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Assembly-line synthesis of organic molecules with tailored shapes

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Molecular 'assembly lines', in which organic molecules undergo iterative processes such as chain elongation and functional group manipulation, are found in many natural systems, including polyketide biosynthesis. Here we report the creation of such an assembly line using the iterative, reagent-controlled homologation of a boronic ester. This process relies on the reactivity of α-lithioethyl tri-isopropylbenzoate, which inserts into carbon–boron bonds with exceptionally high fidelity and stereocontrol; each chain-extension step generates a new boronic ester, which is immediately ready for further homologation. We used this method to generate organic molecules that contain ten contiguous, stereochemically defined methyl groups. Several stereoisomers were synthesized and shown to adopt different shapes—helical or linear—depending on the stereochemistry of the methyl groups. This work should facilitate the rational design of molecules with predictable shapes, which could have an impact in areas of molecular sciences in which bespoke molecules are required.

Nature has evolved highly sophisticated machinery for organic synthesis. An archetypal example is its machinery for polyketide synthesis where a simple thioester is passed from one module to another, undergoing enzyme-catalysed acylation, dehydration, reduction or chain extension multiple times until the target molecule is formed[1]. The process amounts to a molecular assembly line. By iteration and variation of the processing enzymes, nature manufactures an enormously diverse array of polyketides, many of which display high chemical complexity and biological activity (Fig. 1a).

We have sought to emulate nature in a related approach, but using boronic esters rather than thioesters. Our approach is to develop reagents which insert into the C–B bond, and to carry out this process iteratively so that a simple boronic ester is ultimately converted into a complex molecule with full control over its length, its shape and its functionality (Fig. 1b). By making specific molecules in this way, we also planned to obtain further understanding of the role of methyl substituents that are often interspersed along flexible carbon chains in natural products. The methyl groups originate from the metabolism of propionates or by methylation reactions, but nature could equally well have used acetates instead or avoided methylation and so managed with less complex machinery and created less complex organic molecules. The seemingly trivial substitution of a hydrogen atom for a methyl group on a carbon chain must have a powerful underlying evolutionary advantage. It has been suggested that nature uses the methyl groups (together with other polar residues) to give the molecule a predisposition to adopt the required conformation for interaction with its biological target without significant loss of enthalpy or entropy[2–8]. Despite this structural predisposition, the molecule is still flexible enough to change its shape when required (for example for transport across membranes). To probe the singular effect of how methyl substituents affect conformation of carbon chains it would be desirable to make molecules with multiple contiguous methyl groups, but such molecules were previously deemed impossible to prepare[2], in contrast to 1,3-deoxypolypropionates[9,10].

In this Article, we report our success in making such molecules through a highly streamlined process. In particular, through an iterative homologation procedure, we have developed a highly selective assembly-line synthesis process, and by successfully targeting carbon chains carrying ten contiguous methyl groups and no other functionality, we show that the methyl substituents can be used to control the conformation of the molecule with great precision. They act as levers, pushing or pulling the carbon chain and, depending on their specific orientation, they can force the molecule to adopt a linear or helical conformation both in solution and in the solid state. This is analogous to the way in which the primary sequence of amino acids determines their folded shape[11]. Indeed, the iterative homologation process we have developed makes it possible to rationally design and create molecules with predictable shapes without having to incorporate functional groups to bias a particular conformation.

Development of the iterative homologation process

Two broad approaches have been developed for the stereocontrolled homologation of boronic esters: a substrate-controlled method in which a chiral diol on the boronic ester controls the stereochemistry (Matteson homologation[12,13]), and a reagent-controlled method in which chirality in the reagent controls the stereochemistry[14]. The latter method is more direct and more versatile because it enables ready access to alternative stereoisomers. We (and others[15–18]) have focused on reagent-controlled methodology. We have found that Hoppe's lithiated carbamates[19–21] homologate boronic esters with high stereocontrol, and we have applied this methodology in the synthesis of a number of natural products[22–26]. To apply this methodology to iterative homologations, we set the goal of creating a carbon chain with ten contiguous methyl substituents with total stereocontrol (Fig. 1b). This is a daunting task because each step must go to completion without over- or under-homologation and it must proceed with full stereocontrol to obtain pure material, because different chain lengths and different diastereoisomers would be extremely difficult to separate. As an illustration, if each homologation occurred in 98% completion with just 1% over-homologation and 1% under-homologation, then after ten iterative homologations a binomial distribution of products would be obtained in which the major compound, having undergone 10 homologations (a 10-mer), was only 82% pure, contaminated by under- and over-homologation products. If each homologation occurred with 98:2 enantioselectivity, then after ten iterative homologations the product would be a mixture of diastereoisomers that was only 82% pure, which again was undesirable. As a further illustration of the challenge,

