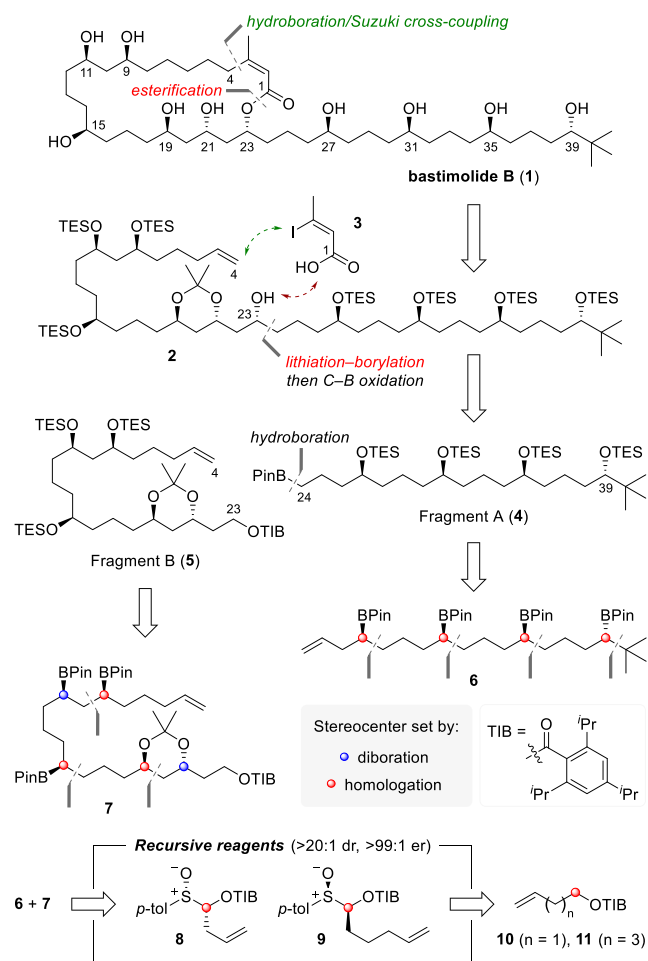


Figure 1. Iterative strategies toward the stereocontrolled synthesis of polyols.

These fragments would be derived from diastereo- and enantiopure poly(boronic esters) **6** and **7**, respectively. Crucially, **6** and **7** could be rapidly constructed by using the new hydroboration/homologation approach for the iterative assembly of 1,5-polyols with sulfoxide **8** as the precursor of metalated TIB ester **A** (Scheme 1).²⁵ In addition, we reasoned that simple modification of this iterative approach by employing elongated TIB ester **9** in the homologation followed by diboration would enable construction of the alternating 1,5- and 1,3-related stereogenic centers in **7**. Overall, our retrosynthetic approach combines efficient iterative reactions in the synthesis of key building blocks with late-stage fragment coupling, culminating in a convergent synthesis with low step count. One distinctive aspect of our synthesis is that both the iterative reactions and the key fragment coupling employ our boronic ester homologations, which occur with exquisite reagent control.

