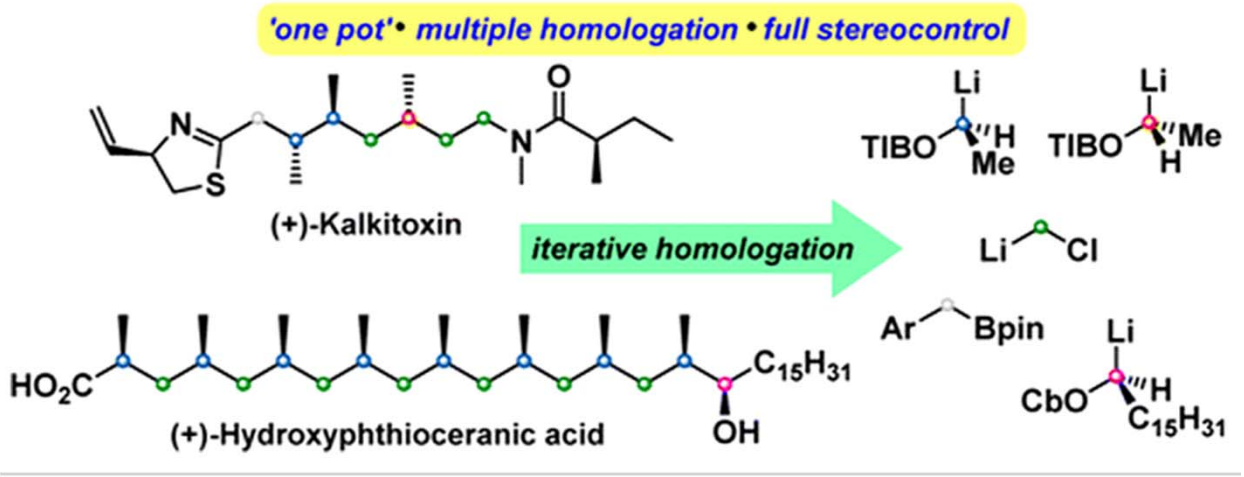
Toward Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis



