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Synthesis of hydroxyphthioceranic acid using a traceless lithiation–borylation–protodeboronation strategy

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In planning organic syntheses, disconnections are most often made adjacent to functional groups, which assist in C–C bond formation. For molecules devoid of obvious functional groups this approach presents a problem, and so functionalities must be installed temporarily and then removed. Here we present a traceless strategy for organic synthesis that uses a boronic ester as such a group in a one-pot lithiation–borylation–protodeboronation sequence. To realize this strategy, we developed a methodology for the protodeboronation of alkyl pinacol boronic esters that involves the formation of a boronate complex with a nucleophile followed by oxidation with $Mn(OAc)_3$ in the presence of the hydrogen-atom donor 4-*tert*-butylcatechol. Iterative lithiation–borylation–protodeboronation allows the coupling of smaller fragments to build-up long alkyl chains. We employed this strategy in the synthesis of hydroxyphthioceranic acid, a key component of the cell-wall lipid of the virulent *Mycobacterium tuberculosis*, in just 14 steps (longest linear sequence) with full stereocontrol.

Organic synthesis involves the coupling together of small molecules, usually followed by functional group interconversions, and subsequent further coupling until a final target molecule has been created. The functional groups, which may not be present in the final molecule, are there to assist in C–C bond formation, and so are integral in any disconnection analysis. As functional groups are the focus of attention, strategic disconnections are usually applied around them, which necessarily constrains both disconnections and strategies. No such constraint applies to molecules devoid of functional groups (for example, archaeal membrane lipids exemplified by glycerol dibiphytanyl glycerol tetraether (GDGT-4) (Fig. 1a))[1] and this liberation provides a blank canvas on which new strategies for molecular assembly can be explored. Ultimately, such novel strategies could be applied to more-functionalized molecules, especially if they enable non-intuitive disconnections to be made that lead to building blocks that are more readily accessible.

Previously, we reported the coupling together of carbamates **1** and boronic esters **2**[2–4], two functional groups that are easily accessible from nature's bountiful supply of alcohols and alkenes (Fig. 1b). We reasoned that if the boronic ester functional group could be removed from the coupled product **3** (ideally in the same pot), we would have effected a traceless coupling of two fragments[5–8]. The overall sequence would represent a powerful new way to assemble molecules, as it would mean that, in terms of retrosynthetic analysis, molecules could be disconnected essentially anywhere, even remote from functionality (Fig. 1c). Although this strategy had been applied to benzylic carbamates, the resulting benzylic boronic esters (where boron is adjacent to functionality) are very easily protodeboronated simply with TBAF·$3H_2O$ (TBAF, tetra-*N*-butylammonium fluoride), so the strategy is not generally applicable[9–12]. The major challenge in realizing this strategy is the protodeboronation of the more-stable secondary alkyl pinacol esters, remote from any functionality (for example, **3** → **4**), as there were no known methods for achieving such a transformation directly, although there were methods for carrying out the overall transformation indirectly[13,14]. In this paper we describe a new protocol for protodeboronation and its tactical use in conjunction with lithiation–borylation as a new strategy for assembling molecules without trace of the functional groups used in their genesis. In addition, we demonstrate the power of this new approach in a short (14 steps), stereoselective and convergent synthesis of hydroxyphthioceranic acid **10**, a key component of the cell-wall lipid of the virulent *Mycobacterium tuberculosis* (MTB).

Results and discussion

We began by focusing on the key protodeboronation step and chose a representative secondary alkyl pinacol boronic ester **5a** for our studies. Treatment of this ester with carboxylic acids at elevated temperatures, as reported by Brown and Murray for the protodeboronation of boranes[15], was ineffective, as was the use of TBAF·$3H_2O$, a reagent that we had employed for the protodeboronation of reactive benzylic and allylic pinacol boronic esters[9,16]. We therefore considered the protonation of the more-reactive boronate complex formed from the addition of *p*-MeOPhLi (**6a**) because such species were found to be reactive nucleophiles[17]. Unfortunately, treatment of the boronate complex **7** with a range of acids was again unsuccessful.

