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High Precision Assembly Line Synthesis for Molecules with Tailored Shapes

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Abstract

Molecular assembly lines, where molecules undergo iterative processes involving chain elongation and functional group manipulation are hallmarks of many processes found in Nature. We have sought to emulate Nature in the development of our own molecular assembly line through iterative homologations of boronic esters. Here we report a reagent (α -lithioethyl triisopropylbenzoate) which inserts into carbon-boron bonds with exceptionally high fidelity and stereocontrol. Through repeated iteration we have converted a simple boronic ester into a complex molecule (a carbon chain with ten contiguous methyl groups) with remarkably high precision over its length, its stereochemistry and therefore its shape. Different stereoisomers were targeted and it was found that they adopted different shapes (helical/linear) according to their stereochemistry. This work should now enable scientists to rationally design and create molecules with predictable shape, which could have an impact in all areas of molecular sciences where bespoke molecules are required.

Introduction

Nature has evolved highly sophisticated machinery for organic synthesis. One of the most beautiful examples 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 formed¹. The process amounts to a molecular assembly line. By iteration and variation of the processing

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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. optimised the recrystallisation 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.

Reprints and permissions information is available at www.nature.com/reprints. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (<http://www.ccdc.cam.ac.uk/>) under deposit numbers CCDC 993442 (**12**), CCDC 993443 (**15**) and CCDC 993441 (**17**).

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enzymes, Nature manufactures an enormously diverse array of polyketides, many of which display high chemical complexity and biological activity (Figure 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 (Figure 1b). By making specific molecules in this way, we are also able 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 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. Hoffmann has 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^{2,3,4,5,6,7,8}. Despite this structural predisposition, the molecule is still flexible enough to change its shape when required (e.g. for transport across membranes). In order 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 prepare² in contrast to 1,3-deoxypolypropionates^{9,10}. In this paper we show 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 10 contiguous methyl groups and no other functionality, we show that the methyl substituents are able to exquisitely control the conformation of the molecule. 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 shape¹¹. Indeed, the iterative homologation process we have developed enables one to rationally design and create molecules with predictable shape even 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} or a reagent-controlled method in which chirality in the reagent controls the stereochemistry¹⁴. The latter method is more direct and more versatile as it enables ready access to alternative stereoisomers. We (and others^{15,16,17,18}) have focussed on reagent-controlled methodology and we have found that Hoppe's lithiated carbamate^{19,20,21} homologate boronic esters with high stereocontrol and have applied this methodology in the synthesis of a number of natural products^{22,23,24,25,26}. In order to apply this methodology to iterative homologations we set the goal of creating a carbon chain with 10 contiguous methyl substituents with total stereocontrol (Figure 1b).

This is a daunting task as each step must go to completion without over- or under-homologation and it must also proceed with full stereocontrol in order to obtain pure material, since 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 10 iterative homologations a binomial distribution of products would be obtained in which the major 10mer was only 82% pure. If each homologation occurred with 98:2 enantioselectivity then after 10 iterative homologations the product would be a mixture of diastereoisomers which was only 82% pure, which again was undesirable. As a further illustration of the challenge, Blakemore recently reported a triple, one-pot homologation of a boronic ester using an α -chloroalkyllithium reagent. In the best case, this gave rise to a mixture of the trimer (19%, 5:80:9:6 dr), dimer (27%, 78: 22 dr) and monomer (5%)²⁷.

Unfortunately, Hoppe's lithiated carbamates (**2**) (Figure 2a) which we had used extensively in synthesis, could not be used as we found that (i) they were prone to give significant quantities of over- and under-homologation products with hindered boronic esters and (ii) they could be obtained in only 97: 3 e.r.. We therefore turned to α -metallated hindered benzoates as alternatives to Hoppe's carbamates as we had found that the superior leaving group ability of the ester over the carbamate enabled difficult homologations to proceed more effectively²⁸. After exploring various alternatives, we found that deprotonation of ethyl tri-isopropylbenzoate **3** with sBuLi/(–)-sparteine²⁸ followed by trapping with Me₃SnCl 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 (Figure 2b)²⁹. Using this method, both enantiomers of the stannane were easily prepared on multigram scale, using commercially available (+)- or (–)-sparteine, without the need for chromatography, and 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 optimised protocol had to be developed for iterative homologation (Figure 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 to the boronate complex. The reaction mixture was then kept at –42 °C for one hour, to allow excess lithiated benzoate **6** to decompose (see SI for details). At this temperature the boronate complex is stable, but, after warming to room temperature 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 which was used directly in a subsequent homologation. Although we were able to conduct up to seven homologations iteratively (without aqueous workup or purification of any intermediates) and obtain pure material, we found it more reliable to remove by-products using an aqueous workup after every third homologation.