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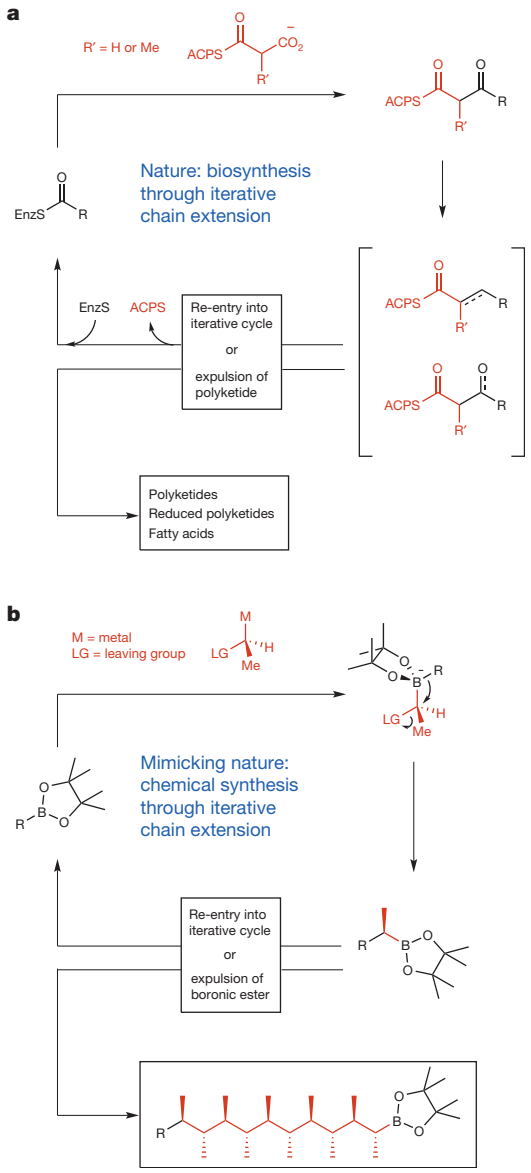

Figure 1 | Iterative approaches to assembly-line synthesis. **a**, Example of polyketide biosynthesis where successive cycles of chain extension and functional-group interconversions generate a diverse array of complex molecules. ACP, acyl carrier protein; Enz, enzyme; Me, methyl. **b**, Proposed reagent-controlled homologation of boronic esters where successive cycles of chain extension enable rapid and streamlined synthesis of stereodefined carbon chains.

