Assembly Line Synthesis

Prof. Varinder Aggarwal
Bristol University

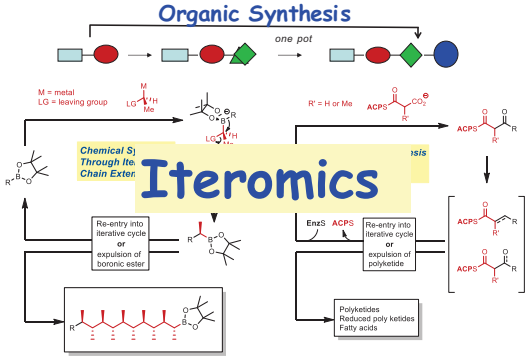
BOSS 2024

Statue of Edward Colston

Black Lives Matter

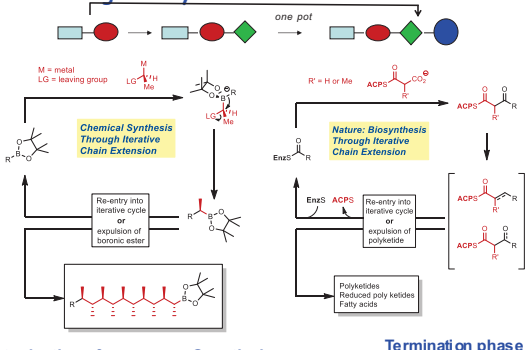
14/6/2020

Organic Synthesis



Iteromics

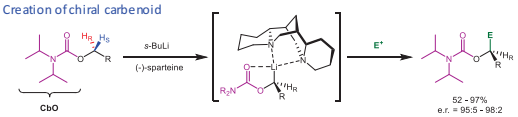
Organic Synthesis – in a boron world



Introduction of boron ○ Growth phase Assembly line synthesis ○ Termination phase (conversion to useful functional group)

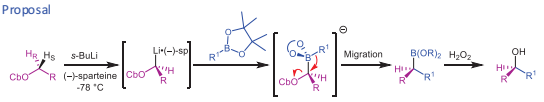
Hoppe's Lithiated Carbamates as Chiral Carbenoids

Creation of chiral carbenoid

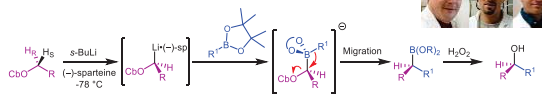


(i) Hoppe, D. *Top. Organomet. Chem.* **2003**, *5*, 61. (ii) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275.
(iii) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990** *29*, 1424.

Proposal

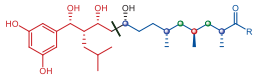


Scope: Borylation of Lithiated Carbenoids



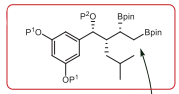
With Stymiest J., Dutheuil G., Mahmood A. *Chem. Int. Ed.*, **2007**, *46*, 7491-7494; With Leonori D. *Acc. Chem. Res.* **2014**, *47*, 3174.

Baulamycin A and B



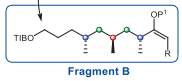
Baulamycin A, R = CH_2CH_3 (3.6 mg)
Baulamycin B, R = CH_3 (2.1 mg)

- Isolated from *Streptomyces tempisquensis* in 2014
- Strong inhibition of the siderophore biosynthesis
- Unpublished total synthesis