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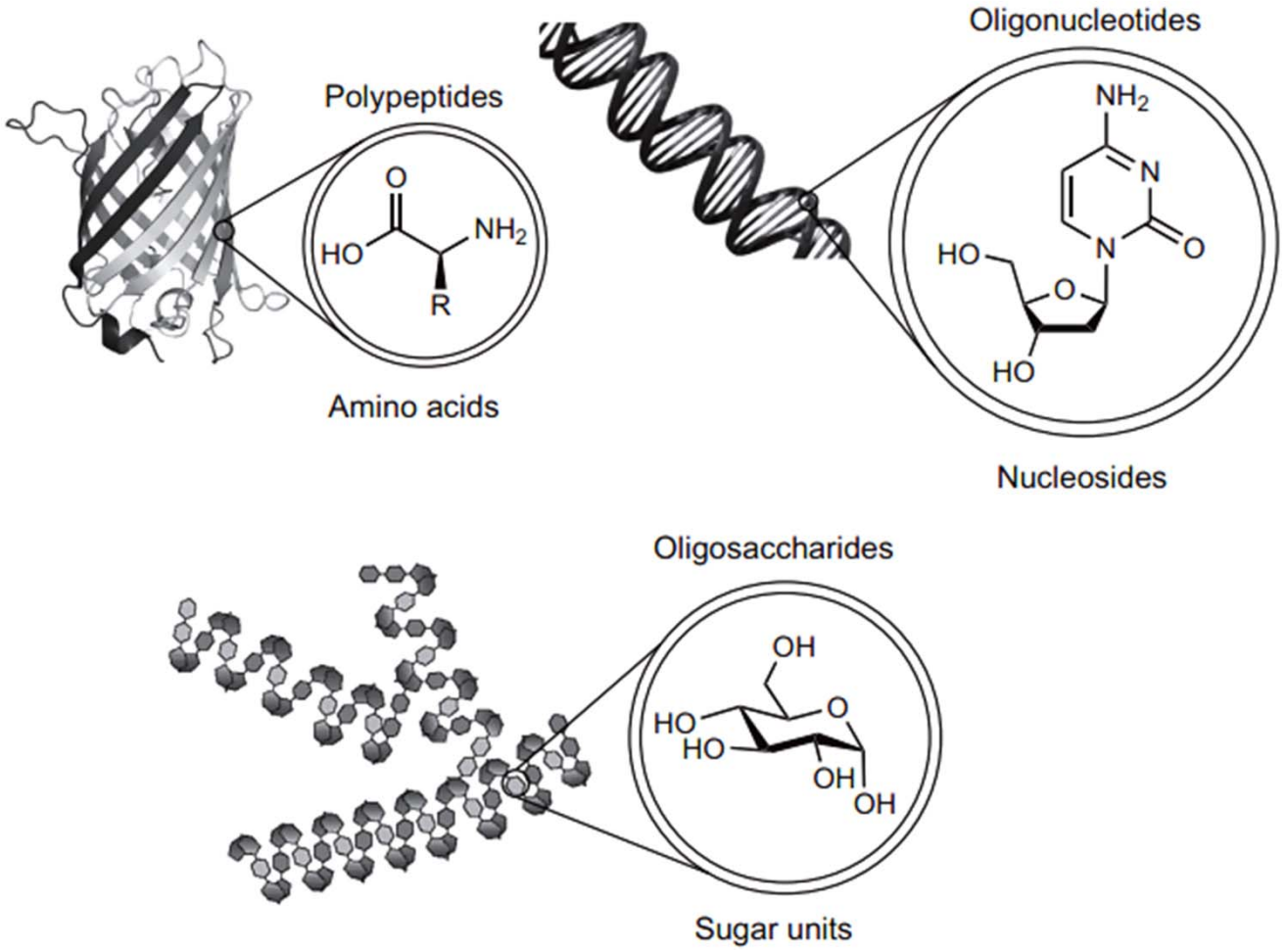
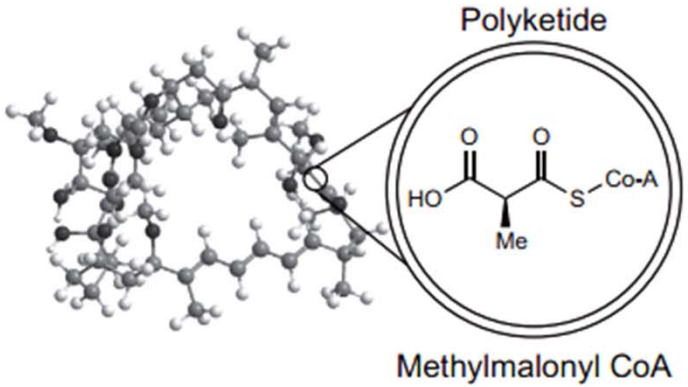
1. Iterative Assembly

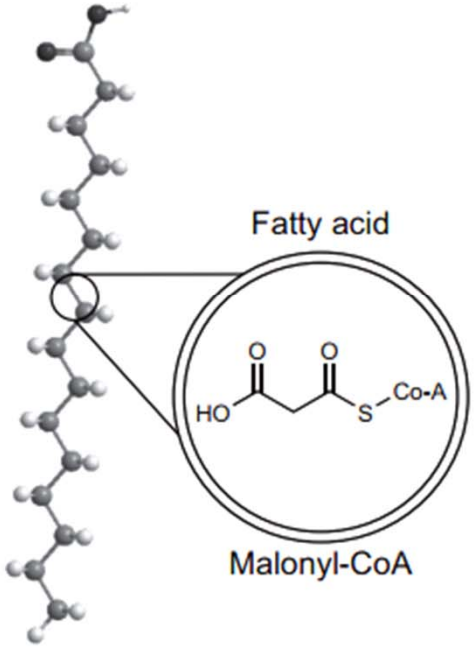


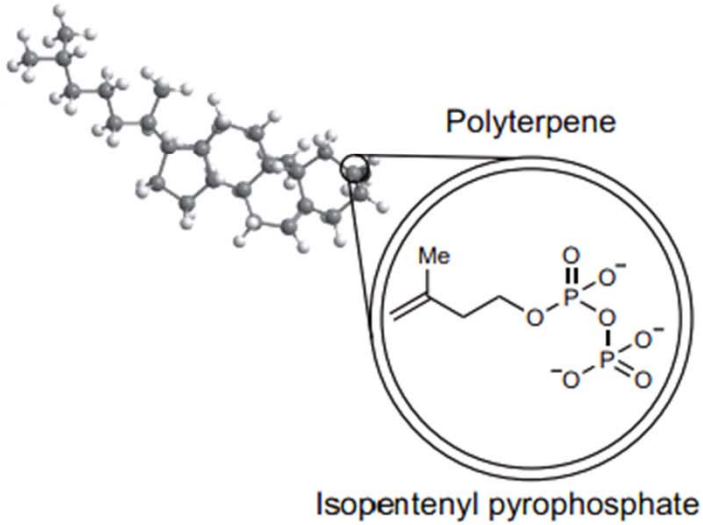
Woerly, E. M.; Roy, J.; Burke, M. D. *Nature Chem*. **2014**, *6*, 484