Having developed an optimised 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 due to the latter's poor solubility in Et₂O. 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 (Figure 3a). Each homologation was followed by GCMS 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 9mer:10mer:11mer demonstrating the extraordinarily high fidelity of each homologation reaction. ¹H and ¹³C NMR showed that it was also essentially one diastereoisomer. As a result of chiral amplification³¹, it would also be a single enantiomer. Based on the Horeau principle³², after 9 homologations using stannane **5** (10³:1 e.r.) on boronic ester **10** (~10²:1 e.r.) the e.r. of the major diastereoisomer should be 10²⁹:1, 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. Hoffmann has proposed that the conformation of carbon chains should be controlled by *syn*-pentane interactions (also known as g⁺g⁻ interactions) between the methyl groups (Figure 4a)^{2,33}. Whilst the all *anti* diastereoisomer **11/12** was not expected to adopt a particular low energy conformation (and the X-ray structure confirmed that), we reasoned that the all *syn* isomer **13** should adopt a helical conformation and the alternating *synanti* diastereomer **17** should adopt a linear conformation (Figure 4b/c)². 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 2nd 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 remained, which might react irreversibly with the boronic ester. However, in the second homologation the slight excess of stannane (**R**)-**5** must have equilibrated with (**S**)-**6** resulting in lower e.r. of the reagent and so generated mixtures of diastereoisomers (Figure 2d). The solution to the problem was to control the stoichiometry more precisely i.e. 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 (Figure 3b). As before, each homologation was followed by GCMS and at the end of the sequence the product was a 1: 94: 5 ratio of 9mer:10mer:11mer again demonstrating the extraordinarily high fidelity of each homologation reaction. ¹H and ¹³C 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 using 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 workup after every third homologation, gave boronic ester **17** in 45% yield (Figure 3c). As before, each homologation was followed by GCMS and at the end of the sequence the product was a 0:97:3 ratio of 9mer: 10mer: 11mer. ¹H and ¹³C 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 not only did the X-ray confirm its structure but it showed that the molecule adopted a perfectly linear conformation.

Solution structure and computational analysis of the all *syn* isomer **14** and the alternating *syn-anti* isomer **18**

The X-ray structures show that in the solid state, the all *syn* isomer **15** adopts a helical conformation and the alternating *syn-anti* isomer **17** adopts a linear conformation, as predicted, based on conformational control dominated by minimising *syn*-pentane interactions. This is reminiscent of the difference in structures adopted by isotactic and syndiotactic polypropylene³⁴ and O'Hagan's polyfluorinated alkanes³⁵. In the case of polypropylene the isotactic form is helical, while 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. It should be noted that whilst small molecules with just 1-2 rotatable bonds can adopt predominantly one conformation, Hoffmann has shown that larger molecules with multiple rotatable bonds do not, because the enthalpic gain in minimising *syn*-pentane interactions is outweighed by the entropic cost of greater rigidity. This is illustrated with alkanes **19**, **20**, **21** of increasing chain length which showed 91%, 76%, and just 58% preference for a single conformer (Figure 4d)³⁶. He concluded that 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 minimising *syn*-pentane interactions since we have twice the number of such interactions without increasing 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 by a combined experimental and computational approach.

Despite the very congested nature of the spectra, NMR spectroscopy of all *syn* isomer alcohol **14** and *syn-anti* isomer ether **18** yields an extensive set of accurate interproton distances (derived from nuclear Overhauser enhancement (NOE) measurements)^{37,38} and ¹H-¹H and ¹H-¹³C 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 deconvoluted to provide an integrated overview of solution behaviour (Figure 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; 9710 and 3970 conformers respectively were assessed). Refined structures, population estimates and predicted *J* couplings were then obtained using electronic structure theory (MP2 with explicit correlation³⁹ using DFT optimised structures and a continuum solvation correction) for a smaller number of conformers of **14a** and **18a** (66 and 50 respectively), based on 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 structure is very strong (Figure 5a) with each carbon-carbon bond along the carbon chain dominated by a single dihedral angle. For **18a**, one linear conformer is predicted to represent 95% of the population, vs. 74% for a helical conformer in the case of **14a** (ignoring end group rotamers). This is one of the highest preferences found to date for a flexible molecule and highlights the value in maximising 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 (Figure 5b), and the quality of agreements 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 (see SI for details).