Renaud's seminal discovery[13,14] that alkyl catechol boronic esters undergo facile homolytic protodeboronation in the presence of air and 4-*t*-butylcatechol (TBC) was highly attractive to us, but he had shown that this process was unique to catechol boronic esters; it was ineffective with pinacol boronic esters. We reasoned that the boronate complex **7** should be much more prone to homolytic cleavage and examined various conditions. We were pleased to find that, on refluxing boronate complex **7** in 1,2-dichloroethane (DCE) (80 °C), the desired product **8** was obtained in 55% yield (Table 1, entry 1). DMF at a higher temperature (130 °C) increased the yields obtained (entry 2). Using the more electron-rich 1,3-$(MeO)_2$PhLi **6b** gave even higher yields of the protodeboronated product **8** (entry 3). In contrast to Renaud's work, it was necessary to perform reactions under argon, because in air oxidation of the boronate to alcohol **9** competed (entry 4). In related studies, Fensterbank and co-workers found that potassium trifluoroborates could be cleaved oxidatively at 120 °C by various oxidants and the resulting radical intermediates trapped with TEMPO (2,2,6,6-

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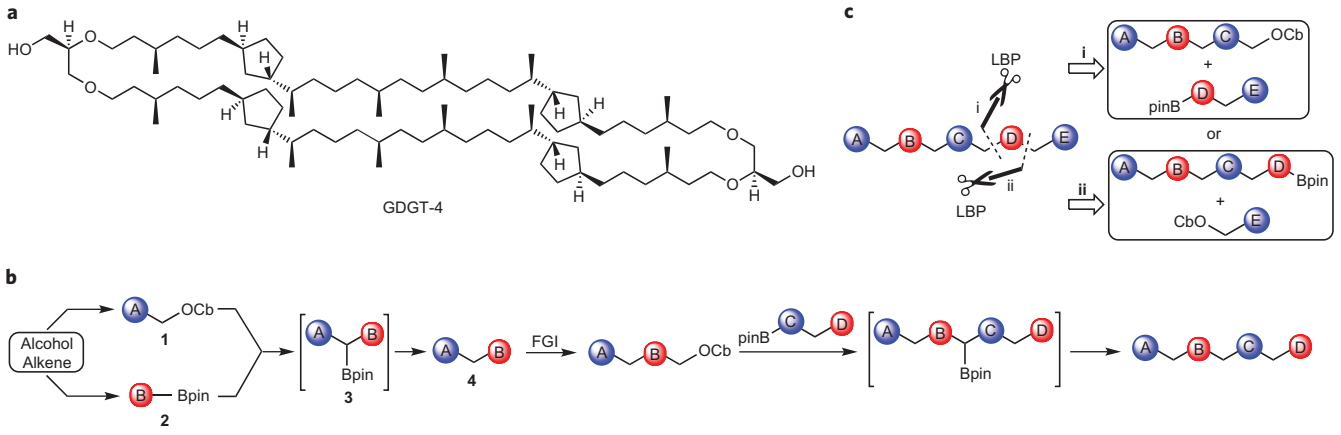
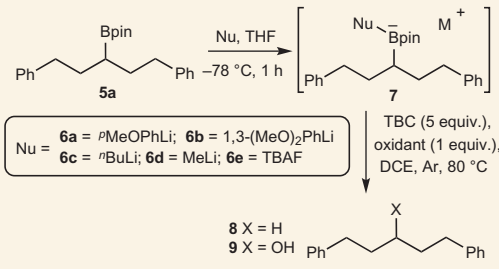


Figure 1 | Complex molecules with limited functionality present in nature and the potential traceless strategy for their synthesis. a, Structure of the GDGT membrane lipid of cosmopolitan pelagic Crenarchaeota. **b**, Lithiation-borylation-protodeboronation (LBP) strategy for the organic synthesis, showing the process for combining two fragments (A and B) followed by the removal of the boronic ester, and its repeated use (fragments C and D). **c**, Possible disconnections of a molecule using the traceless LBP strategy. Cb, *N*,*N*-diisopropyl carbamate; FGI, functional group interconversion.