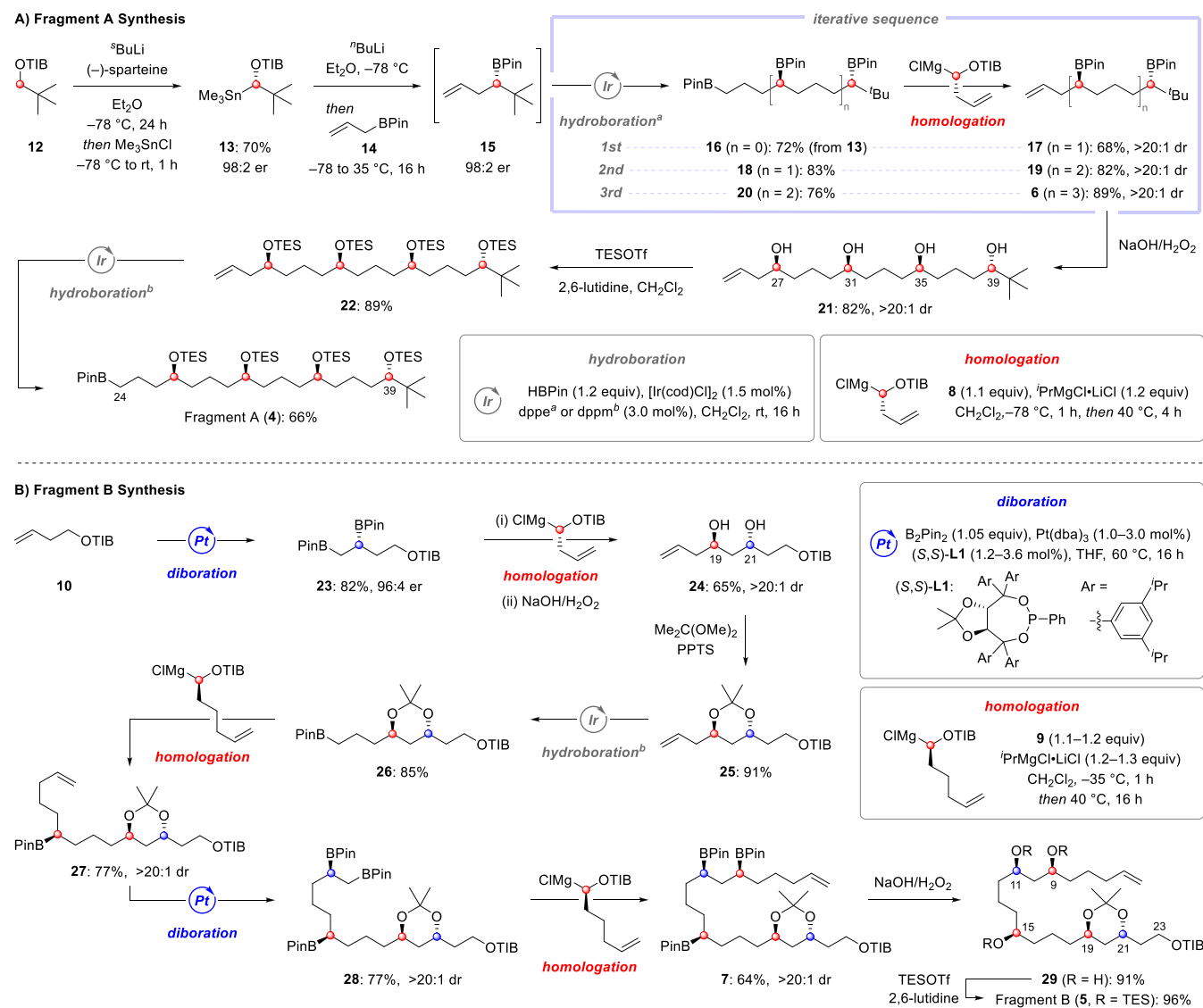
We began our synthesis by targeting fragment A, which required initial synthesis of the sterically hindered neopentyl boronic ester **15** (Scheme 2A). In principle, there are two possible homologation reactions to construct **15**: (1) reaction of metalated butenyl TIB ester **A** with ^tBuBPin or (2) reaction of a metalated neopentyl TIB ester with allylBPin. Unfortunately, the first was unsuccessful due to the failure of **A** (M = Li) to form a boronate complex with ^tBuBPin so we explored the second method.²⁶ Carbenoid formation by deprotonation of neopentyl TIB ester **12** with ^tBuLi in the presence of

Scheme 1. Retrosynthetic Approach to Bastimolide B



(-)-sparteine ($t_{1/2} = \sim 90$ min, -78 °C) followed by addition of allylBPin **14** gave **15** in only 17% ¹H NMR yield but 98:2 er. We reasoned that the high steric demand of the neopentyl carbenoid resulted in low nucleophilicity toward the boronic ester. To reduce steric hindrance, we elected to use diamine-free conditions in the homologation, which could be achieved by generating the carbenoid via tin–lithium exchange of stannane **13**.²⁷ Thus, treatment of **13** with ⁿBuLi followed by trapping with allylBPin **14** and heating delivered homoallylic boronic ester **15** in high yield (94% NMR yield) and enantioselectivity (98:2 er). With **15** in hand, we explored our proposed iterative hydroboration/boronic ester homologation sequence for the construction of 1,5-related stereogenic centers. Without purification, crude **15** was directly engaged in an iridium-catalyzed hydroboration with HBPin to give exclusively the anti-Markovnikov 1,4-bis(boronic ester) **16** in 72% yield over two steps on a multigram scale.²⁸ Homologation of **16** with the magnesiated carbenoid generated *in situ* from bench-stable sulfoxide **8** revealed 1,5-bis(boronic ester) **17** as a single diastereoisomer. The magnesium–sulfoxide exchange and subsequent borylation and 1,2-migration proceeded under mild reaction conditions by using ⁱPrMgCl·LiCl, and no competing addition to the secondary boronic ester was observed. Pleasingly, two further iterations of this hydroboration/homologation sequence provided 1,5-tetra(boronic ester) **6** in 46% yield over four steps on a gram scale. Notably, homologation of boronic ester

Scheme 2. Synthesis of Fragments A (4) and B (5)



20, bearing three secondary boronic esters and one primary boronic ester, resulted in exclusive chemoselective reaction of the primary boronic ester in 89% yield. Oxidation of the tetra(boronic ester) yielded stereochemically pure tetraol **21** with the desired stereochemistry at C27, C31, C35, and C39. Protection of **21** as triethylsilyl ether **22** followed by catalytic hydroboration of the terminal olefin provided primary boronic ester **4** (fragment A) in 11 steps from **12** (12 steps from commercially available neopentanol).

