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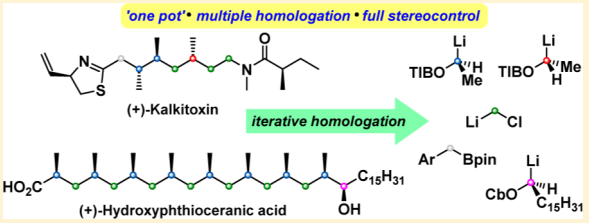
Toward Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis

Sebastien Balieu,[†] Gayle E. Hallett,[†,§] Matthew Burns,[†,§] Teerawut Bootwicha,[†,§] John Studley,[‡] and Varinder K. Aggarwal*[,†]

[†]School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom
[‡]Vertex Pharmaceuticals Limited, Milton Park, Abingdon OX14 4RW, United Kingdom

Supporting Information

ABSTRACT: The iterative homologation of boronic esters using chiral lithiated benzoate esters and chloromethyllithium has been applied to the highly efficient syntheses of two natural products, (+)-kalkitoxin and (+)-hydroxyphthioceranic acid. The chiral lithiated benzoate esters (>99% ee) were generated from the corresponding stannanes, which themselves were prepared by Hoppe–Beak deprotonation of ethyl 2,4,6-triisopropyl-benzoate with *s*-BuLi in the presence of (+)- or (−)-sparteine and trapping with Me_3SnCl followed by recrystallization. In addition, it was found that purification between several homologations could be avoided, substantially increasing both chemical and manpower efficiency. In the case of (+)-kalkitoxin, six iterative homologations were conducted on commercially available *p*-$MeOC_6H_4CH_2Bpin$ to build up the core of the molecule before the C–B bond was converted into the desired C–N bond, without purification of intermediates. In the case of (+)-hydroxyphthioceranic acid, 16 iterative homologations were conducted on *p*-$MeOC_6H_4Bpin$ with only four intermediate purifications before oxidation of the C–B bond to the desired alcohol. The stereocontrolled and efficient syntheses of these complex molecules highlight the power of iterative chemical synthesis using boronic esters.



INTRODUCTION

Methods and strategies for natural product synthesis continue to evolve. An attractive approach, particularly for molecules with common repeat units, is iterative synthesis. Such an approach is extensively used by nature in the synthesis of nucleic acids, proteins, and polysaccharides.[1] Nature also uses this tactic for small-molecule synthesis even though common repeat units are not always immediately apparent. The archetypical example is polyketide synthesis where a simple thioester is passed from one enzyme domain to another, undergoing chain extension, dehydration, or reduction multiple times (growth phase) until the target molecule is formed (Scheme 1a).[2]

In contrast to biological processes, iterative strategies in chemical synthesis are often much less efficient requiring several functional-group interconversions between chain-extension steps.[3] Furthermore, they are usually carried out stepwise with purifications at each stage, which is invariably time-consuming. While nevertheless attractive, such processes fall short of Hendrickson's 1975 original definition of "the ideal synthesis"[4] (a debate to which others have also contributed[5−7]), which he stated should "create a complex skeleton... in a sequence only of successive construction reactions involving no intermediary refunctionalizations and leading directly to the target, not only its skeleton but also its correctly placed functionality." Iterative strategies that do not require functional-group interconversions between chain-extension steps are rare; Yamamoto's aldol reaction[8] is particularly notable and, being the same class of bond construction, it also resembles nature's polyketide synthesis. Homologation of boronic esters[9] provides another exceptional example where "intermediary refunctionalization" is not required because the product of homologation is a new boronic ester.

We recently reported a method for the iterative, reagent-controlled homologation (chain extension) of a boronic ester.[10] This process enabled the conversion of a simple boronic ester into a molecule bearing 10 contiguous methyl substituents with full stereocontrol in an effectively "one-pot" process (Scheme 1b). Each homologation generated a new C–C bond, and did not require functional-group interconversions or purification of intermediates, providing a synthesis that resonated with Hendrickson's ideal synthesis. Of course, the use of stannanes and high molecular weight leaving groups makes it less ideal when benchmarked against other criteria related to green chemistry and atom economy.