Fragment A

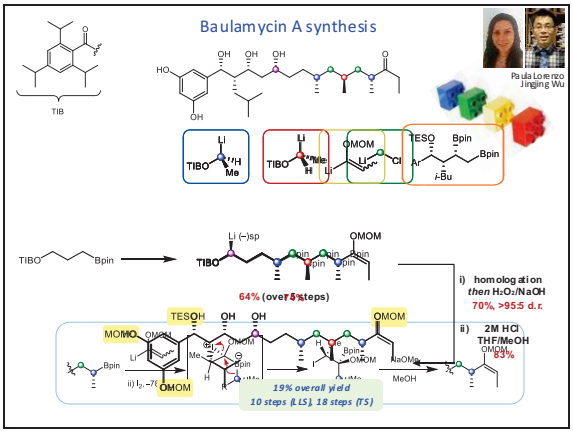
lithiation-borylation



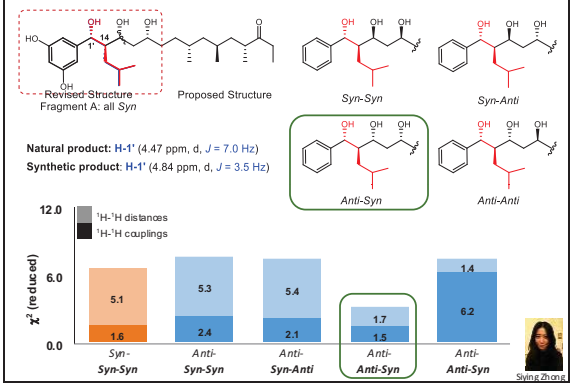
Fragment B

Sherman, D. H. et. al. *J. Am. Chem. Soc.* **2014**, *136*, 1579 (*correction*: **2014**, 10541)

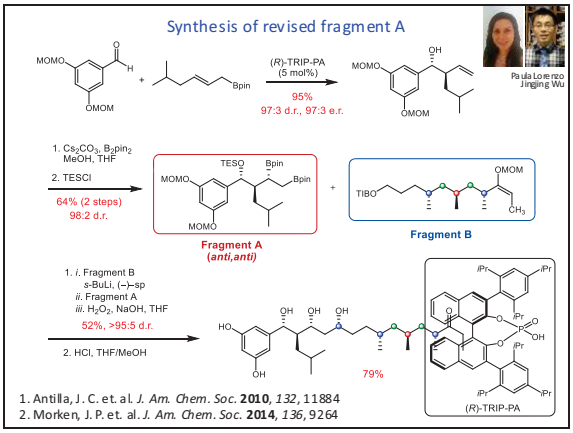
Baulamycin A synthesis



Coupling constant and computational work identifying fragment A



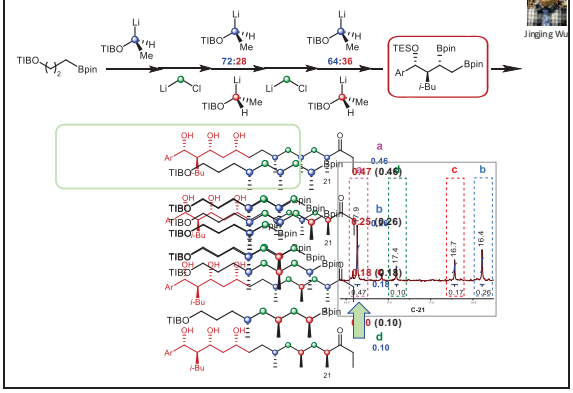
Synthesis of revised fragment A



1. Antilla, J. C. et. al. *J. Am. Chem. Soc.* **2010**, *132*, 11884
2. Morken, J. P. et. al. *J. Am. Chem. Soc.* **2014**, *136*, 9264

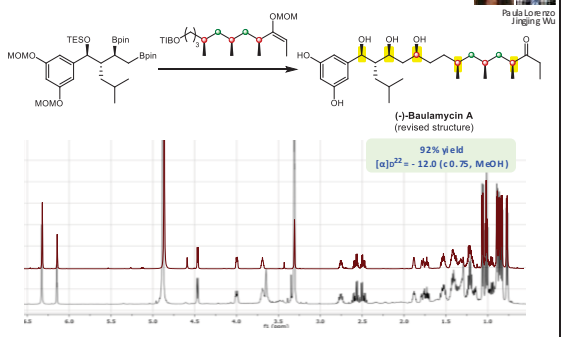
Synthesis of diastereomeric mixture of fragment B


Jingjing Wu



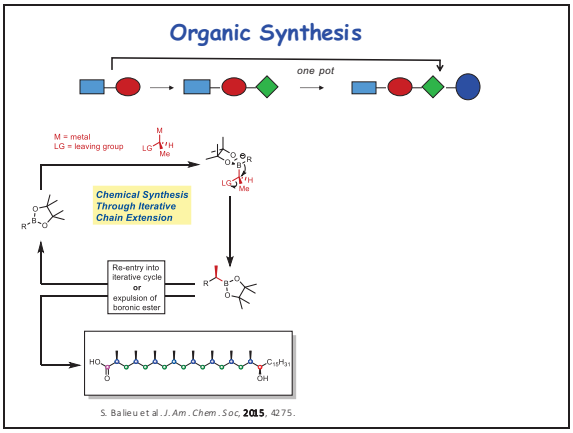
Synthesis of revised structure of (-)-Baulamycin A