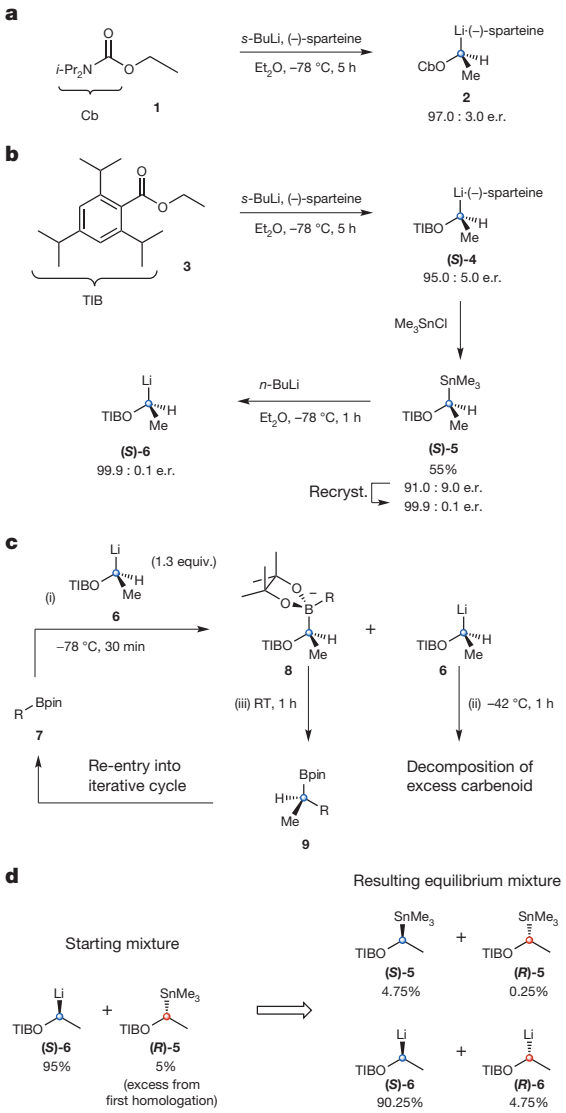

Figure 2 | Methodology used for homologation of boronic esters. **a**, Method for the generation of Hoppe's lithiated carbamate. Bu, butyl; Et, ethyl; *i*-Pr, isopropyl; OCb, *N*,*N*-diisopropyl carbamate. **b**, Method for the generation of α-lithiated hindered benzoate **6** with high enantiomeric ratio from stannane **5**. TIB, 2,4,6-triisopropylbenzoate. **c**, Optimized protocol for iterative homologation of boronic esters. Carbenoid **2** was not suitable for iterative homologations whereas carbenoid **6** was suitable and the protocol for its successful use is shown here. pin, pinacol. RT, room temperature. **d**, Racemization pathway for lithiated benzoate (***S***)**-6** when an excess of stannane (***R***)**-5** is present from the previous homologation. This example shows the ratio of products obtained from a mixture of lithiated benzoate (***S***)**-6** (95%, 99.9:0.1 e.r.) and stannane (***R***)**-5** (5%, 99.9:0.1 e.r.), which leads to lithiated benzoate and stannane of lower enantiomeric ratio (~95:5).

a recent triple, one-pot homologation of a boronic ester using an α-chloroalkyllithium reagent yielded[27], in the best case, a mixture of the trimer (19%, 5:80:9:6 diastereomeric ratio), dimer (27%, 78:22 diastereomeric ratio) and monomer (5%).

Unfortunately, Hoppe's lithiated carbamates (**2**) (Fig. 2a), which we had used extensively in synthesis, could not be employed because we found that they were prone to giving significant quantities of over- and under-homologated products with hindered boronic esters, and that furthermore they could be obtained in only 97:3 enantiomeric ratio (e.r.). We therefore turned to α-metallated hindered benzoates as alternatives to Hoppe's carbamates, because we had found that the superior leaving-group ability of the ester relative to the carbamate enabled difficult homologations to proceed more effectively[28]. After exploring various alternatives, we found that deprotonation of ethyl tri-isopropylbenzoate **3** with *s*-BuLi/(−)-sparteine[28] followed by trapping with Me_3SnCl gave stannane **5** (91:9 e.r.), which could be recrystallized to 99.9:0.1 e.r. The required enantioenriched lithiated benzoate **6** could be easily generated from stannane **5** with *n*-BuLi with retention of stereochemistry[29] (Fig. 2b). Using this method, both enantiomers of the stannane were easily prepared on multigram scale, using commercially available (+)- or (−)-sparteine, without the need for chromatography. In addition, the chiral diamines were re-isolated (and reused) in >80% yield. Having access to substantial quantities of both enantiomers of these derivatives greatly facilitated the iterative homologation process; it was like having the chiral organometallic **6** in a bottle[30].

An optimized protocol had to be developed for iterative homologation to ensure high fidelity (Fig. 2c). Treatment of stannane **5** with *n*-BuLi at −78 °C followed by addition of a boronic ester **7** gave the boronate complex **8**. An excess of stannane **5** (and, therefore, an excess of lithiated benzoate **6**) was used to ensure that all of the boronic ester

was converted into the boronate complex. The reaction mixture was then kept at −42 °C for one hour, to allow excess lithiated benzoate **6** to decompose (Supplementary Information). At this temperature, the boronate complex is stable, but, after warming to room temperature (20 °C) for one hour, the 1,2-migration occurred, giving the homologated product **9**. The ageing at −42 °C for one hour is essential to prevent a small amount (about 0.5%) of the product boronic ester reacting with the excess lithiated benzoate and giving over-homologated product. The reaction was then filtered to remove the insoluble lithium salt of 2,4,6-triisopropylbenzoic acid, to give the crude boronic ester that was used directly in a subsequent homologation. Although we were able to conduct up to seven homologations iteratively (without aqueous work-up or purification of any intermediates) and obtain pure material, we found it more reliable to remove by-products using an aqueous work-up after every third homologation.