The building blocks used as the key repeating unit were chiral lithiated benzoate esters (*S*)-**1** and (*R*)-**1**, which were readily available in high er (Scheme 1c)[10] from the corresponding stannanes which were synthesized using Hoppe–Beak's sparteine-mediated lithiation.[11,12] In the growth phase, this reagent added to the boronic ester to give an

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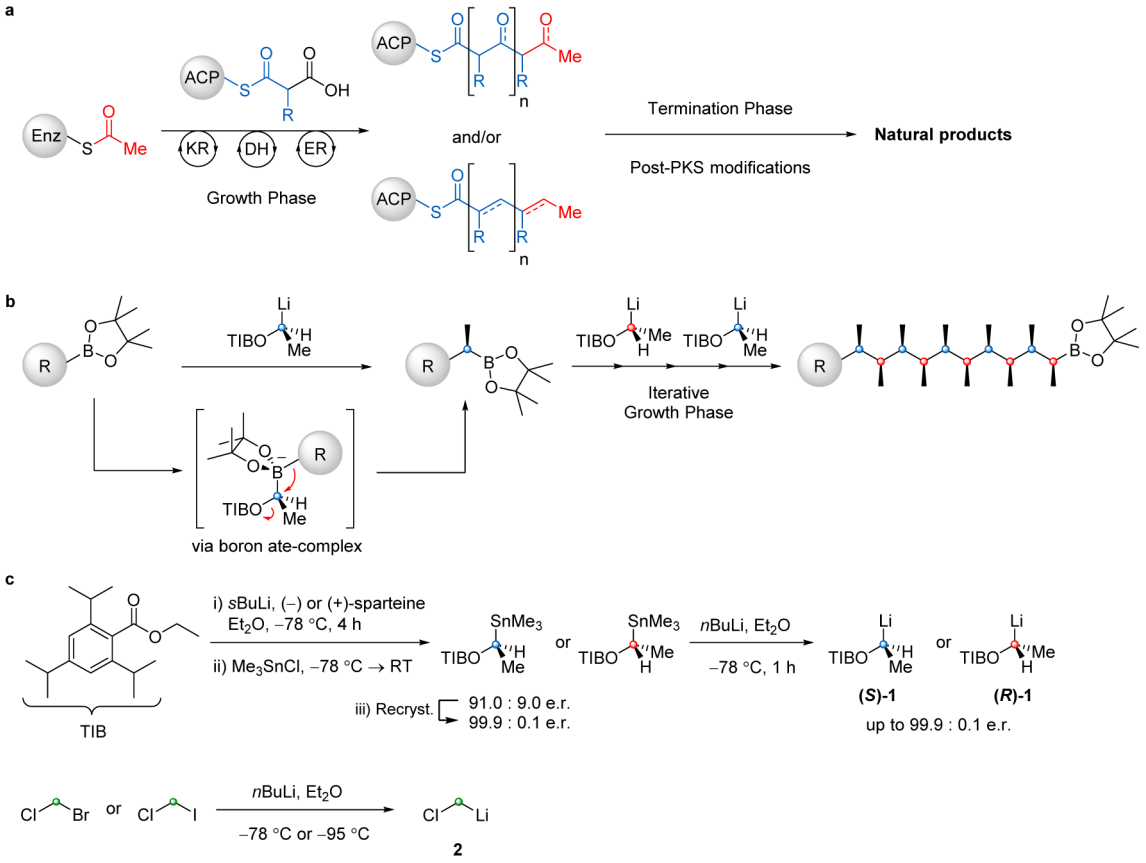
Scheme 1. Iterative Strategies in Synthesis: (a) Nature's Synthesis of Polyketides, (b) Iterative Homologation with Boronic Esters and Its Application in the Stereocontrolled Synthesis of Permethylated Carbon Chains, and (c) Synthesis of the Building Blocks Employed in Homologation of Boronic Esters[a]



[a]ACP, acyl carrier protein; DH, dehydratase; ER, enoyl reductase; Enz, enzyme; KS, ketosynthase; KR, ketoreductase. TIB, 2,4,6-triisopropylbenzoyl.