tetramethylpiperidinyloxy) or methyl vinyl ketone[18]. Again, our aryl boronate complexes were expected to undergo a more-facile oxidative cleavage, as the C–B bond is more electron rich than in the corresponding trifluoroborates. We therefore screened a range of oxidants and found that $Cu(OAc)_2{\cdot}H_2O$ and $Mn(OAc)_3{\cdot}2H_2O$ both performed well (entries 5 and 6). Furthermore, the shorter reaction time and lower temperatures required resulted in cleaner, higher-yielding reactions. Attempts to use air with substoichiometric amounts of $Cu(OAc)_2{\cdot}H_2O$ were less effective (entry 7). The nature of the boronate complex was also examined. We found that the use of *n*-BuLi (entries 8 and 9) or even MeLi (entry 10) was equally effective. Surprisingly, TBAF·$3H_2O$ could also be employed with $Mn(OAc)_3{\cdot}2H_2O$, which shows that even transient boronate complexes could be cleaved oxidatively (entries 11 and 12).

Table 1 | Optimization of protodeboronation of model substrate 5a.



Entry	Nu	Oxidant	Time (h)	8:9	Yield (%)*
1†	**6a**	-	62	100:0	55
2‡	**6a**	-	40	92:8	72(65)
3‡	**6b**	-	40	95:5	85(78)
4‡	**6b**	Air	40	69:31	40
5	**6b**	$Cu(OAc)_2$	18	100:0	96(87)
6	**6b**	$Mn(OAc)_3$	18	100:0	96
7§,‖	**6b**	$Cu(OAc)_2$	72	88:12	71
8	**6c**	$Cu(OAc)_2$	12	100:0	97(95)
9	**6c**	$Mn(OAc)_3$	12	100:0	98(97)
10	**6d**	$Mn(OAc)_3$	12	100:0	94
11‖	**6e**	$Cu(OAc)_2$	12	100:0	72
12‖	**6e**	$Mn(OAc)_3$	8 h	100:0	98(97)

*Gas chromatography yield, values in parentheses are the isolated yield. †A 2:1 ratio of product:ate complex remained. ‡130 °C, dimethylformamide instead of DCE. §10 mol% $Cu(OAc)_2$ under air. ‖Toluene instead of DCE, all the reagents were mixed at once at r.t.

We briefly tested the scope of the protodeboronation reaction with several boronic esters that contained commonly encountered functional groups (esters (**5b**), alkenes (**5c**) and alcohols (see the Supplementary Information)). Using *n*-BuLi (Conditions A) or TBAF (Conditions B) as the nucleophile and $Mn(OAc)_3$ as the oxidant, good yields of protodeboronated products were obtained in all cases (Fig. 2a). Other functional groups that are compatible with the process are also presented in the total synthesis at the end of the paper (see Fig. 5).

To verify the mechanism, reaction with cyclopropylmethyl-substituted boronic ester **5d** was tested (Fig. 2b). In this case, only the ring-opened product of protodeboronation was obtained, which indicates that the reaction occurs via a radical intermediate that undergoes rapid ring opening to relieve ring strain[19].

With a number of simple protocols to effect protodeboronation of secondary pinacol boronic esters, underpinned with mechanistic foundations, we embarked on the new strategy for the total synthesis of hydroxyphthioceranic acid **10**, a molecule of significant global importance in relation to tuberculosis (TB).

Sulfolipid-1 (SL-1). The alarming rise in drug-resistant TB has made it one of the most fatal human diseases in recent years, being responsible for 1.3 million deaths in 2012 alone[20]. It has been estimated that over two billion people[21] are infected with TB globally, which makes it a major health challenge of the 21st century[21]. Although little is known about the molecular mechanisms of MTB virulence it is believed that the cell-wall lipids play an important role in the pathogenesis of this organism[22,23]. Furthermore, the extraordinary thick lipid coat acts as an impenetrable waxy barrier to cytotoxic agents, which makes it especially challenging to combat[24]. The major cell-wall lipid of virulent human MTB has been isolated and identified as SL-1 by Goren *et al.*[25,26] (Fig. 3a). Studies on SL-1 have revealed significant immunomodulatory activity against various immune cells, which makes it a promising component of potential vaccines[22,27]. The complex structure of SL-1 has been characterized as 2,3,6,6′-tetraacyl-α,α′-D-trehalose 2′-sulfate and it has three polydeoxypropionate arms coupled to the sugar core, which have been characterized as hydroxyphthioceranic acid **10** and phthioceranic acid **11** (Fig. 3b)[25,26]. The more-complex side arm, hydroxyphthioceranic acid **10**, was synthesized in 2013 by the groups of Minnaard[28–31] and Schneider[32] in 32 and 23 steps (longest linear sequence), respectively, and with high diastereocontrol.