Having developed an optimized protocol for the homologation of boronic esters, we set about conducting the iterative homologation sequence. We initiated our sequence from biphenyl boronic ester **(*R*)-10** rather than from 4-biphenylboronic acid pinacol ester owing to the latter's poor solubility in Et_2O. Boronic ester **(*R*)-10** was subjected to nine consecutive homologations using lithiated benzoate **(*S*)-6**, with an aqueous work-up being performed after every third homologation, giving boronic ester **11** in 58% yield (Fig. 3a). Each homologation was followed by gas chromatography mass spectrometry (GC–MS), which indicated that very low levels of over- and under-homologation occurred. In fact, at the end of the sequence the product was a 1:97:2 ratio of 9-mer:10-mer:11-mer, demonstrating the extraordinarily high fidelity of each homologation reaction. ^{1}H and ^{13}C NMR showed that it was also essentially one diastereoisomer. As a result of chiral amplification[31], it would also be a single enantiomer. On the basis of the Horeau principle[32], after nine homologations using stannane **5** (10^3:1 e.r.) on boronic ester **10** (~10^2:1 e.r.) the enantiomeric ratio of the major diastereoisomer should be 10^{29}:1, which is considerably greater than Avogadro's number, and so the product is expected to be literally a single enantiomer. An X-ray crystal structure of benzoate ester **12** confirmed the relative stereochemistry of the product.

Having demonstrated a highly effective assembly-line synthesis protocol, we sought to target other specific diastereoisomers. The conformation