intermediate boronate complex, which, after 1,2-migration, gave the homologated boronic ester with >99:1 efficiency and >99:1 stereocontrol. Indeed, boron is a perfect and unique element for iterative homologation[9,10,13,14] as not only does it orchestrate these homologations stereospecifically, but also because a new boronic ester is created after each homologation, ready and primed for the next homologation. The process we created can be likened to a molecular assembly line. Furthermore, by controlling the stereochemistry of the substituents on the carbon chain (using (*S*/*R*)-**1**), we were able to control the shape of the molecule so that it adopted a linear or helical conformation.[10]

Having established the methodology, we wished to demonstrate its potential and versatility for natural product synthesis (the ultimate testing ground) and selected targets that would require different chain-extension steps (growth phase) and different postgrowth modification steps. The syntheses would also enable us to benchmark this strategy against Hendrickson's ideal synthesis. In this paper we show that the core of (+)-kalkitoxin and (+)-hydroxyphthioceranic acid (the side arm of sulfolipid-1) can be made with full stereocontrol and high manpower and high chemical efficiency by using our assembly line synthesis methodology.

RESULTS AND DISCUSSION

Our first target was (+)-kalkitoxin, a neurotoxic lipopeptide isolated from the marine cyanobacterium, *Lyngbya majuscula*.[15] Kalkitoxin demonstrated potent neurotoxicity (LC_{50} 3.86 nM)[16] and blocked the voltage-sensitive Na^+ channel in both mouse neuro-2a cells (EC_{50} 1 nM)[17] and cerebellar granule neuron cultures (EC_{50} 22.7 nM).[18,19] Studies of kalkitoxin's neurotoxicity should provide insight into nerve function, which could lead to new treatments for pain, and certain brain disorders.

(+)-Kalkitoxin has been previously prepared in 16−21 steps with moderate stereocontrol.[20] It bears both 1,2-adjacent methyl groups, which are relatively rare, and 1,3-related methyl groups (1,3-polydeoxypropionate), which are much more common in nature.[3b,d] To access the latter motif, we considered using our methodology in combination with Matteson's homologation of boronic esters with α-chloromethyllithium **2** to insert the required methylene units.[21,22] Our retrosynthetic analysis of (+)-kalkitoxin shows that it could be assembled from fragments **4**, **5**, and **6** (Scheme 2). In order to construct the core fragment **5**, we planned to mask the carboxylic acid as an aromatic ring and use the assembly line synthesis starting from the commercially available boronic ester **8** with building blocks (*S*)-**1**, (*R*)-**1**, and **2** in the appropriate order.

The synthesis of the core **7** involved subjecting the boronic ester **8** to two consecutive homologation reactions with (*S*)-**1**, a

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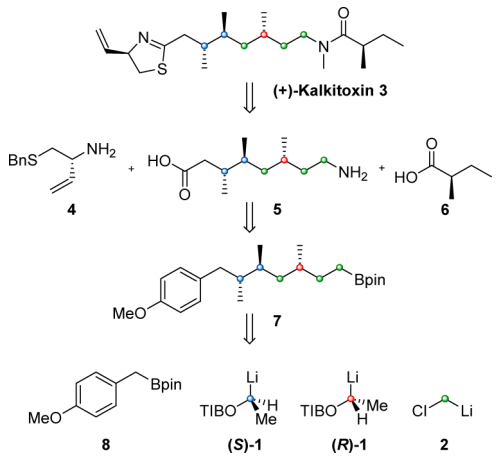
Scheme 2. Retrosynthetic Analysis of (+)-Kalkitoxin