The solution properties thereby 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 Figure 5c. However, whilst a tight helix is observed in the X-ray structure of **15** which does one complete turn for every six carbon atoms, we found that the solution conformation of **14/14a** is a loose helix, where the carbon chain does one complete turn for every nine carbon atoms. The observed 'loosening', results from significant deviation of the dihedral angles along the chain away from the idealised angles (60/180 degrees) observed in the solid-state. As shown in Figure 4e, as the chain coils, the greater interaction between the (larger) alkyl chains forces the chains apart slightly (>60 degree dihedral angles) resulting in a small opening of the helix, which is counterbalanced by compressing the angle between the smaller methyl groups (<60 degree dihedral angles)³³.

In solution, a left-handed helix (*M*) is observed for **14/14a** whilst in the solid state the same diastereoisomer **15** adopts a right-handed helix (*P*). This is probably due to the different end groups (OH vs O-(4-nitro)benzoate). For efficient crystal packing the nitrobenzoate group

will prefer an extended (*anti*) conformation at θ_1 (Figure 5), acting as the principal large inductor group, and this terminal stereocenter induces the sense of handedness down the carbon chain³⁶. Due to the pseudo-change in chirality of this stereocenter, the opposite helical sense is created down the carbon chain.

Conclusions

In summary, we have developed a practical method for the reagent-controlled homologation of a boronic ester, which can be conducted iteratively and with total stereocontrol. As these reactions are totally dominated by reagent control, no matched and mis-matched 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. This contrasts with alternative iterative strategies which usually require several functional group interconversions between chain extension steps^{42,43,44,45}. However, Burke's iterative Suzuki-Miyaura cross-coupling^{46,47,48}, Negishi's zirconium catalysed asymmetric carboalumination reaction⁴⁹ and Yamamoto's aldol reaction⁵⁰ 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 10 contiguous methyl substituents with full stereocontrol. This is the longest array of contiguous alkyl substituents along a carbon chain reported to date. Different stereoisomers have been targeted and their conformations were determined by X-ray 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, but 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 enabling science should have an impact in all areas of molecular sciences where bespoke molecules are required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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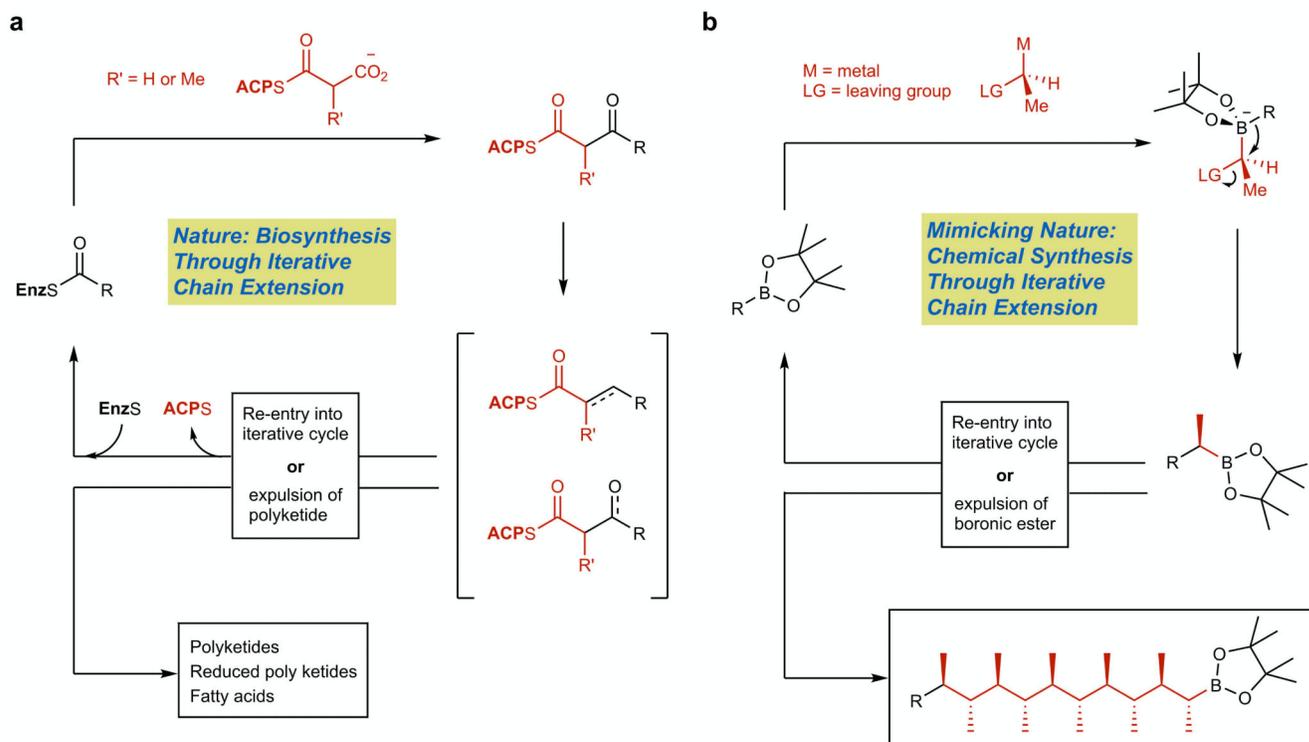