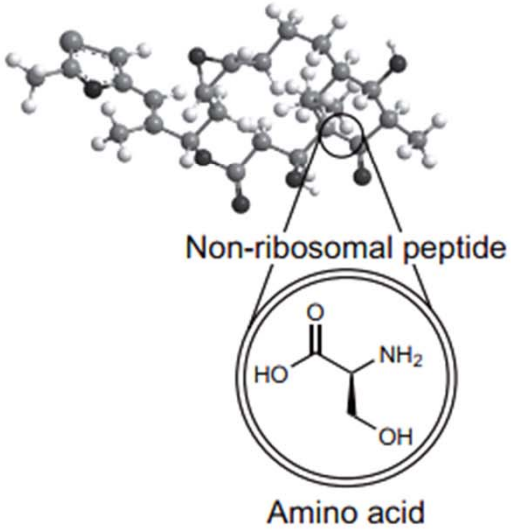
1. Iterative Assembly



Systematic approach based on building blocks should make many **small molecules similarly attainable**







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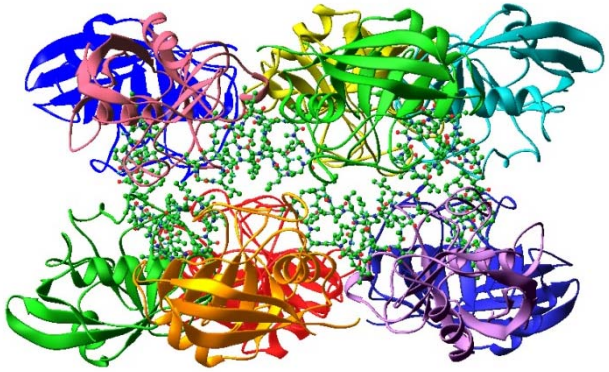
2. Iterative Strategies