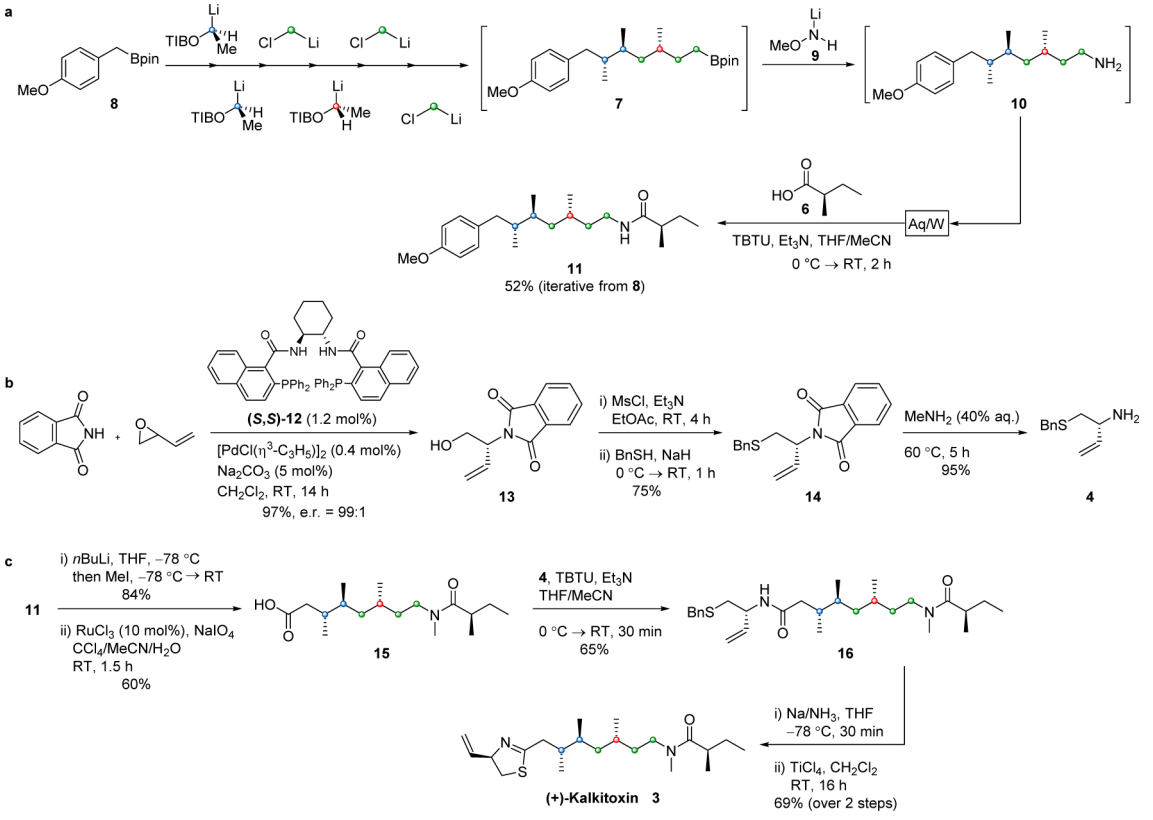


methylene insertion with **2**, a homologation reaction with (*R*)-**1**, and two further methylene insertion reactions, culminating in boronic ester **7** (Scheme 3a). Having completed the growth phase, the termination phase involved converting the boronic ester into the amine using lithiated methoxyamide **9** as described by Morken.[23] The whole sequence was carried out with just simple benchtop filtrations of the reaction mixture between the homologation steps and without any other purification. After the first aqueous workup in the sequence, the crude amine **10** was directly coupled to the chiral acid **6**[24] giving amide **11** in 52% yield and with >95:5 dr and >99:1 er. The complete assembly line synthesis only required a single purification!

A novel synthesis of the amino thioether fragment **4** was devised on the basis of Trost's dynamic kinetic asymmetric transformation (DYKAT)[25] as shown in Scheme 3b. Thus, reaction of phthalimide with butadiene monoepoxide gave allylic imide **13** in 97% yield and 99:1 er.[26] Subsequent activation of the alcohol as the mesylate, displacement by benzylmercaptan, and aminolysis gave the final required building block, amine **4**.

The completion of the synthesis of (+)-kalkitoxin is shown in Scheme 3c. Amide **11** was first methylated and subsequently treated with $RuCl_3$ in the presence of $NaIO_4$[27] to give carboxylic acid **15**. A small amount of oxidation of the N-Me group was also observed during this process,[28] but it could be minimized by careful monitoring of the reaction. The remaining steps followed literature precedent.[20a,b] Amide **16** was prepared by coupling acid **15** with amine **4**. Finally, deprotection of the thiol and cyclization completed the synthesis of (+)-kalkitoxin, identical in every respect to the literature. The synthesis of amide **11** was accomplished rapidly in only 4 days with only one purification, and without having to deviate from described protocols.[10,21] The entire synthesis required only five chromatographic purifications during the longest linear sequence. Determining the step count is not clear-cut, but if the assembly-line process is counted as one step, then the total step count (longest linear sequence) amounts to just seven steps.