Figure 1. Iterative approaches to assembly line synthesis

a Example of polyketide biosynthesis where successive cycles of chain extension and

functional group interconversions generate a diverse array of complex molecules. **b**

Proposed reagent controlled homologation of boronic esters where successive cycles of chain extension enable rapid and streamlined synthesis of stereodefined carbon chains.

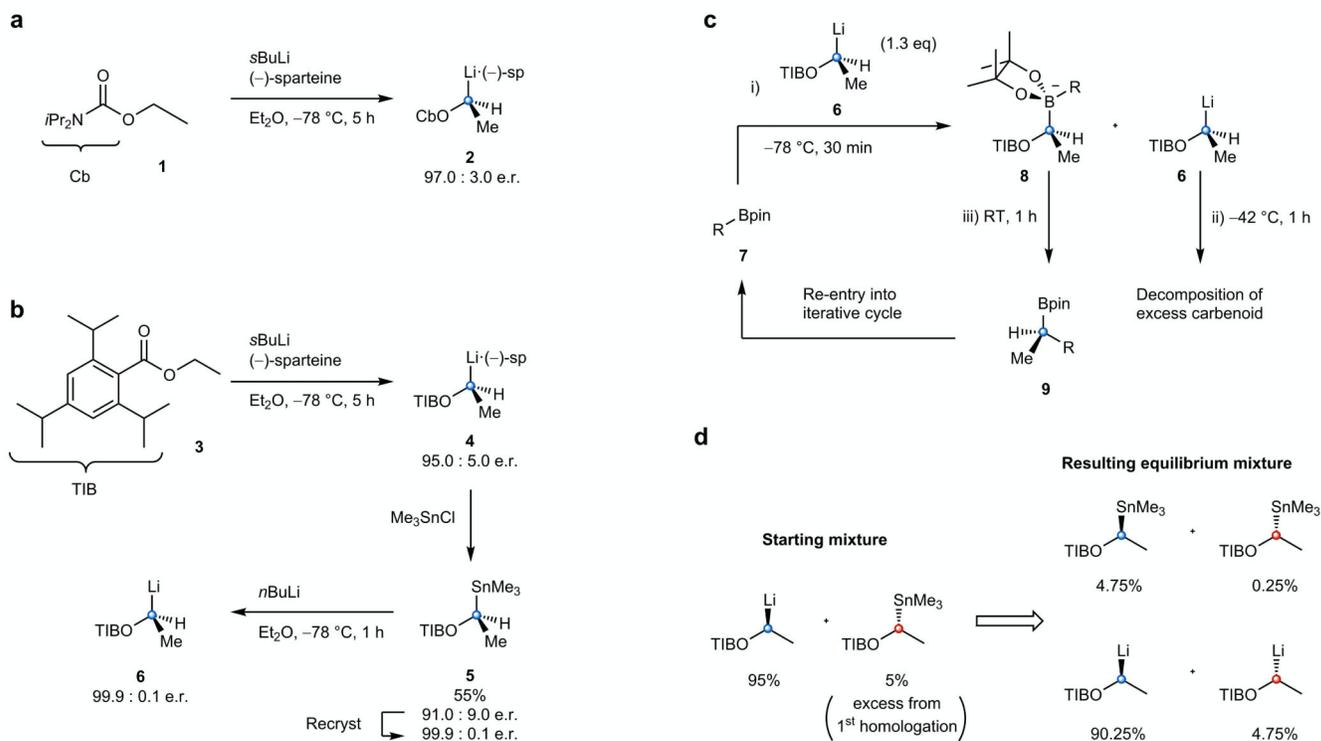


Figure 2. Methodology used for homologation of boronic esters

a Method for the generation of Hoppe's lithiated carbamate. **b** Method for the generation of α -lithiated hindered benzoate **6** with high e.r. from stannane **5**. **c** Optimised protocol for iterative homologation of boronic esters. pin = pinacol. Carbenoid **2** was not suitable for iterative homologations whereas carbenoid **6** was suitable and the protocol for its successful use is shown in pane **c**. **d** Racemisation 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 e.r. (~95:5 e.r.).

