Total Synthesis of the Antimitotic Marine Macrolide (–)-Leiodermatolide

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1. Background

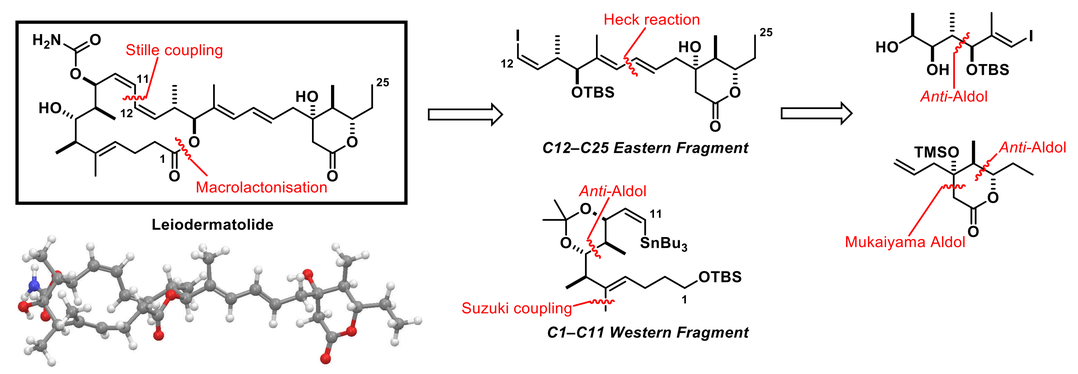
- Isolated from the listhid sponge *Leiodermatium sp.* in 2008.[1]
- Exhibits potent and selective antiproliferative activity against a range of cancer cell lines.[2]

Cell line	*A549 (lung)*	*PANC-1 (pancreatic)*	*DLD-1 (colorectal)*	*NCI/ADR-RES (ovarian)*	*P388 (leukaemia)*	*Vero monkey kidney (Control)*
IC*$_{50}$ *(nM)	*3.3*	*5.0*	*8.3*	*233*	*3.3*	*211*

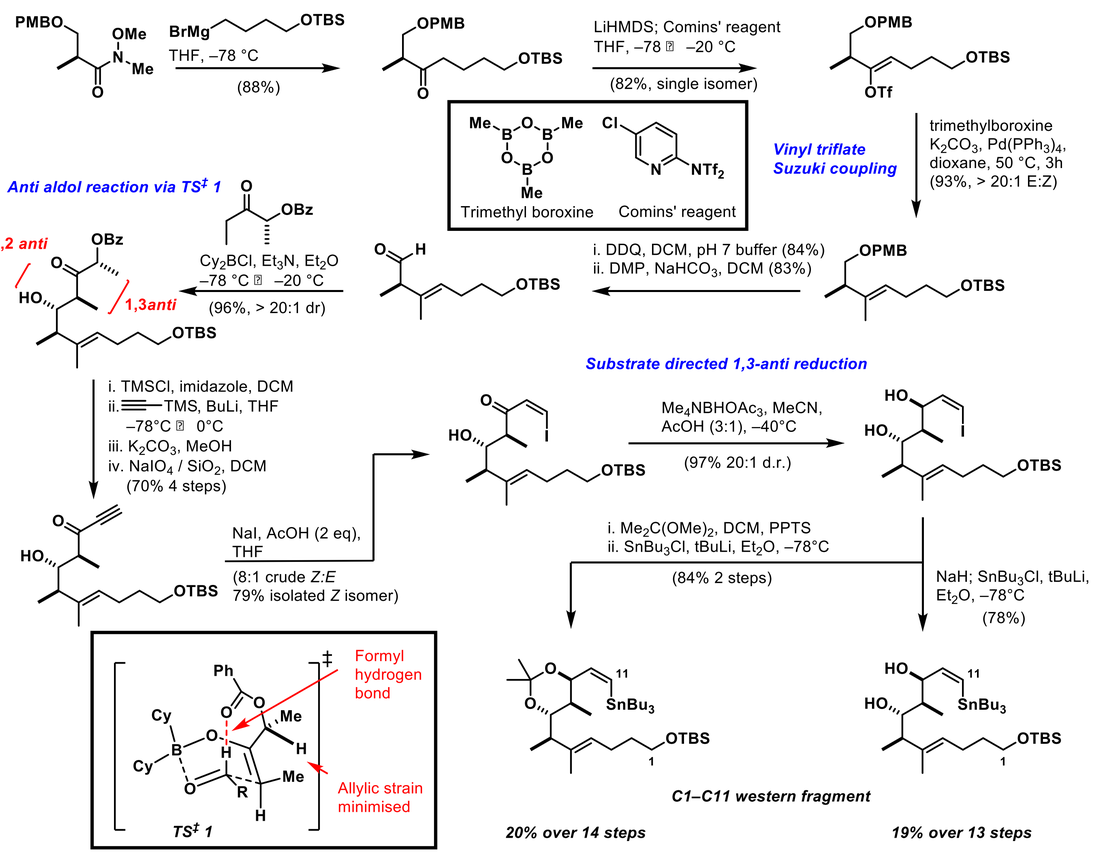
- Interacts with tubulin *via* an unknown mode of action but one distinct to that of other tubulin binding compounds such as taxol and discodermolide.
- Structure of macrocyclic core and side chain reassigned by NMR analysis and DP4 methodology in 2010.[2]
- We aimed to develop a synthesis that could produce further material for biological testing and provide easy access to a variety of analogues for structure–activity relationship studies.