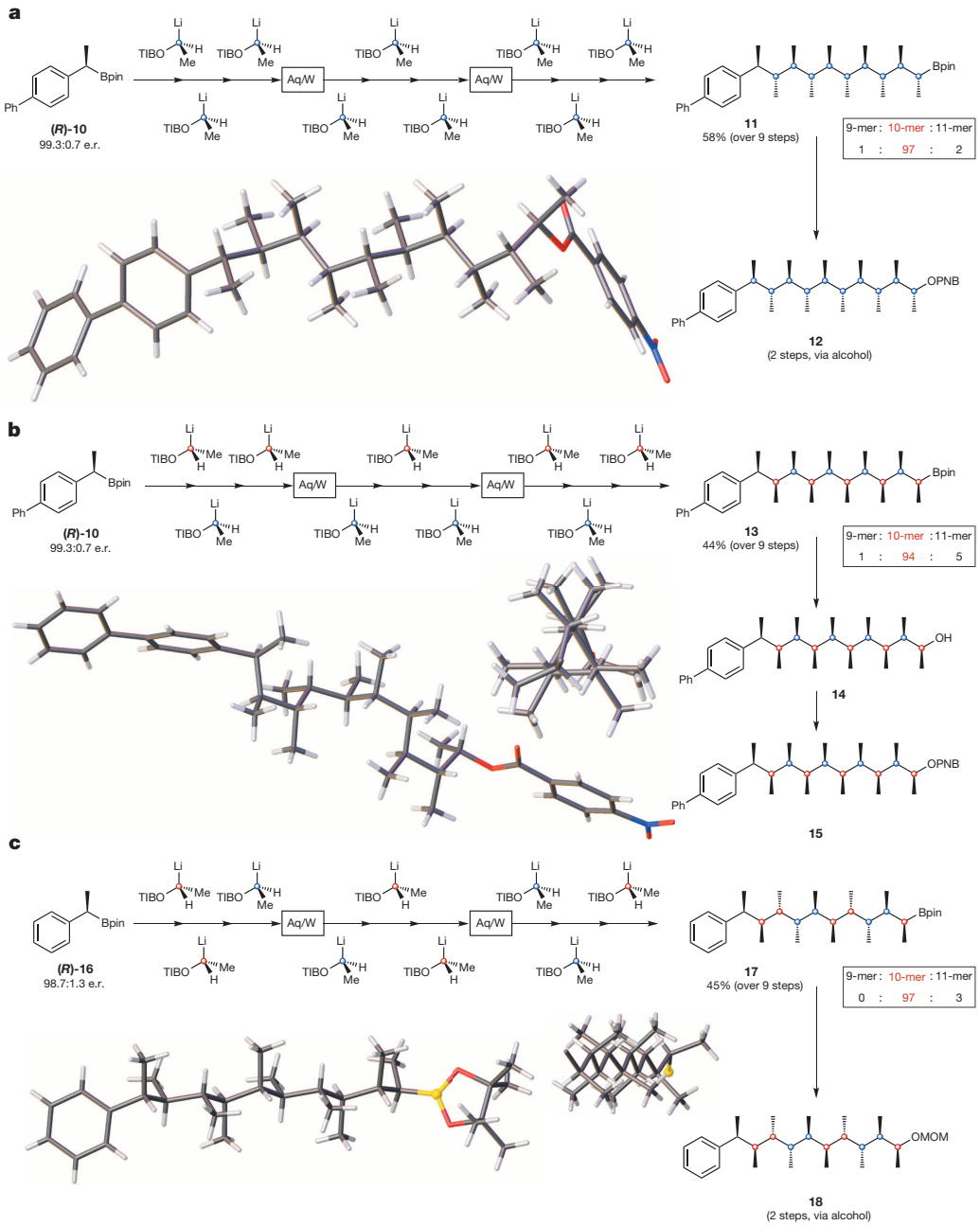

Figure 3 | Iterative assembly-line synthesis. a, Synthesis of the all-*anti* isomer boronic ester **11** and X-ray structure of the *p*-nitro benzoate derivative **12**. **b**, Synthesis of the all-*syn* isomer boronic ester **13** and X-ray structure (two views) of the *p*-nitro benzoate derivative **15**. **c**, Synthesis of the alternating *syn-anti* isomer boronic ester **17** with X-ray structure (two views) and the methoxymethyl ether (MOM) derivative **18**. The X-ray structures show that the all-*syn* isomer adopts a helical conformation, the alternating *syn-anti* isomer adopts a linear conformation, and the all-*anti* isomer does not adopt a regular conformation. Conditions for homologation: (1) addition of boronic ester to lithiated benzoate, −78 °C, 30 min; (2) −42 °C, 1 h; (3) room temperature, 1 h; (4) filter; (5) repeat. The ratios of boronic ester homologues were obtained by GC–MS analysis (Supplementary Information). Aq/W, aqueous work-up; Ph, phenyl; PNB, *p*-nitro benzoate. Blue and red dots specify which carbenoid (**6**) was used and incorporated into the product: blue dots represent **(*S*)-6** carbenoid derived from (−)-sparteine; red dots represent **(*R*)-6** carbenoid derived from (+)-sparteine.

of carbon chains should be controlled by *syn*-pentane interactions (also known as g^+g^- interactions) between the methyl groups[2,33] (Fig. 4a). Although the all-*anti* diastereoisomer **11** or **12** was not expected to adopt a particular low-energy conformation (as confirmed by the X-ray structure), we reasoned that the all-*syn* isomer **13** should adopt a helical conformation and the alternating *syn-anti* diastereoisomer **17** should adopt a linear conformation[2] (Fig. 4b, c). Our unique methodology provided a method to make such molecules and an opportunity to test whether *syn*-pentane interactions alone could control the chain conformation of otherwise flexible molecules.

Attempts to make the all-*syn* isomer, which required alternating between the enantiomers of the stannane, initially proved problematic. Analysis of the second homologation product showed that it was only a 95:5 mixture of diastereoisomers. Careful experimentation revealed the source of the problem. In the first homologation, stannane **(*R*)-5** was used in a slight excess (0.05 equiv. excess) over *n*-BuLi to ensure that no *n*-BuLi, which might react irreversibly with the boronic ester, remained. However, in the second homologation the slight excess of stannane **(*R*)-5** must have equilibrated with **(*S*)-6**, resulting in the reagent having a lower enantiomeric ratio, and so generated mixtures of diastereoisomers (Fig. 2d). The solution to the problem was to control the stoichiometry more precisely, that is, to use a 1.00:1.00 ratio of stannane **5** to *n*-BuLi. Using this modification, the assembly-line synthesis process was launched as before, alternating between the enantiomers of the stannane, and the all-*syn* isomer **13** was prepared in 44% yield (Fig. 3b). As before, each homologation was followed by GC–MS, and at the end of the sequence the product was a 1:94:5 ratio of 9-mer:10-mer:11-mer, again demonstrating the extraordinarily high fidelity of each homologation reaction. ^{1}H and ^{13}C NMR showed that it was also essentially one diastereoisomer and was expected to be a single enantiomer. An X-ray crystal structure of benzoate ester **15** confirmed the relative stereochemistry of the product and showed that in the solid state the flexible carbon backbone of the molecule adopted a perfect right-handed (*P*) helical conformation. The carbon chain does one complete turn every six carbon atoms in the backbone of the molecule.

The synthesis of the alternating *syn-anti* diastereoisomer required the use of alternating pairs of the stannane enantiomers. Performing the iterative homologation from biphenyl boronic ester **(*R*)-10** led to insoluble intermediates after six homologations, and so the phenyl analogue **(*R*)-16** was used instead. Re-launching the iterative homologation sequence as before from boronic ester **(*R*)-16**, with an aqueous work-up after every third homologation, gave boronic ester **17** in 45% yield (Fig. 3c). As before, each homologation was followed by GC–MS, and at the end of the sequence the product was a 0:97:3 ratio of 9-mer:10-mer:11-mer. ^{1}H and ^{13}C NMR showed that it was also essentially one diastereoisomer and was expected to be a single enantiomer. The boronic ester **17** was itself crystalline, and X-ray crystallography not only confirmed its structure but also showed that the molecule adopted a perfectly linear conformation.