The synthesis of fragment B started from homoallylic TIB ester **10** (Scheme 2B), which is also the precursor of recursive reagent sulfoxide **8**; this maximized the convergency of our approach by reducing the number of distinct building blocks for the construction of bastimolide B. Enantioselective Pt-catalyzed diboration with B_2Pin_2 gave enantioenriched 1,2-bis(boronic ester) **23** with 96:4 er on a multigram scale.²⁹ Homologation of **23** with sulfoxide **8**, followed by oxidation of the 1,3-bis(boronic ester), yielded diol **24** as a single diastereoisomer after chromatographic purification (>20:1 dr). The *anti* configuration of the diol was confirmed by ^{13}C NMR analysis of acetonide **25**.³⁰ Oxidation and protection of the C19–C21 diol at this stage not only ensured

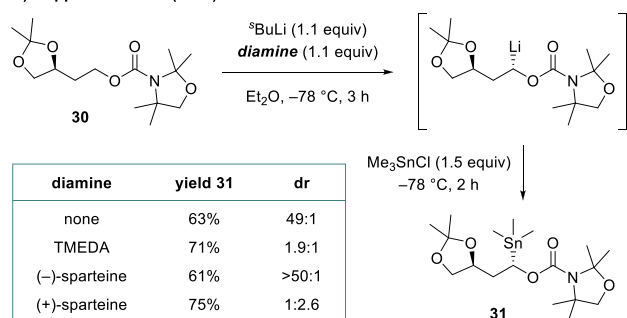
diastereopurity of this intermediate but also provided a suitable protecting group to aid in the late-stage lithiation–borylation at C23 for the coupling of fragments A and B (*vide infra*). Iridium-catalyzed hydroboration of the terminal olefin with pinacolborane gave primary boronic ester **26** in 85% yield. Homologation of **26** with sulfoxide **9** proceeded smoothly to afford secondary boronic ester **27** as a single diastereoisomer in 77% yield. Once the remote stereocenter at C15 was set via reagent-controlled homologation, catalyst-controlled diastereoselective diboration of the terminal olefin was conducted with (*S,S*)-**L1** to afford the 1,2-bis(boronic ester) **28**. One further homologation with the recursive reagent **9** allowed the installation of the desired 1,5,7-tris(boronic ester) with the correct stereochemistry at C9, C11, and C15. Simultaneous oxidation of the three boronic esters, followed by *O*-TES protection, led to fragment B (**5**). Overall, our iterative approach utilizing a combination of diboration and hydroboration coupled with boron homologations with recursive reagents enabled fragment B to be constructed in 10 steps from **10** with excellent stereocontrol.

With fragments **4** and **5** in hand, we turned our attention to their union through a stereocontrolled lithiation–borylation

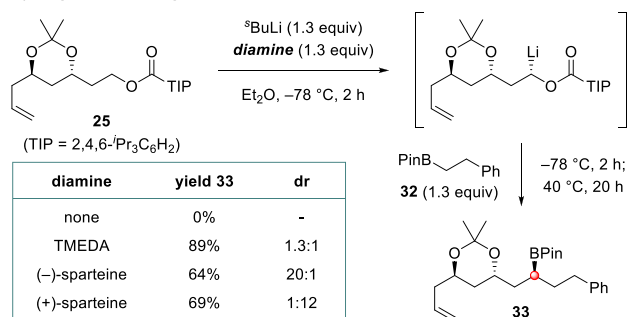
reaction.^{20,31} Before embarking on this key C–C bond forming reaction, we wanted to explore what level of substrate control might be imparted by the neighboring six-ring acetonide moiety in TIB ester **5**. Previously, Hoppe reported that the five-ring acetonide in carbamate **30** exerted strong control over stereoselectivity in the deprotonation with ^sBuLi in the absence of diamine ligands (Scheme 3A).³² However, our attempts at a

Scheme 3. Study of Effects of Substrate Control on Asymmetric Lithiation

A) Hoppe's lithiation (1995)