Paula Lorenzo
Jingjing Wu



J. Wu, P. Lorenzo, S. Zhong, M. Ali, E. L. Myers, C. Butts, V.K. Aggarwal, *Nature*, **2017**, *547*, 436–440.

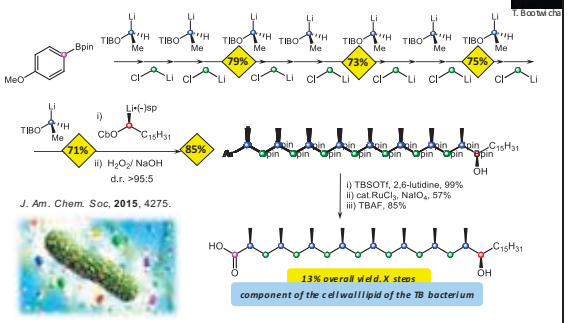
Organic Synthesis



S. Balieu et al. *J. Am. Chem. Soc*, **2015**, 4275.

Total Synthesis of Hydroxyphthioceranic Acid

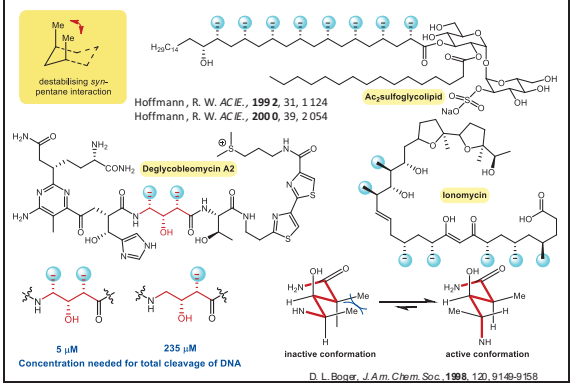
T. Bootwicha



J. Am. Chem. Soc, **2015**, 4275.

Minnaard, 32 Steps (LLS), 38 Steps (TS), *Chem. Sci.* **2013**, *4*, 709.
Schneider, 23 Steps (LLS), 36 Steps (TS), *Angew. Chem. Int. Ed.* **2013**, *52*, 8968.
Aggarwal, 14 Steps (LLS), 17 Steps (TS), *Nature. Chem.* **2014**, *6*, 810; *J. Am. Chem. Soc*, **2015**, 4275.

Nature: role of the Me groups

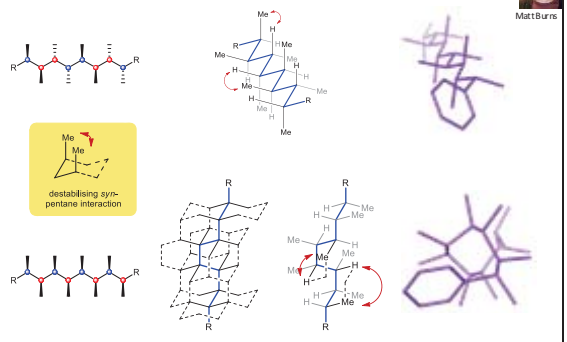


Hoffmann, R. W. *ACIE.*, **1992**, 31, 1124
Hoffmann, R. W. *ACIE.*, **2000**, 39, 2054

D. L. Boger, *J. Am. Chem. Soc.*, **1998**, 120, 9149-9158

Molecular conformation

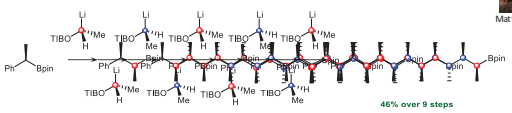
Matt Burns

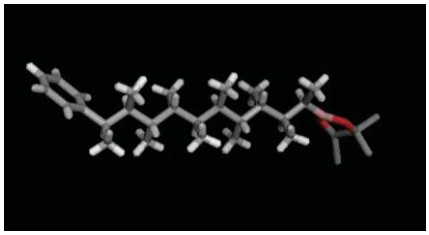


Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.*, **1992**, 31, 1124
Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.*, **2000**, 39, 2054