NMR and computational analysis of solution structures

The X-ray structures show that in the solid state, the all-*syn* isomer **15** adopts a helical conformation and that the alternating *syn-anti* isomer **17** adopts a linear conformation, as predicted, on the basis of conformational control dominated by minimizing *syn*-pentane interactions. This is reminiscent of the difference between the respective structures adopted by isotactic and syndiotactic polypropylene[34] and O'Hagan's polyfluorinated alkanes[35]. In the case of polypropylene the isotactic form is helical, whereas the syndiotactic form exhibits more complex behaviour, with linear structures in some cases. In the case of polyfluorinated alkanes, the all-*syn* isomer adopted a helical conformation and the alternating *syn-anti* isomer adopted a linear conformation, although here the preference was dominated by electronic rather than steric effects. However, crystal packing will influence conformation in the solid state, and we were keen to examine whether similar conformations existed in solution. We note that although small molecules with only one or two rotatable bonds can adopt predominantly one conformation, larger molecules with multiple rotatable bonds do not, because the enthalpic gain in minimizing *syn*-pentane interactions is outweighed by the entropic cost of greater rigidity: this is illustrated by alkanes **19**, **20** and **21**, which are of increasing chain length and showed 91%, 76% and just 58% preference for a single conformer[36] (Fig. 4d). It is therefore extremely difficult to make larger molecules that adopt largely one conformation. In our case, we expected an increase in the enthalpic gain in minimizing *syn*-pentane interactions because we have twice the number of such interactions with no increase in the number of rotatable bonds, and so expected a higher preference for a single conformer. However, this gain is moderated by the increase in the number of gauche interactions, which reduces the difference in energy between different conformers. We therefore embarked on establishing the solution conformation using a combined experimental and computational approach.

Despite the very congested nature of the spectra, NMR spectroscopy of all-*syn* isomer **14** and *syn-anti* isomer **18** yields an extensive set of accurate interproton distances[37,38] (derived from measurements of the nuclear Overhauser effect) and ^{1}H–^{1}H and ^{1}H–^{13}C couplings. Using *ab initio* calculated structures, relative free energies and spin–spin couplings for the family of conformers for each species, these observations can be deconvolved to provide an integrated overview of solution behaviour (Fig. 5).

Molecular mechanics was used to exhaustively explore conformational space for model compounds **14a** and **18a** (analogues of **14** and **18**, respectively, but with truncated end-groups; 9,710 and 3,970 conformers were respectively assessed). Refined structures, population estimates and predicted *J* couplings were then obtained using electronic structure theory (MP2 with explicit correlation[39] using density functional theory-optimized structures and a continuum solvation correction) for a smaller number of conformers of **14a** and **18a** (66 and 50, respectively), on the basis of all low-energy molecular mechanics structures plus a few manually selected structures suggested by the NMR analysis.

In both cases, calculations predict that several different conformers are populated at room temperature; however, in each case, the preference for linear and helical structures is very strong (Fig. 5a) with each C–C bond along the carbon chain dominated by a single dihedral angle. For **18a**, one linear conformer is predicted to represent 95% of the population, versus 74% for a helical conformer in the case of **14a** (ignoring end-group rotamers). This is one of the highest preferences found so far for a flexible molecule, and highlights the value in maximizing the density of *syn*-pentane interactions to control conformation. The calculated and measured NMR properties for **14**/**14a** and **18**/**18a** agree very well, provided that all reasonably highly populated conformers are included (Fig. 5b), and the levels of agreement are in line with those obtained for accurate conformational assignments in less flexible molecules[37,40,41]. The corresponding alcohol of the all-*anti* isomer boronic ester **11** appears highly disordered by NMR and computational analysis, as predicted (Supplementary Information).

The solution properties thus show that these systems behave as ensembles of structures from which the dominant linear and helical character clearly emerges. The calculated major low-energy conformers for the helical molecule **14a** and the linear molecule **18a** are shown in Fig. 5c. However, although a tight helix is observed in the X-ray structure of **15**, which completes one turn for every six carbon atoms, we found that the solution conformation of **14**/**14a** is a loose helix, where the carbon chain completes one turn for every nine carbon atoms. This loosening results from significant deviation of the dihedral angles along the chain from the ideal angles (60° or 180°) observed in the solid state. As shown in Fig. 4e, as the chain coils the greater interaction between the (larger) alkyl chains forces the chains apart slightly (>60° dihedral angles), resulting in a small opening of the helix that is counterbalanced by a decrease in the angle between the smaller methyl groups[33] (<60° dihedral angles).