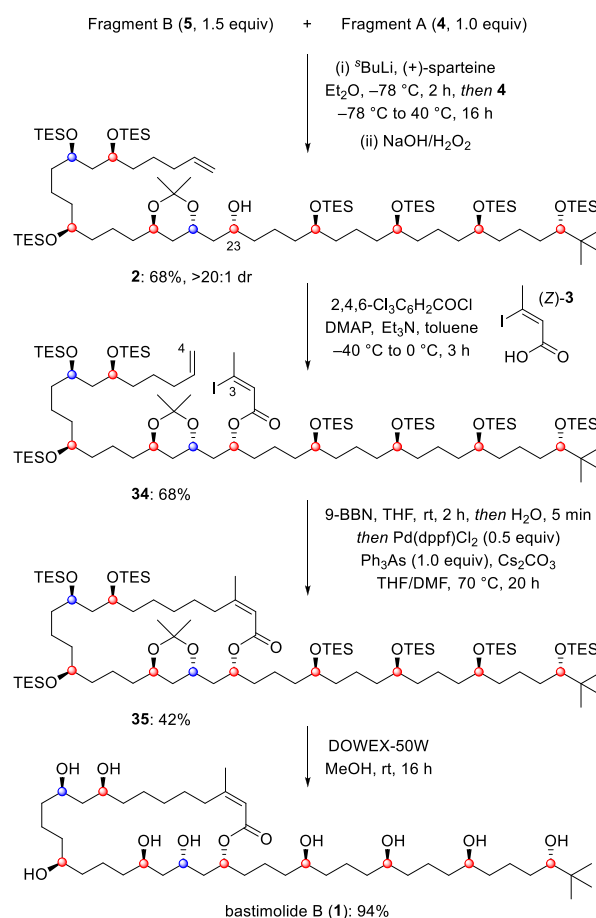


B) Fragment Coupling Model Reaction



diamine-free lithiation–borylation using model acetonide-containing TIB ester **25** and boronic ester **32** were unsuccessful due to the failure of **25** to be deprotonated under these conditions (Scheme 3B). We attribute this contrasting reactivity to the weaker complexation of ^sBuLi to the six-membered acetonide in **25** compared to the five-membered acetonide in **30**. Hoppe found that substrate control in the deprotonation of **30** could be largely overridden with diamine ligands, including TMEDA and sparteine. Fortunately, we found that addition of TMEDA enabled the coupling of **25** and **32** to proceed in excellent yield. Using TMEDA the diastereoselectivity was low, indicating no substrate control, but using (+)- or (-)-sparteine enabled either diastereoisomer of **33** to be obtained with high selectivity. Further studies by ReactIR revealed that deprotonation of **25** was exceptionally fast ($t_{1/2}$ deprotonation \sim 2 min at -78 °C) and that borylation was essentially instantaneous with primary boronic ester **32**.³³ These conditions for the lithiation–borylation of model TIB ester **25** were successfully implemented in the coupling of the advanced fragments A and B (Scheme 4), and subsequent oxidation gave alcohol **2** in 68% yield with excellent stereocontrol at C23 (>20:1 dr). Although a significant excess of TIB ester **5** was required for optimum yield, unreacted **5** could easily be recovered by chromatographic purification. The lithiation–borylation between **5** and **4** not only provided the open-chain backbone of bastimolide B with all the correct functionality and stereochemistry in place,

Scheme 4. Fragment Coupling and Completion of the Synthesis of Bastimolide B



but boronic ester oxidation also revealed the alcohol required for closure of the 24-membered macrolactone without having to manipulate protecting groups. The final stages of the synthesis involved esterification of the alcohol at C23 under modified Yamaguchi conditions with acid (Z)-3.³⁴ In the following one-pot protocol, the terminal olefin underwent hydroboration with 9-BBN followed by stereoretentive Suzuki cross-coupling with the (Z)-iodoalkene, giving the 24-membered macrolactone **35** in 42% yield.^{35,36} This macrocyclization approach demonstrated the power of intramolecular Suzuki cross-coupling both for macrolactone formation and for the installation of a Z-configured alkene in a particularly challenging setting.³⁷ Finally, deprotection of the O-TES and acetonide groups in macrolide **35** occurred smoothly in methanol with DOWEX acidic resin, affording a pure sample of bastimolide B (**1**, 94% yield). The synthetic material matched the natural sample in all aspects (¹H NMR, ¹³C NMR, HRMS, IR, optical rotation, and ECD), confirming the proposed structure, and its absolute stereochemistry. Using very high ¹³C resolution (<0.01 ppm) data from pure-shift HSQC and HSQC-TOCSY NMR methods, we were also able to establish the two- and three-bond connectivity of the molecule and fully assign every ¹H and ¹³C NMR signal. It is worth noting that although the ¹H and ¹³C NMR of our synthetic sample matched the data for the natural product, many of the assignments of the NMR signals did not (see the Supporting Information for details). Fortunately, these errors in the ¹H/¹³C assignments did not detract from the 2D and 3D

structure determination in the original report because their structure proposal was informed by comparison to X-ray analysis of the related natural product bastimolide A rather than relying exclusively on NMR.^{21,22}

In conclusion, we have shown that homologation of boronic esters using a magnesiated butenyl TIB ester followed by hydroboration of the terminal alkene provides an iterative method for the generation of 1,5-polyols with full stereocontrol. This method has been applied to a 16-step (LLS) synthesis of bastimolide B (26 steps in total) with full stereocontrol. Reagent-controlled boronic ester homologations were used to create all the key C–C bonds, including a late-stage fragment coupling, as well as installing eight of the ten stereogenic centers, with the remaining two installed by asymmetric diboration. Four of the six 1,5-related stereocenters were generated by using the magnesiated-butenyl building block in homologations of poly(boronic esters) which showed essentially complete selectivity in favor of reaction at the primary boronic ester, even in the presence of multiple secondary boronic esters. This versatile methodology will undoubtedly find further applications in synthesis.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c03192>.

Experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Varinder K. Aggarwal – School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.; orcid.org/0000-0003-0344-6430; Email: v.aggarwal@bristol.ac.uk

Authors

Daniele Fiorito – School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.