Retrosynthesis. Our retrosynthetic analysis (Fig. 3c) began with a stereocontrolled lithiation–borylation[2] disconnection at C17–C18.

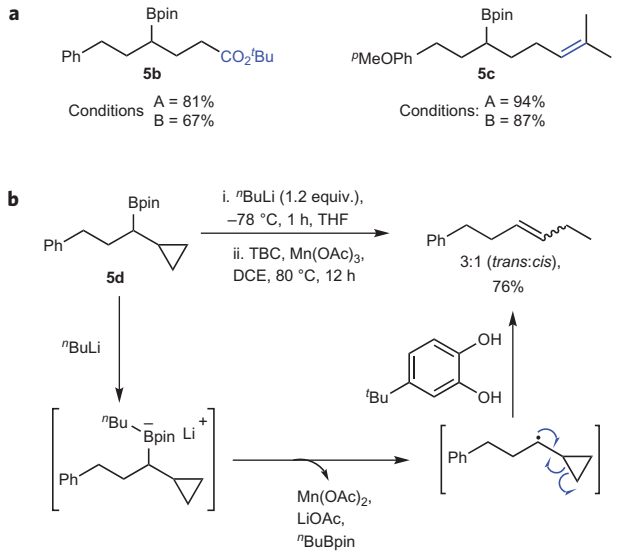


Figure 2 | Brief survey of the scope and mechanism of the protodeboronation reaction. a, Functional groups tested for compatibility with protodeboronation under two sets of conditions. Conditions A: *n*-BuLi, TBC, $Mn(OAc)_3{\cdot}2H_2O$, DCE, 12 h, 80 °C; Conditions B: TBAF, TBC, $Mn(OAc)_3{\cdot}2H_2O$, DCE, 12 h, 80 °C. **b**, Radical clock to probe the mechanism of the protodeboronation reaction. The formation of the ring-opened product indicates that protodeboronation occurs via a radical intermediate as shown.

This would lead to polydeoxypropionate **12**, which could be assembled by combining the appropriate building blocks through non-selective lithiation–borylation reactions followed by protodeboronation. Rather than disconnecting **12** in the middle, we found that disconnection at C11–C12 followed by a further disconnection at C5–C6 would require a smaller number of distinct building blocks for the subsequent assembly (**13** and **14**). The building blocks **13** and **14** can be prepared easily from the commercially available alcohol **15**. Furthermore, coupling together enantiopure building blocks in the assembly of **12** would result in complete stereocontrol without diastereoisomer contamination, a considerable benefit over alternative diastereocontrolled processes.

Total synthesis of hydroxyphthioceranic acid 10. Our synthesis began with the conversion of the commercially available monoacetylated 1,5-diol **15** into the required building blocks **13** and **14** (Fig. 4). Alcohol **15** can also be prepared easily on a multigram scale via enzymatic resolution of the corresponding diol, which itself can be prepared from simple materials without the need for chromatographic purification[33–35]. Following carbamoylation of alcohol **15**, the acetate was hydrolysed and the primary alcohol protected as the methoxymethyl (MOM) ether to give building block **13** in quantitative yield.

Building block **14** was also prepared from the same monoacetate **15** (Fig. 4). After protection as the *t*-butyldiphenylsilyl (TBDPS) ether, hydrolysis of the ester and carbamoylation led to carbamate **16**. Lithiation followed by treatment with pinacolborane (HBpin) gave pinacol boronic ester **17** in good yield[36]. To prepare boronic ester **14** with the stereochemistry required, we needed to deprotonate ethyl carbamate with *s*-BuLi/(+)-sparteine. Fortunately, both enantiomers of sparteine are commercially available (see Supplementary Information for details), although O'Brien's synthetic (+)-sparteine surrogate can also be employed[37,38]. Thus, deprotonation of ethyl carbamate with *s*-BuLi/(+)-sparteine