In solution a left-handed helix (*M*) is observed for **14**/**14a**, whereas in the solid state the same diastereoisomer **15** adopts a right-handed helix (*P*). This is probably due to the different end-groups (OH versus

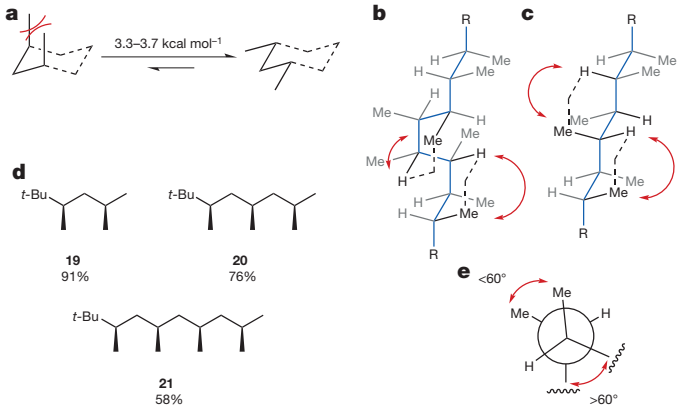

Figure 4 | The effect of *syn*-pentane and other intramolecular steric interactions on conformation of molecules. **a**, Energy penalty incurred with a *syn*-pentane interaction. **b**, Expected helical conformation of the all-*syn* isomer **13**, where methyl groups along the carbon chain avoid *syn*-pentane interactions (red arrows). **c**, Expected linear conformation of the alternating *syn-anti* isomer **17**, where methyl groups along the carbon chain avoid *syn*-pentane interactions (red arrows). **d**, Carbon chains bearing *syn*-1,3-dimethyl units, and the percentage occupancy of a single dominant conformation[36]. **e**, Minor distortion in the conformation of the carbon chain of the all-*syn* isomer **14** (helical molecule), as determined by NMR and computational analysis. Because of 1,4-steric interactions, the carbon chain is pushed farther apart causing significant deviation from the ideal dihedral angles.

O-(4-nitro)benzoate). For efficient crystal packing, the nitrobenzoate group will prefer an extended (*anti*) conformation at θ_I (Fig. 5), acting as the principal large inductor group, and this terminal stereocentre induces the sense of handedness down the carbon chain[36]. Owing to the pseudo-change in chirality of this stereocentre, the opposite helical sense is created down the carbon chain.

Conclusion

We have developed a practical method for the reagent-controlled homologation of a boronic ester, which can be conducted iteratively and with total stereocontrol. Because these reactions are totally dominated by reagent control, no matched and mismatched effects are observed, enabling different stereoisomers to be targeted and prepared with equal ease. In addition, each chain extension step generates a new boronic ester, ready and primed for further homologation without requiring extra manipulation, making the process considerably more rapid and streamlined than alternative iterative strategies, which usually require several functional group interconversions between chain extension steps[42–45]. However, iterative Suzuki–Miyaura cross-coupling[46–48], zirconium-catalysed asymmetric carboalumination reactions[49] and triple-aldol cascade reactions[50] represent notable exceptions where additional steps between iterations are not required.

Thus, using our iterative homologation sequence we have been able to convert simple boronic esters into complex molecules bearing ten contiguous methyl substituents with full stereocontrol. Different stereoisomers have been targeted and their conformations were determined by X-ray crystallography and NMR and analysed computationally. All three methods of analysis showed that both in the solid state and in solution the all-*anti* isomer did not adopt a particular conformation, whereas the all-*syn* isomer adopted a helical conformation and the alternating *syn-anti* isomer adopted a linear conformation. In the latter two cases, the methyl groups along the carbon chain were able to force the molecule to adopt these particular conformations as a result of *syn*-pentane interactions alone. By incorporating the effect of *syn*-pentane interactions on conformation and using the iterative homologation process we have developed, molecules with predictable shape can now be rationally designed and created. This should have an impact in all areas of molecular sciences where bespoke molecules are required.