Scheme 3. Synthesis of (+)-Kalkitoxin: (a) Assembly-Line Synthesis of the Core of (+)-Kalkitoxin, (b) Synthesis of the Amine Fragment 4, and (c) Coupling of the Two Fragments and Completion of the Synthesis of (+)-Kalkitoxin[a]



[a]Aq/W, aqueous work-up; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

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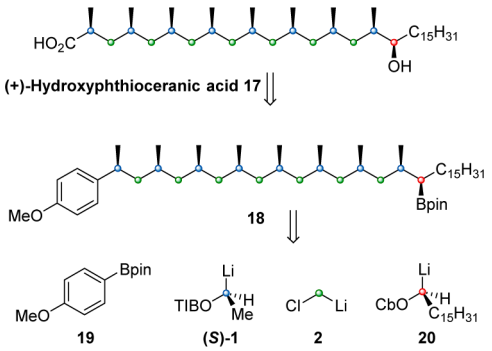
In order to explore the limits of the assembly line synthesis we targeted (+)-hydroxyphthioceranic acid **17** which would potentially require a staggering 16 sequenced homologations. This molecule is a component of sulfolipid-1 (SL-1), a major constituent of the cell-wall lipid of virulent human *Mycobacterium tuberculosis* (MTB).[29] Studies on SL-1 have revealed significant immunomodulatory activity against various immune cells, thus making it a highly promising component of potential tuberculosis vaccines.[30] (+)-Hydroxyphthioceranic acid was synthesized in 2013 by the groups of Minnaard[31] and Schneider[32] in 23−32 steps (longest linear sequence), and high diastereocontrol. Recently, we reported a convergent enantioselective 14-step synthesis employing a traceless lithiation−borylation−protodeboronation strategy.[33]

By alternating the addition of building blocks (*S*)-**1** and **2** to boronic ester **19** multiple times and then adding **20**, our second target, (+)-hydroxyphthioceranic acid, could potentially be obtained in just a few steps with full stereocontrol as shown in the retrosynthetic analysis in Scheme 4. In practice sequentially

Scheme 4. Retrosynthetic Analysis of (+)-Hydroxyphthioceranic Acid, a Key Component of Sulfolipid-1[a]

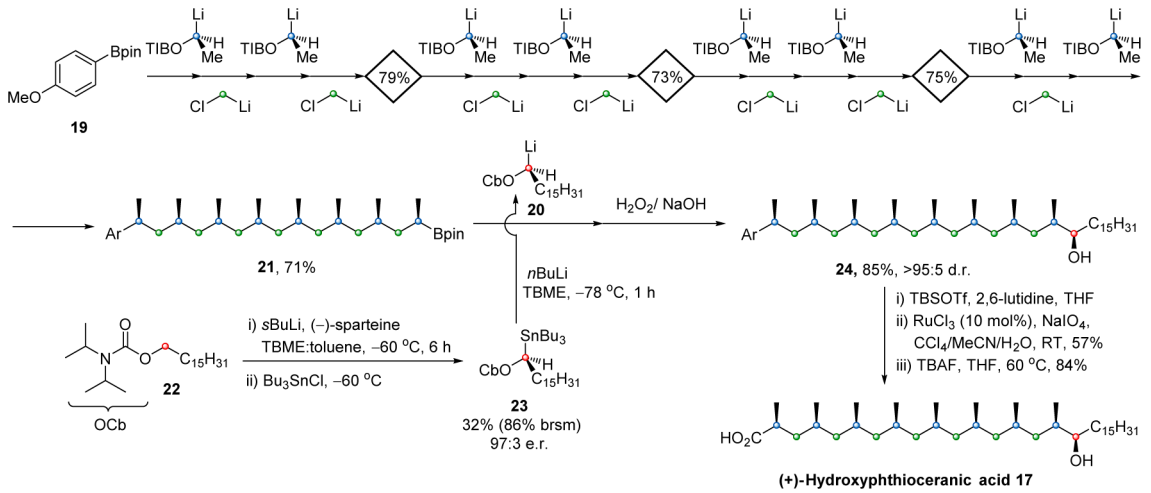


[a]OCb = *N*,*N*-di-*iso*propylcarbamoyl.