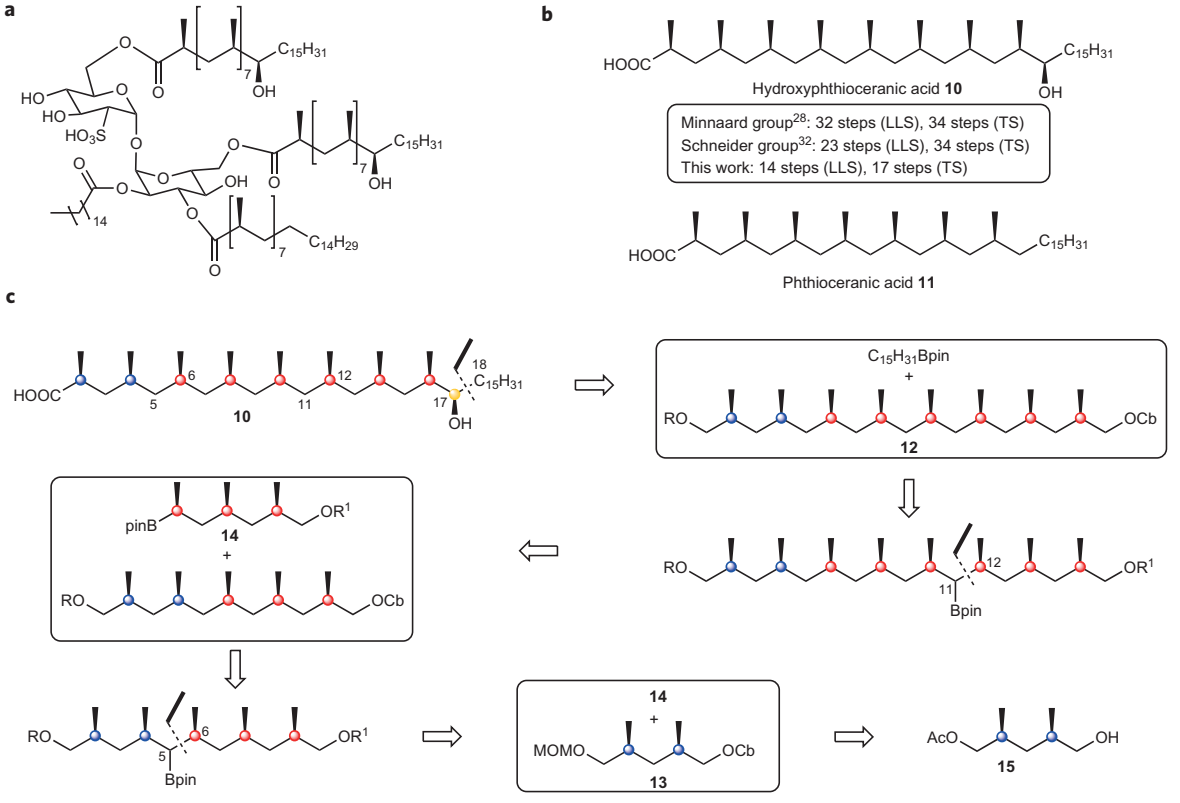


Figure 3 | Complex molecules of interest in this study associated with the cell-wall lipid of MTB. a, Structure of SL-1 the major cell-wall lipid of virulent human MTB. **b**, Structures of two polydeoxypropionates that are coupled to the sugar core of SL-1, hydroxyphthioceranic acid **10** and phthioceranic acid **11**. Syntheses of **10** have recently been reported by the Minnaard group[28] and by the Schneider group[32]. **c**, Retrosynthetic analysis of hydroxyphthioceranic acid **10**. This shows how we envisaged building the molecule from simpler fragments. LLS, longest linear sequence; TS, total number of steps.