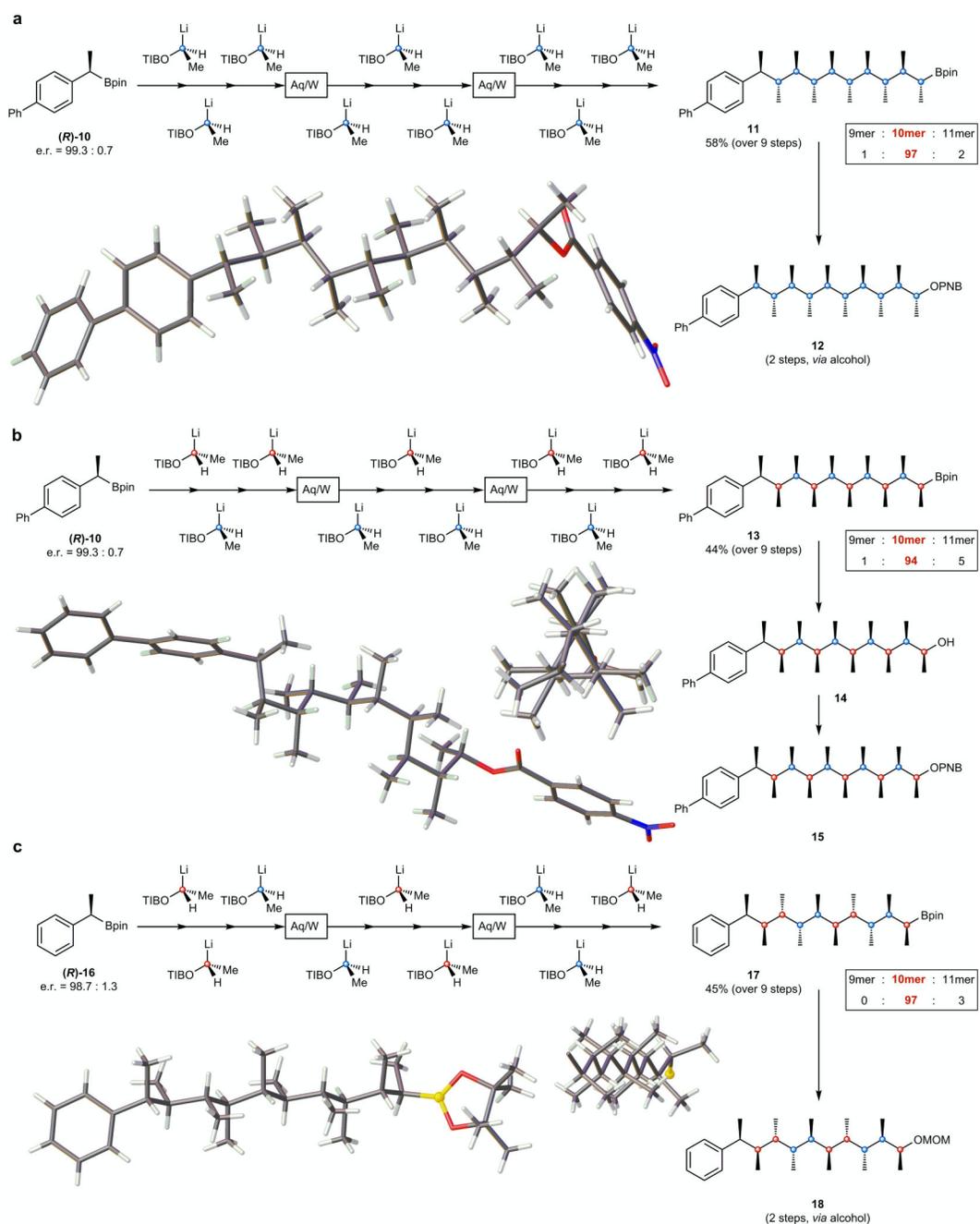


Figure 3. Iterative assembly line synthesis

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 MOM ether 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: a) addition of

boronic ester to lithiated benzoate, $-78\text{ }^{\circ}\text{C}$, 30 min b) $-42\text{ }^{\circ}\text{C}$, 1 h c) room temperature, 1 h, d) filter e) repeat. The ratios of boronic ester homologues were obtained by GCMS analysis (see SI). pin = pinacol; Ar = PhC_6H_4 .; PNB = *p*-nitro benzoate; Aq/W = aqueous workup.