2. Retrosynthesis

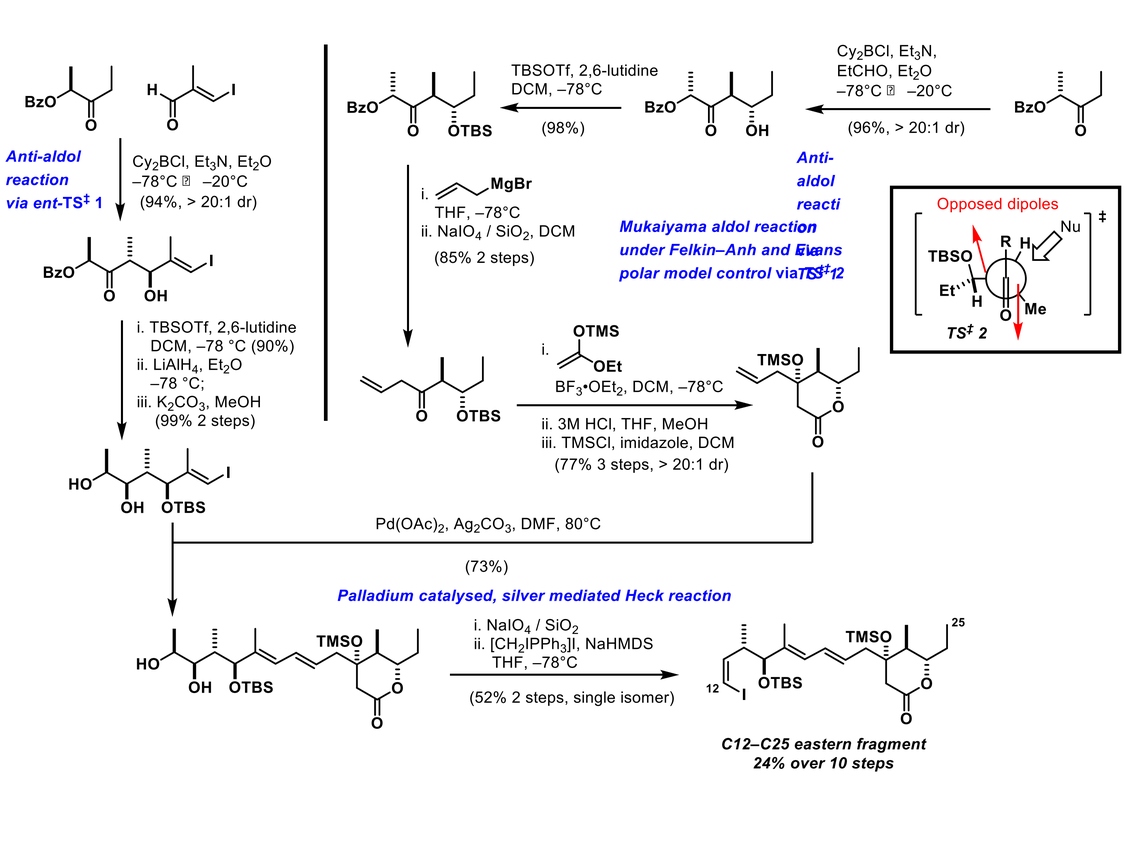
- Convergent strategy based on introduction of the dienes *via* palladium-catalysed cross-coupling of three key fragments.
- Allows for easy generation of structural modifiation.
- *Anti*-selective boron-mediated aldol reactions set up the three stereoclusters.[3]