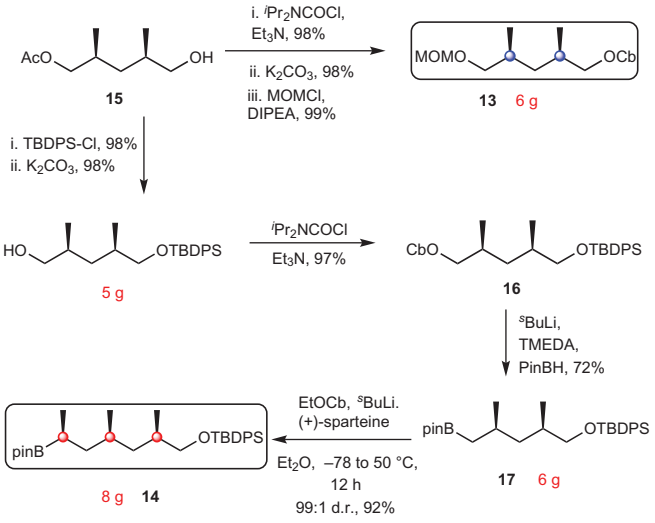


Figure 4 | Synthesis of building blocks 13 and 14 used in the synthesis of hydroxyphthioceranic acid 10. DIPEA, *N,N*-diisopropylethylamine.

followed by the addition of pinacol boronic ester **17** and heating gave the homologated product **14** in 92% yield and 99:1 d.r.

With substantial quantities of the required building blocks in hand, we set about their union using our lithiation–borylation–protodeboronation (LBP) sequence (Fig. 5). Thus, deprotonation of carbamate **13** with *s*-BuLi/TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) followed by the addition of boronic ester **14** gave the homologated boronic ester **18** in 91% isolated yield (1:1 d.r.)[2]. For protodeboronation, although the use of aryllithium or TBAF was unsuccessful, the use of *n*-BuLi with TBC and $Mn(OAc)_3{\cdot}2H_2O$ gave the protodeboronated product **19** in 68% yield (Fig. 5). The two-stage LBP was also carried out in one pot to give product **19** in a similar yield (63%) as that of the two-step process. Desilylation with TBAF followed by carbamoylation afforded the intermediate carbamate **20** in 97% yield.

A further lithiation of carbamate **20** and addition of the same boronic ester building block **14** gave the homologated boronic ester **21** in 85% yield. Unfortunately, the final protodeboronation of this much more hindered boronic ester was found to be considerably more challenging: the boronate complex did not even form with aryllithium reagents, but did with *n*-BuLi, although the desired product **22** was isolated in only a disappointing 18% yield. Fortunately, using MeLi under the standard protocol with TBC and $Mn(OAc)_3{\cdot}2H_2O$ gave the protodeboronated product in 61% yield. The two-stage reaction of LBP was also carried out in one pot to give product **22** in a similar yield (54%) (Fig. 5). Evidently, the protodeboronation step is sensitive to the steric environment around boron and it was extremely useful to have a suite of methods available at our disposal that could be used according to need. Desilylation with TBAF followed by carbamoylation afforded the final carbamate **12** in 96% yield (Fig. 5).

The final stereoselective coupling of carbamate **12** and pinacol boronic ester **24** initially proved challenging because boronic ester **24** was not soluble in diethyl ether at −78 °C, which resulted in poor yields. Fortunately, it was soluble in *t*-butyl methyl ether (TBME). Thus, stereoselective deprotonation of carbamate **12** with *s*-BuLi/(+)-sparteine in TBME followed by addition of boronic ester **24** and heating gave an intermediate boronic ester that was oxidized directly to alcohol **25** in 88% isolated yield (d.r. >95:5). Deprotection of the MOM group followed by chemoselective oxidation of the primary alcohol to the acid[39–41] in the presence of the secondary alcohol afforded hydroxyphthioceranic acid **10**, the target natural product, in 90% isolated yield (Fig. 5). The acid **10** was converted into the corresponding methyl ester with $TMSCHN_2$ (TMS, trimethylsilyl) and was found to be identical in all respects with the reported data.