Iterative homologations

Matt Burns

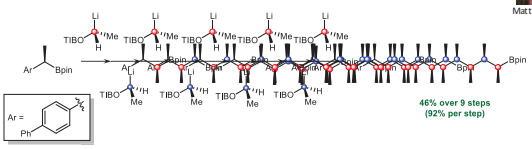




M. Burns et. al. *Nature*, **2014**, *513*, 183.

Iterative homologations

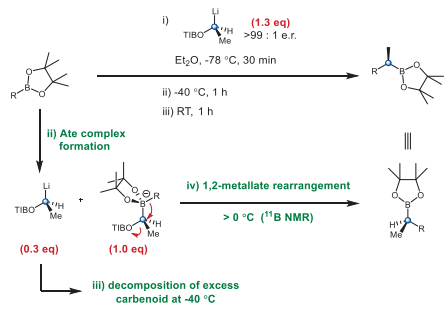
Matt Burns



M. Burns et. al. *Nature*, **2014**, *513*, 183.

Origin of success of single homologation

Matt Burns
Sebastien Bailau



M. Burns et. al. *Nature*, **2014**, *513*, 183.

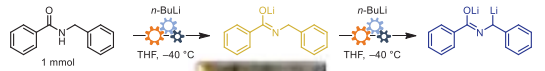
Automated Assembly Line Synthesis

Preparation of the platform:

- Automated cleaning of the glass-array with H_2O:THF, followed by a rinse with THF and a rinse with hexane (then drying under vacuum at 100 °C for 1h)
- Purge the platform with N_2 for 2h

V. Fasano R. Mykura

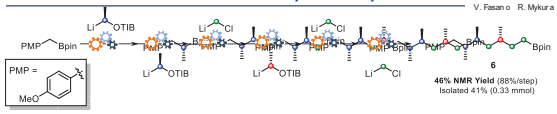
Automated titration



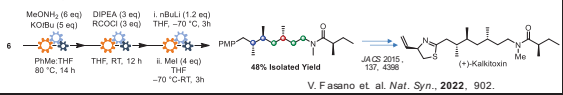
Experimental title = 1.60 M (as sold by Sigma)
Using anhydrous TBME as system solvent

Automated Assembly Line Synthesis

V. Fasano R. Mykura

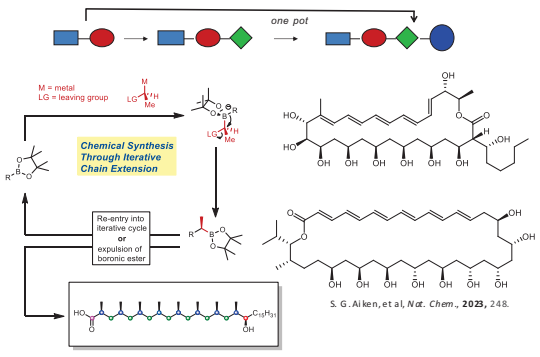


46% NMR Yield (88%/step)
Isolated 41% (0.33 mmol)



V. Fasano et. al. *Nat. Syn.*, **2022**, 902.

Organic Synthesis

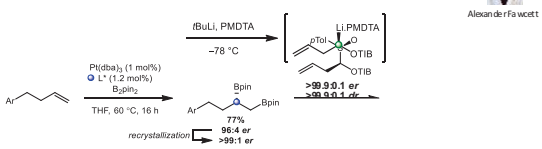


S. Ballieu et al. *J. Am. Chem. Soc*, **2015**, 4275.

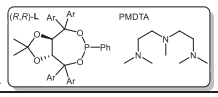
S. G. Aiken, et al, *Nat. Chem*., **2023**, 248.

Iterative Synthesis of 1,3-polyols

Alexander Fawcett

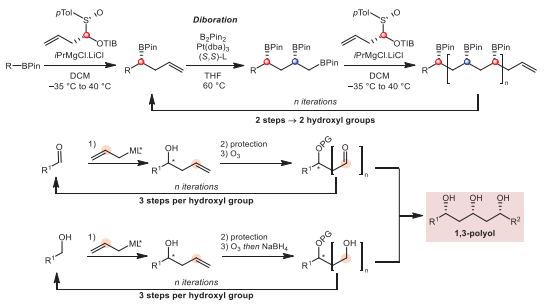


Morken, J. P.; *J. Am. Chem. Soc*. **2013**, *135*, 11222.