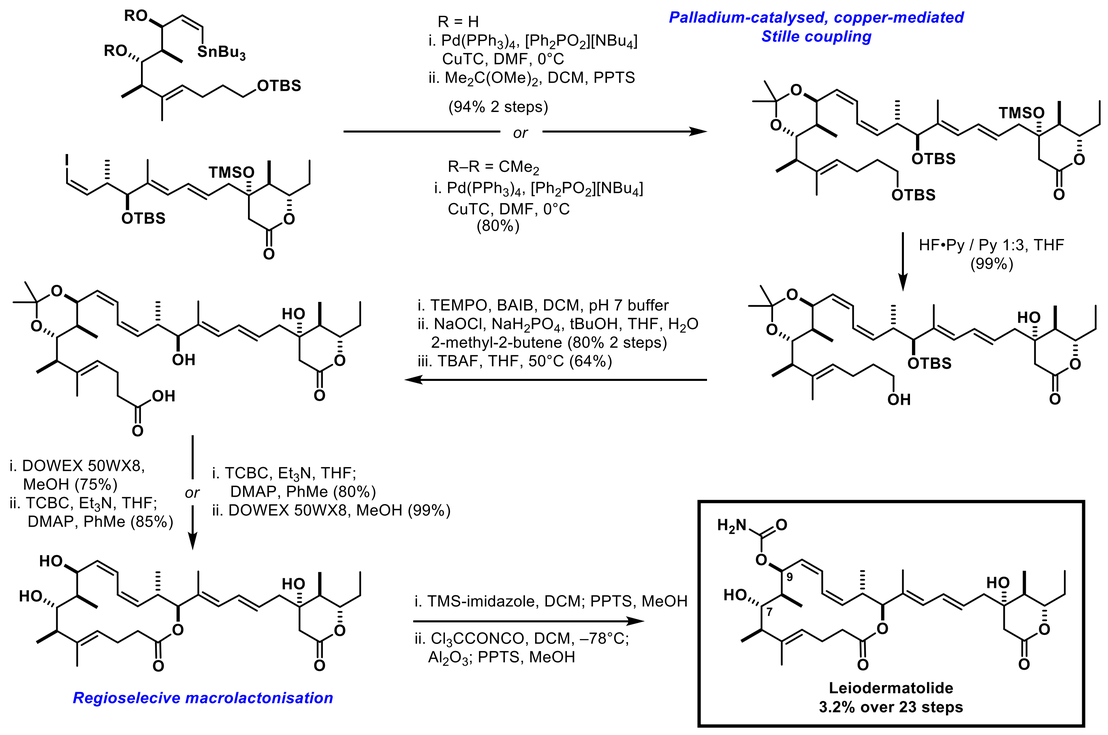
3. C1–C11 Western Fragment



4. C12–C25 Eastern Fragment



5. Completion of the Synthesis



6. Conclusions

- The total synthesis of (–)-leiodermatolide has been achieved in 23 steps LLS (35 steps overall) from a known Roche ester-derived Weinreb amide.[4]
- Three highly diastereoselective boron-mediated *anti*-aldol reactions are used to set up 6 of the 9 stereocentres.
- Three different palladium-catalysed cross-coupling reactions are used to form the diene regions and trisubstituted double bond with high geometrical purity.
- A site-selective macrolactonisation closes the 16-membered macrolactone in high yield.
- Future work will focus on the production of both modified and simplified analogues for structure–activity relationship studies with the aim of probing the mode of action.

1. Wright, A. E.; Reed, J. K.; Roberts, J.; Longley, R. E.; U.S. Patent 7,626,043, Dec 1, 2009; *Chem. Abstr.* **2008**, *148*, 230104.
2. Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlanska, D.; Reed, J. K.; Wright, A. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 3219.
3. Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083.
4. Paterson, I.; Ng, K. K.-H.; Williams, S.; Millican, D. C.; Dalby, S. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 2692

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