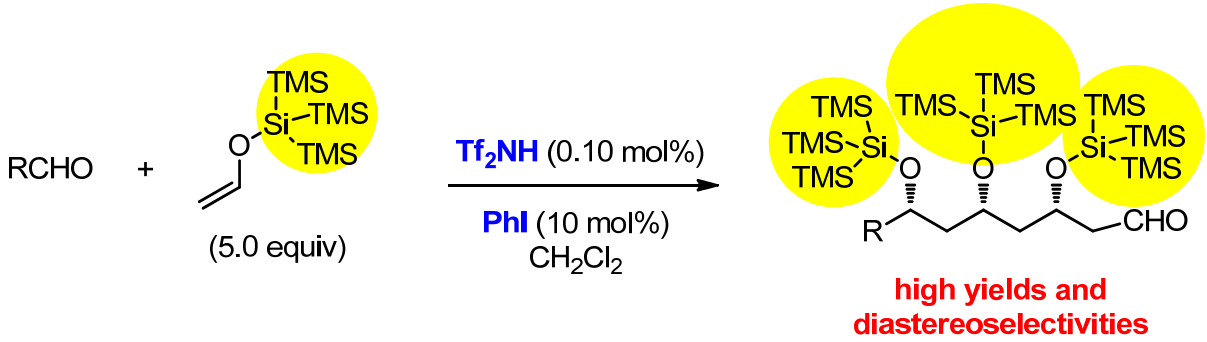


Iterative Strategies

Biological processes — **Chemical synthesis**

FG interconversions between chain-extension steps

1. Triple aldol cascade reaction

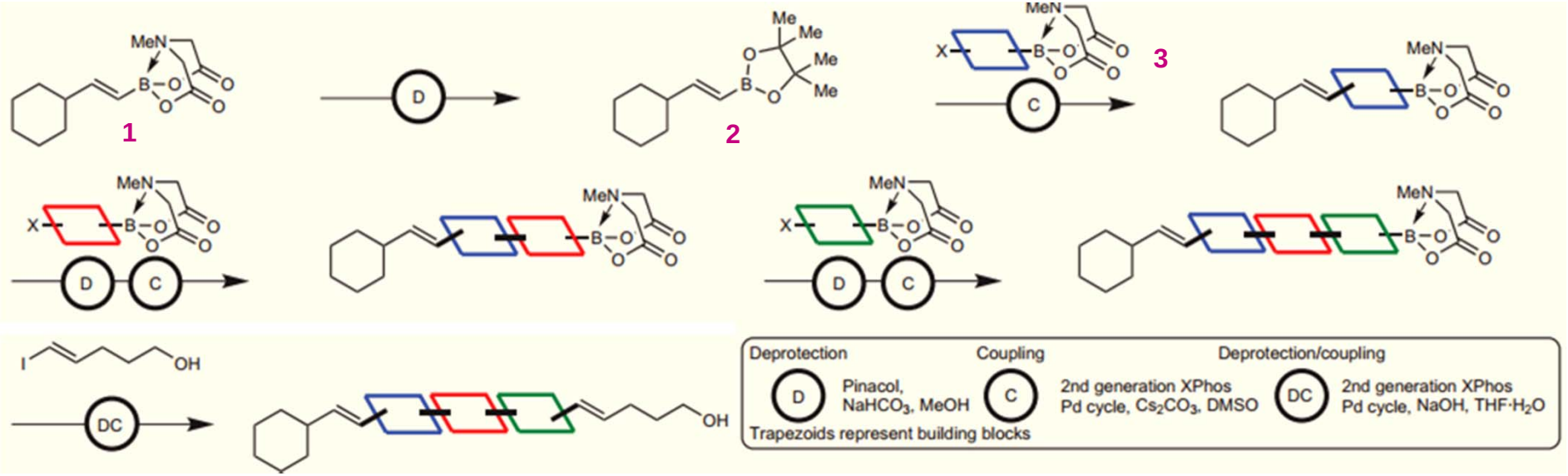


Brian, J. A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 2747

2. Iterative Strategies

2. Synthesis of most polyene natural product motifs using just 12 building blocks and one coupling reaction

How many bifunctional MIDA boronate building blocks would be required to make most of the polyene motifs found in nature ?



1) MIDA boronate
2) Alkenyl pinacol boronate
3) Haloalkenyl MIDA boronate

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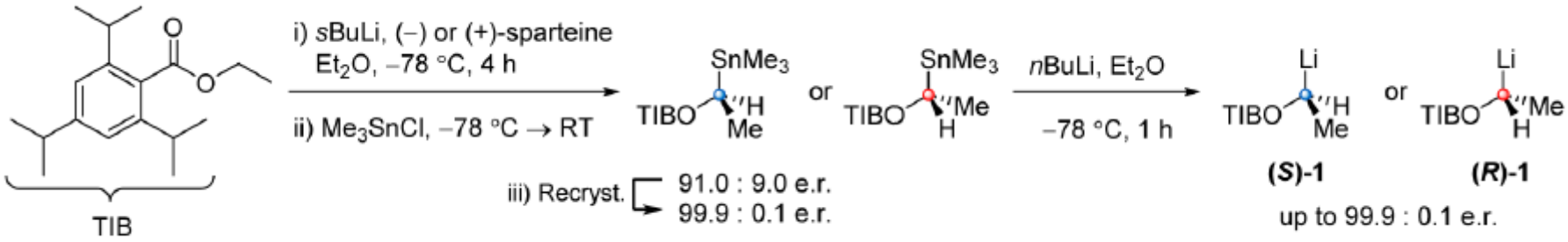
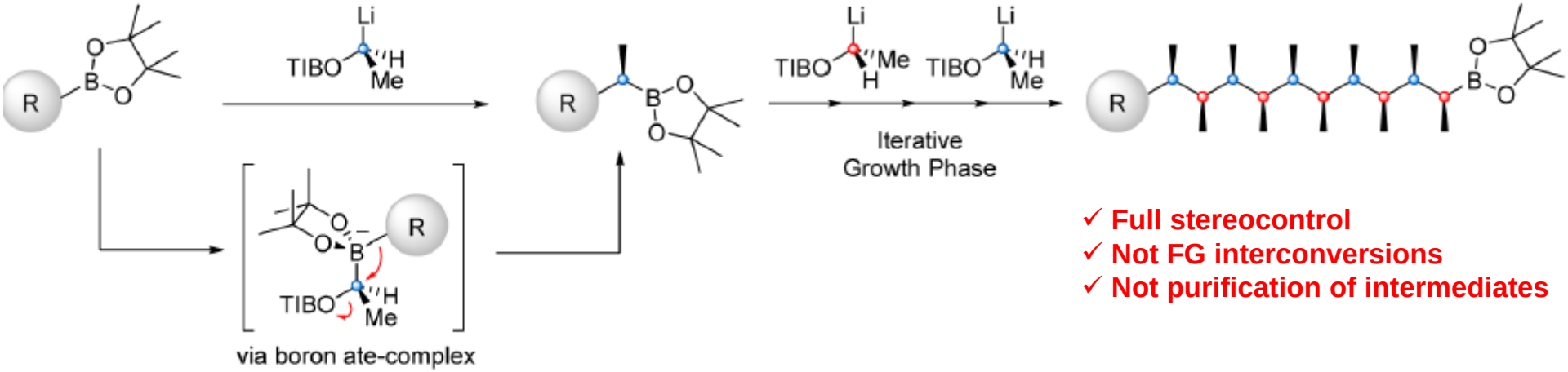
2. Iterative Strategies