S. G. Aiken, et al, *Nat. Chem*., **2023**, 248 (finally).

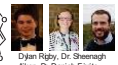
Iterative Synthesis of 1,3-polyols



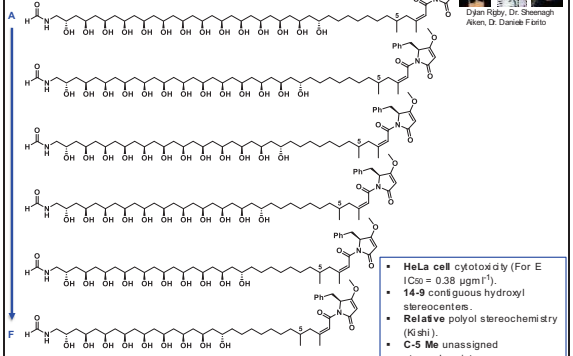
Krische, Leighton, Brown, Roush, Corey, Antilla, Schaus, Soderquist, Carreira, Keck, Duthaler, Hoveyda, Kishi, Hoffmann ...

S. G. Aiken, J. M. Bateman, H-H Liao, A. Fawcett, T. Bootwicha, P. Vincetti, E. L. Myers, A. Noble, V. K. Aggarwal, *Nat. Chem*., **2023**, 248.

Mycapolyols A-F



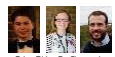
Dylan Rigby, Dr. Sheenagh Aiken, Dr. Daniele Fiorito



- **HeLa cell** cytotoxicity (For E IC_{50} = 0.38 $\mu g\,ml^{-1}$).
- **14-9** contiguous hydroxyl stereocenters.
- **Relative** polyol stereochemistry (Kishi).
- **C-5 Me** unassigned stereochemistry.

Fusetani, N. *et al*, *Org. Lett.* **2005**, 7, 2233.

Mycapolyol E



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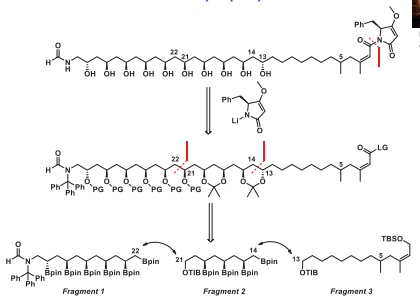
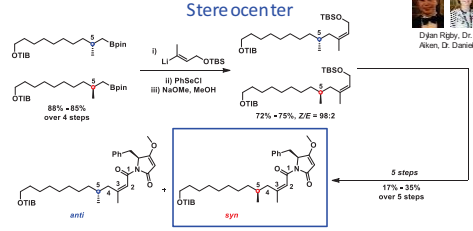
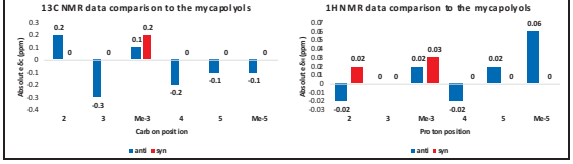


- Late-stage **head-group** installation.
- **Three fragments**.
- **Fragments unification** by regioselective, stereospecific homologation.

Fragment 3 and the Undefined Methyl Stereocenter

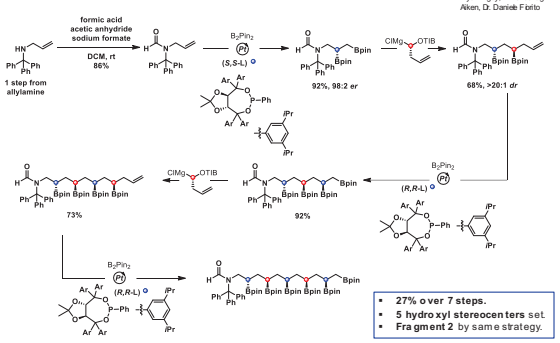
Dylan Rigby, Dr. Sheenagh Aiken, Dr. Daniele Fiorito





Fragment 1

Dylan Rigby, Dr. Sheenagh Aiken, Dr. Daniele Fiorito

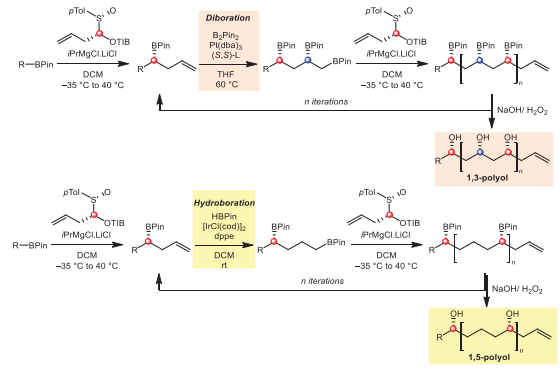


- **27% over 7 steps.**
- **5 hydroxyl stereocenters** set.
- **Fragment 2** by same strategy.