Selbi Keskin – School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.; Present Address: Department of Chemistry, Faculty of Arts and Sciences, Giresun University, 28200 Giresun, Turkey; orcid.org/0000-0003-0664-9903

Joseph M. Bateman – School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.

Malcolm George – School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.

Adam Noble – School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.; orcid.org/0000-0001-9203-7828

Complete contact information is available at: <https://pubs.acs.org/10.1021/jacs.2c03192>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.F. thanks the Swiss National Science Foundation for an Early Postdoc Mobility Fellowship (P2GEP2_194799). S.K. thanks TUBITAK (The Scientific and Technological Research Council of Turkey) BIDEB-2219 international postdoctoral research fellowship programme for financial support. M.G. thanks the Bristol Chemical Synthesis Centre for Doctoral

Training, funded by EPSRC (EP/S024107/1) and the University of Bristol for a PhD studentship. We thank Prof W. Gerwick (UC San Diego, Scripps institute of Oceanography) for providing the original NMR data of bastimolide B. We thank Prof. C. P. Butts and S. G. Aiken (University of Bristol) for fruitful scientific discussion and Siying Zhong for preliminary investigations into homologation with stannane 13.

■ REFERENCES

- (1) (a) Staunton, J.; Weissman, K. J. Polyketide Biosynthesis: A Millennium Review. *Nat. Prod. Rep.* **2001**, *18*, 380. (b) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J. Nat. Prod.* **2020**, *83*, 770.
- (2) (a) Yeung, K.-S.; Paterson, I. Advances in the Total Synthesis of Biologically Important Marine Macrolides. *Chem. Rev.* **2005**, *105*, 4237. (b) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. Tetrahydrofuran-Containing Macrolides: a Fascinating Gift from the Deep Sea. *Chem. Rev.* **2013**, *113*, 4567. (c) Liu, H.; Lin, S.; Jacobsen, K. M.; Poulsen, T. B. Chemical Syntheses and Chemical Biology of Carboxyl Polyether Ionophores: Recent Highlights. *Angew. Chem., Int. Ed.* **2019**, *58*, 13630.
- (3) (a) Schetter, B.; Mahrwald, R. Modern Aldol Methods for the Total Synthesis of Polyketides. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506. (b) Kan, S. B. J.; Ng, K. K.-H.; Paterson, I. The Impact of the Mukaiyama Aldol Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 9097. (c) Gati, W.; Yamamoto, H. Second Generation of Aldol Reaction. *Acc. Chem. Res.* **2016**, *49*, 1757.
- (4) (a) Smith, A. B., III; Wuest, W. M. Evolution of Multi-Component Anion Relay Chemistry (ARC): Construction of Architecturally Complex Natural and Unnatural Products. *Chem. Commun.* **2008**, 5883. (b) Deng, Y.; Smith, A. B., III Evolution of Anion Relay Chemistry: Construction of Architecturally Complex Natural Products. *Acc. Chem. Res.* **2020**, *53*, 988.
- (5) (a) Yus, M.; González-Gómez, J. C.; Foubelo, F. Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, 5595. (b) Boiarska, Z.; Braga, T.; Silvani, A.; Passarella, D. Brown Allylation: Application to the Synthesis of Natural Products. *Eur. J. Org. Chem.* **2021**, 2021, 3214.
- (6) (a) Feng, J.; Kasun, Z. A.; Krische, M. J. Enantioselective Alcohol C–H Functionalization for Polyketide Construction: Unlocking Redox-Economy and Site-Selectivity for Ideal Chemical Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 5467. (b) Doerksen, R. S.; Meyer, C. C.; Krische, M. J. Feedstock Reagents in Metal-Catalyzed Carbonyl Reductive Coupling: Minimizing Preactivation for Efficiency in Target-Oriented Synthesis. *Angew. Chem., Int. Ed.* **2019**, *58*, 14055.
- (7) Xu, S.; Negishi, E. Zirconium-Catalyzed Asymmetric Carboalumination of Unactivated Terminal Alkenes. *Acc. Chem. Res.* **2016**, *49*, 2158.
- (8) Roseblade, S. J.; Pfaltz, A. Iridium-Catalyzed Asymmetric Hydrogenation of Olefins. *Acc. Chem. Res.* **2007**, *40*, 1402.
- (9) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. Iterative Strategies for the Synthesis of Deoxypropionates. *Chem. Commun.* **2010**, 46, 2535.
- (10) (a) Leonori, D.; Aggarwal, V. K. Lithiation-Borylation Methodology and Its Application in Synthesis. *Acc. Chem. Res.* **2014**, *47*, 3174. (b) Yeung, K.; Mykura, R. C.; Aggarwal, V. K. Lithiation–Borylation Methodology in the Total Synthesis of Natural Products. *Nat. Synth.* **2022**, *1*, 117.
- (11) (a) Sailes, H.; Whiting, A. The Control of Remote Asymmetric Centers via Reduction of Acyclic Carbonyl Functions. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1785. (b) Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. Acyclic Stereocontrol Between Remote Atom Centers via Intramolecular and Intermolecular Stereo-Communication. *Tetrahedron* **2001**, *57*, 2917. (c) Clayden, J. Transmission of

Stereochemical Information over Nanometre Distances in Chemical Reactions. *Chem. Soc. Rev.* **2009**, *38*, 817.