treating boronic ester **19** with (*S*)-**1**, followed by a one-carbon homologation with **2**, and then repeating this pair of homologations seven further times (15 homologations in total) gave boronic ester **21** with full stereocontrol (Scheme 5). The homologations at the start of the sequence were as efficient as those at the end, thus showing that steric and conformational effects of the growing carbon chain had minimal effects and that the reagents were highly reliable. However, while this challenging sequence worked well most of the time, occasionally one of the homologations occurred with lower efficiency part way through the sequence (perhaps because of adventitious impurities), producing an unacceptable mixture of *n*:*n*−1 homologation products [90:10−99:1; our threshold acceptance was >99:1 (*n*:*n*−1) for each homologation], which were difficult to separate. For reliability, we therefore conducted chromatographic purifications after each set of four homologations, and this enabled us to consistently prepare boronic ester **21** in high yield, high purity, and full stereocontrol.

The final homologation with carbamate **22** initially proved challenging due to its very poor solubility in Et_2O or TBME at −78 °C. Interestingly, a related C12 carbamate had been deprotonated under quite different conditions to standard conditions [*s*-BuLi (4 equiv)/(−)-sparteine (4 equiv), −78 °C, 15 h vs *s*-BuLi (1.4 equiv)/(−)-sparteine (1.4 equiv), −78 °C, 5 h], perhaps reflecting its low solubility in the medium.[34] However, this reagent stoichiometry could not be employed in lithiation−borylation because the excess (unreacted) *s*-BuLi would add irreversibly to the boronic ester. We therefore considered using the corresponding stannane **23** as this could be used as a precursor to lithiated carbamate **20** (by treatment with *n*-BuLi[35]) without using excess organolithium. Additionally, the stannane was expected to be more soluble in diethyl ether. After optimization, we found that stannane **23** could be prepared by partial lithiation of carbamate **22** at −60 °C using *s*-BuLi (1.4 equiv)/(−)-sparteine (1.4 equiv) for 6 h and subsequent trapping with Bu_3SnCl in 32% yield (86% brsm) and 97:3 er. We were pleased to find that the stannane was completely soluble in TBME at low temperature. Treatment of **23** with *n*-BuLi and subsequent addition of boronic ester **21** gave the desired boronic ester, completing the growth phase of the assembly line synthesis. In situ oxidation gave alcohol **24** in 85% yield from **21** with >95:5 dr. Protection of the alcohol, $RuCl_3$-catalyzed oxidation of the aromatic ring[27] and

Scheme 5. Total Synthesis of (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis[a]



[a]Ar = *p*-$MeOC_6H_4$.

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deprotection then gave the target compound (+)-hydroxyphthioceranic acid **17**, which was identical in all respects to the literature compound. The whole synthesis was completed in just one month with only seven purifications steps and full stereocontrol. The step count is again not clear-cut, but if the assembly line process is counted as five steps (the number of aqueous work-ups and purifications), then the total step count amounts to eight steps.

■ CONCLUSIONS

The two short syntheses of (+)-kalkitoxin and (+)-hydroxyphthioceranic acid demonstrate the power of the assembly-line synthesis strategy for the highly stereocontrolled synthesis of two different natural products with high chemical and manpower efficiency. Because the homologations reactions are dominated by reagent control, matched and mismatched effects are not observed,[10] which therefore enables the same strategy to be employed in the synthesis of different diastereoisomers. The syntheses come close to Hendrickson's definition of "an ideal synthesis" because most transformations involved bond constructions steps and did not require functional-group interconversions between iterative steps. Clearly, the methodology is ideally suited to natural products with carbon chains bearing simple alkyl groups, as has been demonstrated. However, most natural products contain polar functional groups, and being able to introduce ketone or hydroxyl functions with stereocontrol would greatly enhance the scope of this methodology. Studies in this area are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedure and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

v.aggarwal@bristol.ac.uk

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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