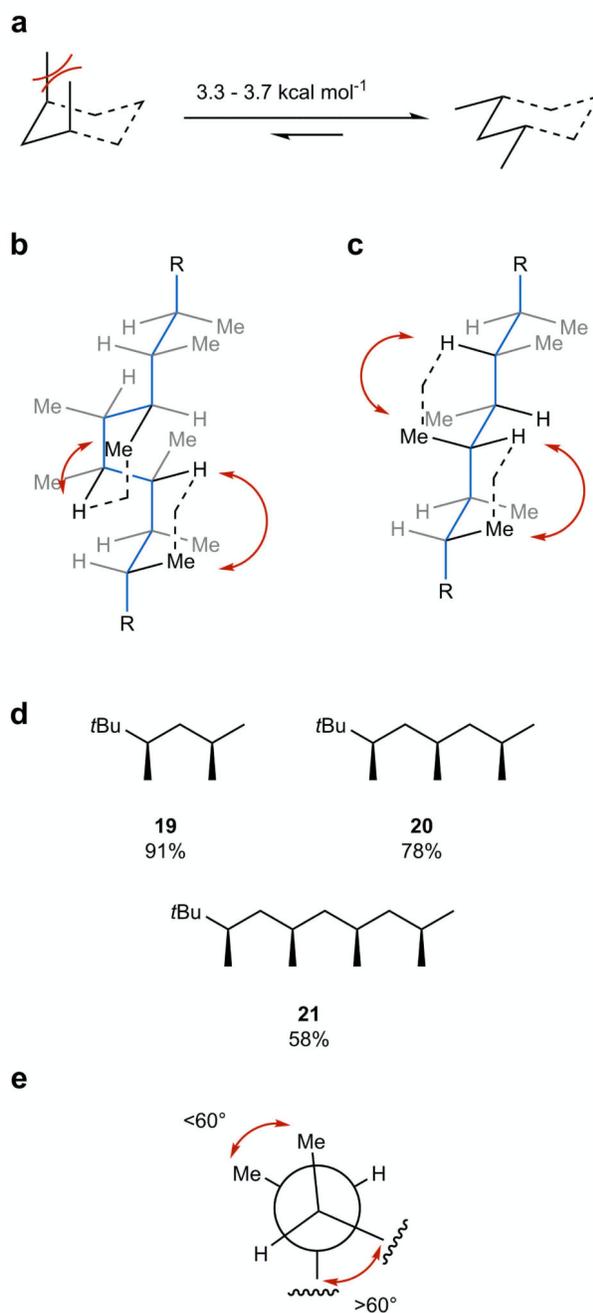


Figure 4. The effect of *syn*-pentane and other intramolecular steric interactions on conformation of molecules

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** Hoffmann's examples of carbon chains bearing *syn*-1,3-dimethyl units and the percentage occupancy of a single dominant conformation. **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 further apart causing significant deviation from the idealised dihedral angles.