(12) (a) Friestad, G. K.; Sreenilayam, G. 1,5-Polyols: Challenging Motifs for Configurational Assignment and Synthesis. *Pure Appl. Chem.* **2011**, *83*, 461. (b) Friedrich, R. M.; Friestad, G. K. Inspirations from Tetrafibricin and Related Polyketides: New Methods and Strategies for 1,5-Polyol Synthesis. *Nat. Prod. Rep.* **2020**, *37*, 1229.

(13) (a) BouzBouz, S.; Cossy, J. Tetrafibricin: Synthesis of the C1–C13, C15–C25, and C27–C40 Fragments. *Org. Lett.* **2004**, *6*, 3469. (b) Kumpulainen, E. T. T.; Kang, B.; Krische, M. J. C(21)–C(40) of Tetrafibricin via Metal Catalysis: Beyond Stoichiometric Chiral Reagents, Auxiliaries, and Premetalated Nucleophiles. *Org. Lett.* **2011**, *13*, 2484.

(14) (a) Flamme, E. M.; Roush, W. R. Enantioselective Synthesis of 1,5-anti- and 1,5-syn-Diols Using a Highly Diastereoselective One-Pot Double Allylboration Reaction Sequence. *J. Am. Chem. Soc.* **2002**, *124*, 13644. (b) Chen, M.; Roush, W. R. Enantioselective Synthesis of (*Z*)- and (*E*)-2-Methyl-1,5-anti-Pentenediols via an Allene Hydroboration-Double-Allylboration Reaction Sequence. *J. Am. Chem. Soc.* **2013**, *135*, 9512.

(15) (a) Paquette, L. A.; Chang, S.-K. The Polyol Domain of Amphidinol 3. A Stereoselective Synthesis of the Entire C(1)–C(30) Sector. *Org. Lett.* **2005**, *7*, 3111. (b) Gudipati, V.; Curran, D. P. Synthesis of C1–C20 and C21–C40 Fragments of Tetrafibricin. *Tetrahedron Lett.* **2011**, *52*, 2254.

(16) (a) Friestad, G. K.; Sreenilayam, G. Versatile Configuration-Encoded Strategy for Rapid Synthesis of 1,5-Polyol Stereoisomers. *Org. Lett.* **2010**, *12*, 5016. (b) Friedrich, R. M.; Sreenilayam, G.; Hackbarth, J.; Friestad, G. K. Unified Strategy for 1,5,9- and 1,5,7-Triols via Configuration-Encoded 1,5-Polyol Synthesis: Enantioselective Preparation of γ -Sulfonyl- α -Silyloxyaldehydes and Iterative Julia–Kocienski Coupling. *J. Org. Chem.* **2018**, *83*, 13636.

(17) (a) Oishi, T.; Kanemoto, M.; Swasono, R.; Matsumori, N.; Murata, M. Combinatorial Synthesis of the 1,5-Polyol System Based on Cross Metathesis: Structure Revision of Amphidinol 3. *Org. Lett.* **2008**, *10*, 5203.

(18) Molga, K.; Szymkuć, S.; Gołębiowska, P.; Popik, O.; Dittwald, D.; Moskal, M.; Roszak, R.; Mlynarski, J.; Grzybowski, B. A. A Computer Algorithm to Discover Iterative Sequences of Organic Reactions. *Nat. Synth.* **2022**, *1*, 49.

(19) (a) Zheng, K.; Xie, C.; Hong, R. Bioinspired Iterative Synthesis of Polyketides. *Front. Chem.* **2015**, *3*, 32. (b) Lehmann, J. W.; Blair, D. J.; Burke, M. D. Towards the Generalized Iterative Synthesis of Small Molecules. *Nat. Rev. Chem.* **2018**, *2*, 1.

(20) Aiken, S.; Bateman, J.; Liao, H.-H.; Fawcett, A.; Bootwicha, T.; Vincetti, P.; Myers, E.; Noble, A.; Aggarwal, V. Iterative Synthesis of 1,3-Polyboronic Esters with High Stereocontrol: Applications to Bahamaolide A and Polyfunctionalised Hydrocarbons. *ChemRxiv* **2022**, DOI: 10.26434/chemrxiv-2022-g2h9s.

(21) Shao, C.-L.; Mou, X.-F.; Cao, F.; Spadafora, C.; Glukhov, E.; Gerwick, L.; Wang, C.-Y.; Gerwick, W. H. Bastimolide B, an Antimalarial 24-Membered Marine Macrolide Possessing a *tert*-Butyl Group. *J. Nat. Prod.* **2018**, *81*, 211.