3a. Synthesis of the building blocks (*Hoppe−Beak's sparteine-mediated lithiation*)



3b. Iterative homologation with boronic esters



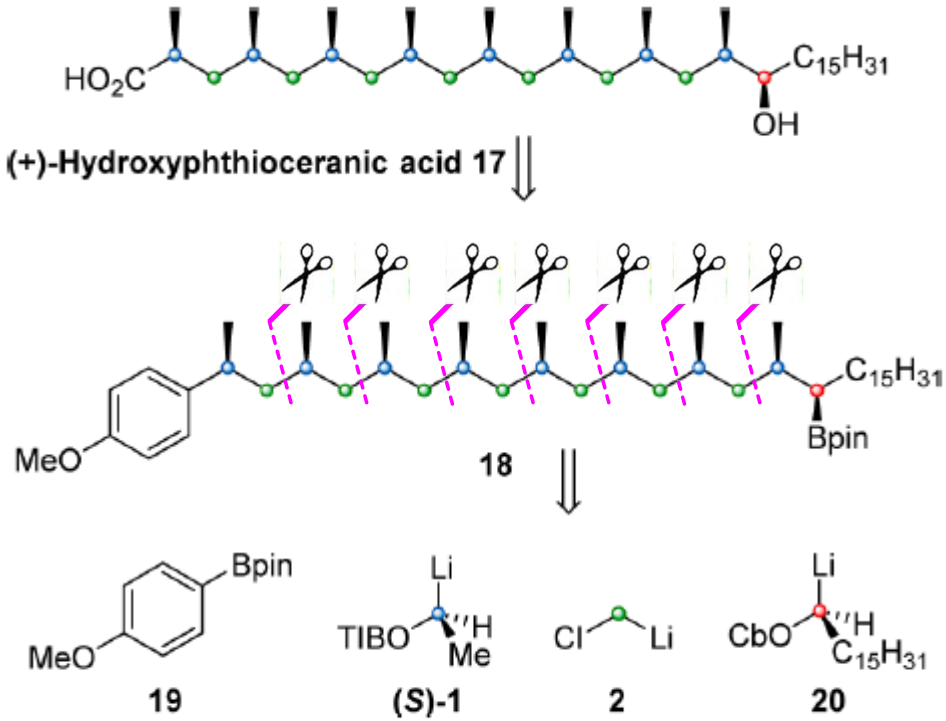
✓ **Full stereocontrol**
✓ **Not FG interconversions**
✓ **Not purification of intermediates**

Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183

3. Retrosynthetic Analysis of (+)-Hydroxyphthioceranic Acid

component of the cell wall lipid of the TB bacterium

Minnaard's group (23 steps)
Schneider's group (32 steps)