In conclusion, we have shown that lithiation–borylation followed by protodeboronation provides a new traceless strategy for linking fragments together derived from easily accessible alcohols and

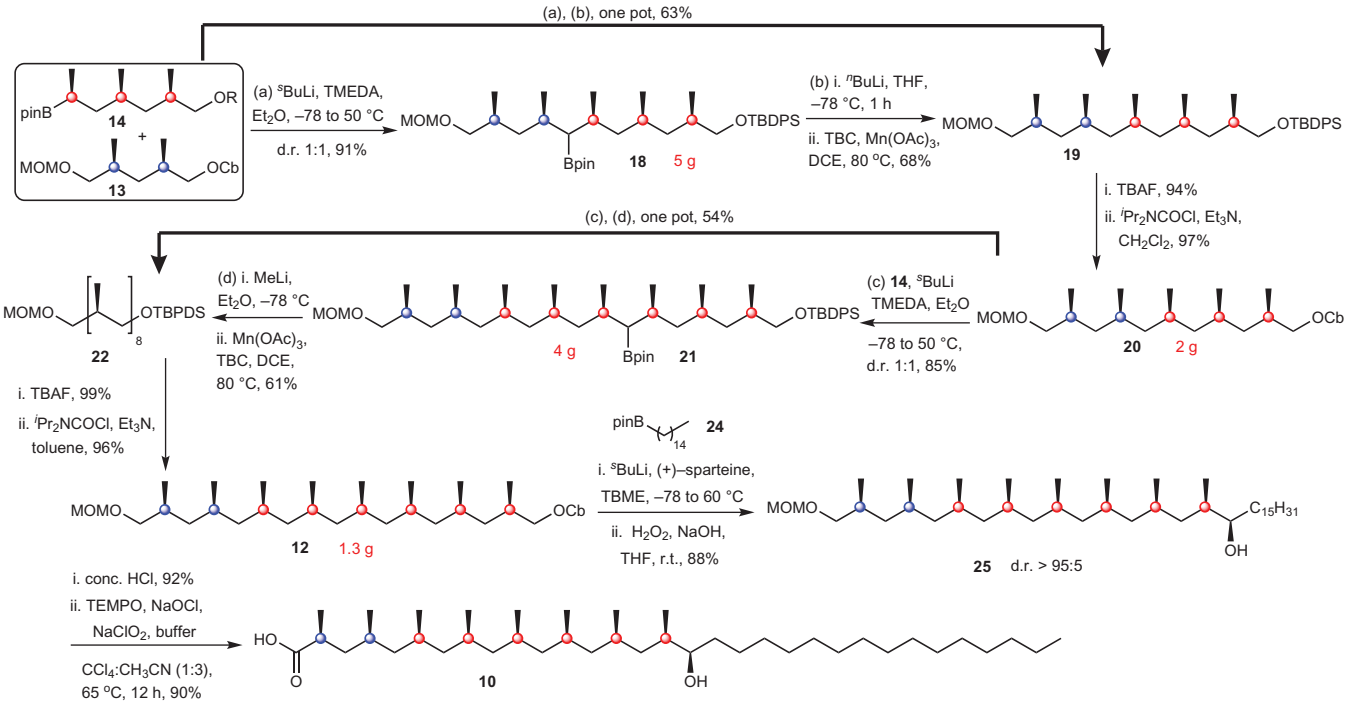


Figure 5 | Total synthesis of hydroxyphthioceranic acid 10. The starting materials and reagents used to construct hydroxyphthioceranic acid **10** are shown in this figure. Bold arrows indicate a one-pot transformation. This figure shows how just two simple building blocks, **13** and **14**, can be combined through iterative LBP (one pot) ultimately to construct hydroxyphthioceranic acid **10** in just nine steps with full stereocontrol. r.t., room temperature.

boronic esters. A new protocol for the protodeboronation of alkyl pinacol boronic esters was developed for this strategy, which involved the formation of a boronate complex (with RLi or TBAF) followed by oxidation with $Mn(OAc)_3$ in the presence of TBC. This new disconnection was successfully applied to a total synthesis of hydroxyphthioceranic acid **10** in just 14 steps, with essentially complete stereocontrol. The practicality of the synthesis has been demonstrated by carrying out the sequence on a multigram scale. Moreover, our 14-step synthesis is substantially shorter than any previous synthesis, which demonstrates the power of the LBP strategy.

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Author contributions

V.K.A. conceived the project and wrote the manuscript with R.R. R.R planned and carried out the experiments. R.R. and V.K.A. discussed the experiments and results.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to V.K.A.

Competing financial interests

The authors declare no competing financial interests.