(22) Shao, C.-L.; Linington, R. G.; Balunas, M. J.; Centeno, A.; Boudreau, P.; Zhang, C.; Engene, N.; Spadafora, C.; Mutka, T. S.; Kyle, D. E.; Gerwick, L.; Wang, C.-Y.; Gerwick, W. H. Bastimolide A, a Potent Antimalarial Polyhydroxy Macrolide from the Marine Cyanobacterium *Okeania hirsute*. *J. Org. Chem.* **2015**, *80*, 7849.

(23) (a) Cockram, P. E.; Smith, T. K. Active Natural Product Scaffolds against Trypanosomatid Parasites: A Review. *J. Nat. Prod.* **2018**, *81*, 2138. (b) Fotie, J. Marine Natural Products as Strategic Prototypes in the Development of a New Generation of Antimalarial Agents. In *Discovery and Development of Therapeutics from Natural Products Against Neglected Tropical Diseases*; Brahmachari, G., Ed.; Elsevier: 2019; Chapter 2.

(24) (a) Quintard, A.; Sperandio, C.; Rodriguez, J. Modular Enantioselective Synthesis of an Advanced Pentahydroxy Intermediate of Antimalarial Bastimolide A and of Fluorinated and Chlorinated Analogues. *Org. Lett.* **2018**, *20*, 5274. (b) Kumar, N. S.; Ramulu, B. J.;

Ghosh, S. Stereoselective Synthesis of the C19–C39 Fragment of Bastimolide A. *SynOpen* **2021**, *5*, 285.

(25) (a) Casoni, G.; Kucukdisli, M.; Fordham, J. M.; Burns, M.; Myers, E. L.; Aggarwal, V. K. α -Sulfinyl Benzoates as Precursors to Li and Mg Carbenoids for the Stereoselective Iterative Homologation of Boronic Esters. *J. Am. Chem. Soc.* **2017**, *139*, 11877. (b) Blair, D. J.; Chitti, S.; Trobe, M.; Kostyra, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. Automated Iterative Csp^3 –C Bond Formation. *Nature* **2022**, *604*, 92.

(26) Watson, C. G.; Balanta, A.; Elford, T. G.; Essafi, S.; Harvey, J. N.; Aggarwal, V. K. Construction of Multiple, Contiguous Quaternary Stereocenters in Acyclic Molecules by Lithiation-Borylation. *J. Am. Chem. Soc.* **2014**, *136*, 17370.

(27) (a) Binanzer, K.; Fang, G. Y.; Aggarwal, V. K. Asymmetric Synthesis of Allylsilanes by the Borylation of Lithiated Carbamates: Formal Total Synthesis of (–)-Decarestrictine D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4264. (b) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. Use of Alkyl 2,4,6-Triisopropylbenzoates in the Asymmetric Homologation of Challenging Boronic Esters. *Chem. Commun.* **2011**, *47*, 12592.

(28) (a) Crudden, M. C.; Hleba, Y. B.; Chen, A. C. Regio- and Enantiocontrol in the Room-Temperature Hydroboration of Vinyl Arenes with Pinacol Borane. *J. Am. Chem. Soc.* **2004**, *126*, 9200. (b) Yamamoto, Y.; Fujikawa, R.; Umamoto, T.; Miyaura, N. Iridium-Catalyzed Hydroboration of Alkenes with Pinacolborane. *Tetrahedron* **2004**, *60*, 10695. (c) Fiorito, D.; Mazet, C. Ir-Catalyzed Selective Hydroboration of 2-Substituted 1,3-Dienes: A General Method to Access Homoallylic Boronates. *ACS Catal.* **2018**, *8*, 9382.

(29) (a) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. Catalytic Enantioselective 1,2-Diboration of 1,3-Dienes: Versatile Reagents for Stereoselective Allylation. *Angew. Chem., Int. Ed.* **2012**, *51*, 521. (b) Coombs, J. R.; Haeflner, F.; Kliman, L. T.; Morken, J. P. Scope and Mechanism of the Pt-Catalyzed Enantioselective Diboration of Monosubstituted Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 11222.

(30) Rychnovsky, S. D.; Rogers, B.; Yang, G. Analysis of Two Carbon-13 NMR Correlations for Determining the Stereochemistry of 1,3-Diol Acetonides. *J. Org. Chem.* **1993**, *58*, 3511.

(31) For examples of lithiation–borylation reactions in polyhydroxy natural product synthesis, see: (a) Fawcett, A.; Nitsch, D.; Ali, M.; Bateman, J. M.; Myers, E. L.; Aggarwal, V. K. Regio- and Stereoselective Homologation of 1,2-Bis(Boronic Esters): Sterecontrolled Synthesis of 1,3-Diols and Sch 725674. *Angew. Chem., Int. Ed.* **2016**, *55*, 14663. (b) Wu, J.; Lorenzo, P.; Zhong, S.; Ali, M.; Butts, C. P.; Myers, E. L.; Aggarwal, V. K. Synergy of Synthesis, Computation and NMR Reveals Correct Baulamycin Structures. *Nature* **2017**, *547*, 436. (c) Bootwicha, T.; Feilner, J. M.; Myers, E. L.; Aggarwal, V. K. Iterative Assembly Line Synthesis of Polypropionates with Full Stereocontrol. *Nat. Chem.* **2017**, *9*, 896. (d) Millan, A.; Grigol Martinez, P. D.; Aggarwal, V. K. Stereocontrolled Synthesis of Polypropionate Fragments based on a Building Block Assembly Strategy using Lithiation-Borylation Methodologies. *Chem.—Eur. J.* **2018**, *24*, 730. (e) Linne, Y.; Bonandi, E.; Tabet, C.; Geldsetzer, J.; Kalesse, M. The Total Synthesis of Chondrochloren A. *Angew. Chem., Int. Ed.* **2021**, *60*, 6938.