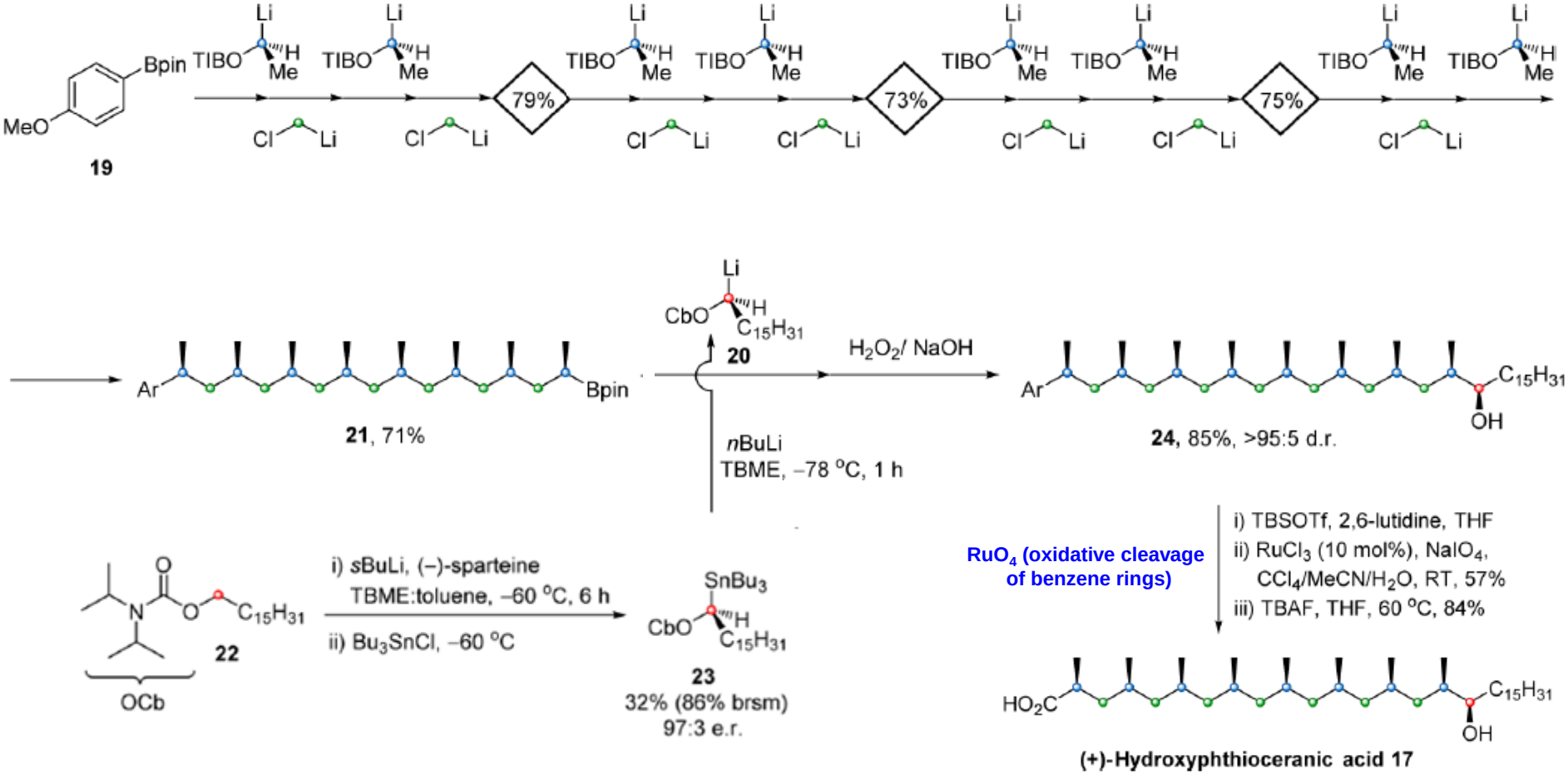


OCb = *N,N*-di-*iso*propylcarbamoyl

"15 homologations in total"

- Geerdink, D.; ter Horst, B.; Lepore, M.; Mori, L.; Puzo, G.; Hirsch, A. K. H.; Gilleron, M.; de Libero, G.; Minnaard, A. J. *Chem. Sci*. **2013**, *4*, 709
- Pischl, M. C.; Weise, C. F.; Müller, M. A.; Pfaltz, A.; Schneider, C. *Angew. Chem. Int. Ed*. **2013**, *52*, 8968

4.Total Synthesis of (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis



The synthesis was completed in just one month with only seven purifications steps
12,5% overall yield

5. Conclusions

The stereocontrolled syntheses of these complex molecules highlight the power of iterative chemical synthesis using boronic esters