Fragment Unification

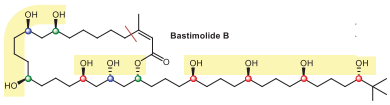
Dylan Rigby, Dr. Sheenagh Aiken, Dr. Daniele Fiorito

Iterative Synthesis of 1,5-polyols



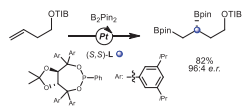
Iterative Total Synthesis of Bastimolide B

Selbi Keskin, Daniele Fiorito



Iterative Total Synthesis of Bastimolide B

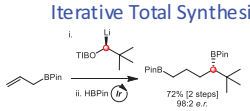
Selbi Keskin, Daniele Fiorito



D. Fiorito, S. Keskin, J. M. Bateman, M. George, A. Noble, V. K. Aggarwal, *J. Am. Chem. Soc.*, **2022**, 7995.

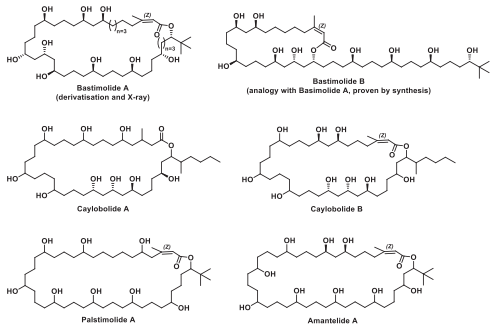
Iterative Total Synthesis of Bastimolide B

Selbi Keskin, Daniele Fiorito



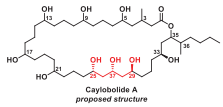
D. Fiorito, S. Keskin, J. M. Bateman, M. George, A. Noble, V. K. Aggarwal, *J. Am. Chem. Soc.*, **2022**, 7995.

Structurally related macrolides



Malcolm George

Caylobolide A structural assignment overview

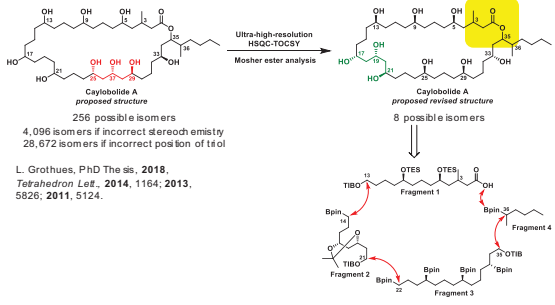


256 possible isomers

L. Grothues, PhD Thesis, **2018**, *Tetrahedron Lett.*, **2014**, 1164; **2013**, 5826; **2011**, 5124.

Malcolm George

Caylobolide A structural assignment overview



256 possible isomers

4,096 isomers if incorrect stereochemistry

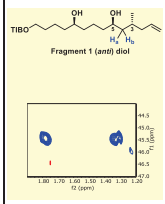
28,672 isomers if incorrect position of tiol

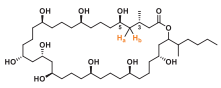
8 possible isomers

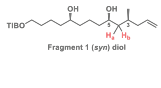
L. Grothues, PhD Thesis, **2018**, *Tetrahedron Lett.*, **2014**, 1164; **2013**, 5826; **2011**, 5124.

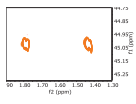
Malcolm George

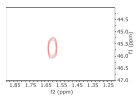
Caylobolide A: C3-C5 relative stereochemistry





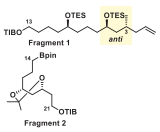






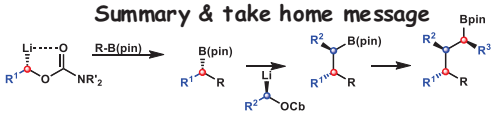
- Relative stereochemistry of C3-C5 is ***anti*** → determined by NMR comparison to the two potential diastereomers of Fragment 1
- **4** potential isomers remaining

Caylobolide A: "mixture method" total synthesis



- Major component of the mixture matched the natural product
- Out of **28,672** isomers, identified correct isomer
- 16 steps LLS, 5.6% overall yield from citronellol

Summary & take home message



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