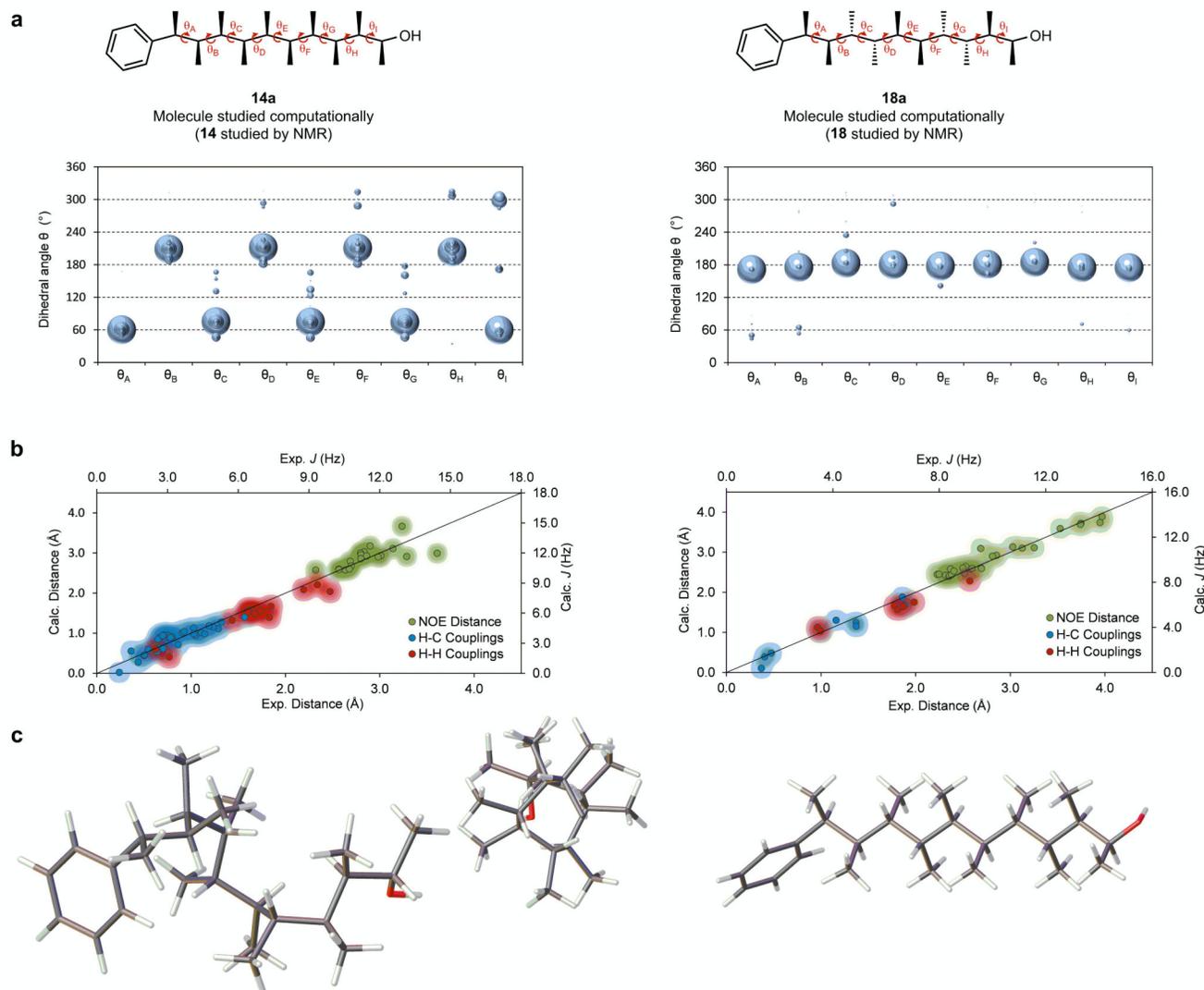


Figure 5. Solution conformations of compounds 14 and 18

a Theoretically predicted properties of the ensemble of conformations of model compounds **14a** and **18a**. Each populated conformer is shown as 9 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 . **b** Correlation between theoretically predicted NMR properties (interproton-distance, green, and ^1H - $^1\text{H}/^1\text{H}$ - ^{13}C scalar j -couplings, red and blue) for the ensemble of conformers of **14a** and **18a** and experimentally observed values (interproton-distance, bottom and scalar J -couplings, top) of **14** and **18**. Each dot is shown with a radius related to the expected experimental deviation of the corresponding property. 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** and **18a**.