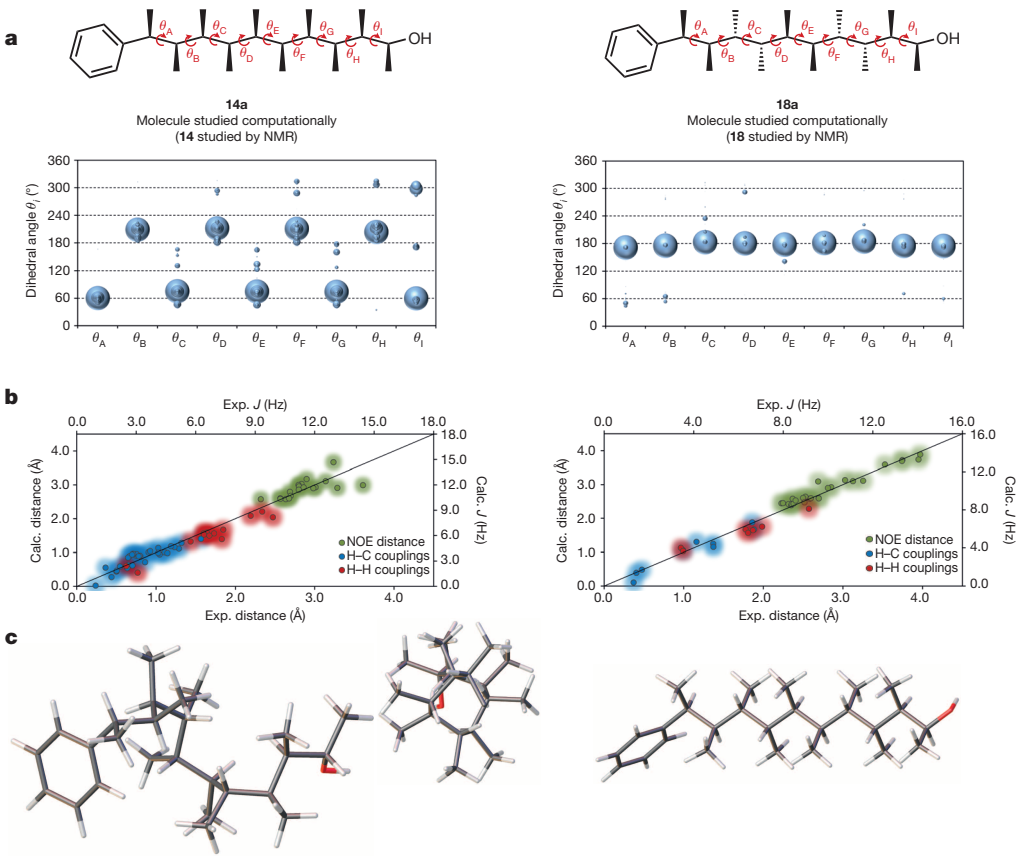

Figure 5 | Solution conformations of compounds 14 and 18. **a**, Theoretically predicted properties of the ensemble of conformations of model compounds **14a** and **18a**. Each populated conformer is shown as nine dots, of size proportional to the calculated relative abundance of that conformer, and with a position defined by the calculated value of the corresponding backbone dihedral angle, θ_i ($i = A, \ldots, I$). **b**, Correlation between theoretically predicted NMR properties (interproton distance, green (NOE; nuclear Overhauser effect); ^1H–^1H and ^1H–^{13}C scalar J couplings, respectively red and blue) for the ensemble of conformers of **14a** (left) and **18a** (right) and experimentally observed values (interproton distance, bottom; scalar J couplings, top) of **14** and **18**. Each dot is associated with errors of ~5% in interproton distance and approximately ±1 Hz in J. The calculations predict **14a** to be predominantly helical in nature, with **18a** overwhelmingly populating linear conformers. NMR measurements in solution are completely in line with this predicted behaviour. **c**, Structure of the calculated dominant conformations of **14a** (left) and **18a** (right). Grey, carbon; white, hydrogen; red, oxygen.

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Author Contributions V.K.A. designed the project. M.B. conducted and designed the experiments and analysed the data. S.E. performed computational studies and analysed the data with J.N.H. J.R.B. and S.P.B. performed the NMR experiments and analysed the data with C.P.B. M.P.W. conducted the preliminary experiments with lithiated carbamates. S.B. optimized the recrystallization conditions for stannane **5**. J.W.D. supervised M.B. while working at Novartis. V.K.A., M.B., J.N.H. and C.P.B. wrote the manuscript.

Author Information X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database with accession numbers CCDC 993442 (**12**), CCDC 993443 (**15**) and CCDC 993441(**17**). Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to V.K.A. (v.aggarwal@bristol.ac.uk), C.P.B. (craig.butts@bristol.ac.uk) for NMR work or J.N.H. (jeremy.harvey@bristol.ac.uk) for computational work.