(32) Helmke, H.; Hoppe, D. Chelation-Directed Asymmetric Lithiation and C-Substitution of 1,2,4-Butanetriol Acetonide. *Synlett* **1995**, *9*, 978.

(33) Mykura, R. C.; Veth, S.; Varela, A.; Dewis, L.; Farndon, J. J.; Myers, E. L.; Aggarwal, V. K. Investigation of the Deprotonative Generation and Borylation of Diamine-Ligated α -Lithiated Carbamates and Benzoates by in Situ IR spectroscopy. *J. Am. Chem. Soc.* **2018**, *140*, 14677.

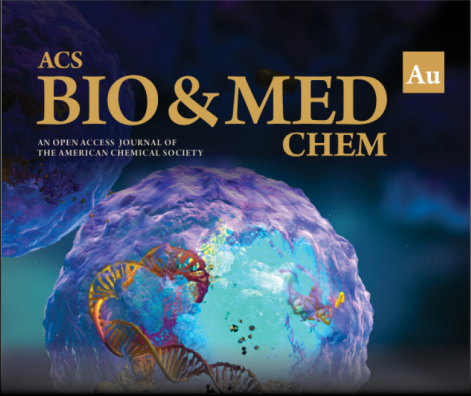
(34) (a) Glaus, F.; Dedic, D.; Tare, P.; Nagaraja, V.; Rodrigues, L.; Ainsa, J. A.; Kunze, J.; Schneider, G.; Hartkoorn, R. C.; Cole, S. T.; Altmann, K.-H. Total Synthesis of Ripostatin B and Structure-Activity Relationship Studies on Ripostatin Analogs. *J. Org. Chem.* **2018**, *83*,

7150. (b) Schrof, R.; Altmann, K.-H. Studies Toward the Total Synthesis of the Marine Macrolide Salarin C. *Org. Lett.* **2018**, *20*, 7679.

(35) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. The B-Alkyl Suzuki-Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(36) (a) Johnson, C. R.; Braun, M. P. A Two-Step, Three-Component Synthesis of PGE1: Utilization of α -Iodoenones in Pd(0)-Catalyzed Cross-Couplings of Organoboranes. *J. Am. Chem. Soc.* **1993**, *115*, 11014. (b) Ohba, M.; Kawase, N.; Fujii, T. Total Syntheses of (\pm)-Agelasimine-A, (\pm)-Agelasimine-B, and (\pm)-Purino-Diterpene and the Structure of Diacetyl agelasimine-A. *J. Am. Chem. Soc.* **1996**, *118*, 8250. (c) Kallan, N. C.; Halcomb, R. L. Synthesis of the Ring System of Phomactin D Using a Suzuki Macrocyclization. *Org. Lett.* **2000**, *2*, 2687. (d) Chemler, S. R.; Danishefsky, S. J. Transannular Macrocyclization via Intramolecular B-Alkyl Suzuki Reaction. *Org. Lett.* **2000**, *2*, 2695. (e) Bauer, M.; Maier, M. E. Synthesis of the Core Structure of Salicylilalamide A by Intramolecular Suzuki Reaction. *Org. Lett.* **2002**, *4*, 2205. (f) Gagnon, A.; Danishefsky, S. J. Evaluation of Diene Hierarchies for Diels-Alder Reactions en route to Xestocyclamine A: Elaboration of an Ansa Bridge by B-Alkyl Suzuki Macrocyclization. *Angew. Chem., Int. Ed.* **2002**, *41*, 1581. (g) Mohr, P. J.; Halcomb, R. L. Total Synthesis of (+)-Phomactin A Using a B-Alkyl Suzuki Macrocyclization. *J. Am. Chem. Soc.* **2003**, *125*, 1712.


(37) Saridakis, I.; Kaiser, D.; Maulide, N. Unconventional Macrocyclizations in Natural Product Synthesis. *ACS Cent. Sci.* **2020**, *6*, 1869.




ACS
BIO & MED
AN OPEN ACCESS JOURNAL OF
THE AMERICAN CHEMICAL SOCIETY
CHEM Au

Editor-in-Chief: **Prof. Shelley D. Minteer**, University of Utah, USA

Deputy Editor
Prof. Squire J. Booker
Pennsylvania State University, USA

Open for Submissions 

pubs.acs.org/biomedchemau  ACS Publications
Most Trusted. Most Cited. Most Read.