Chemoenzymatic Total Synthesis of Lansai B

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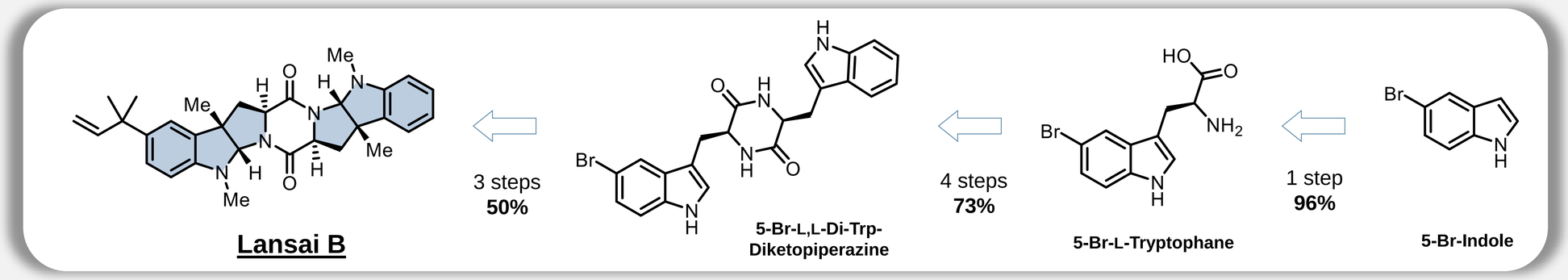
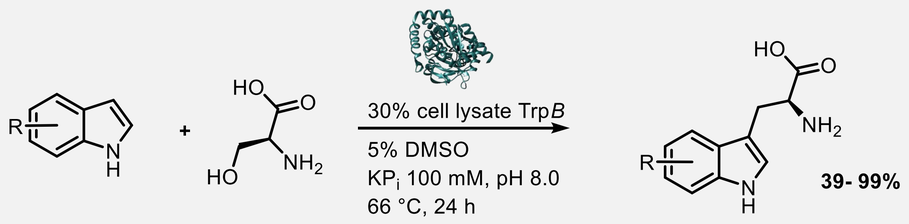


Many natural products containing a pyrroloindole structural motif exhibit different kinds of biological activities like antibacterial and anticancer effects. The selective synthesis of the hexahydropyrrolo[2,3-b]indole motif with its rigid tricyclic molecular architecture remains challenging. Particularly methylation is hard to accomplish chemically since most methods provide just poor yields while not being dia- or enantioselective.

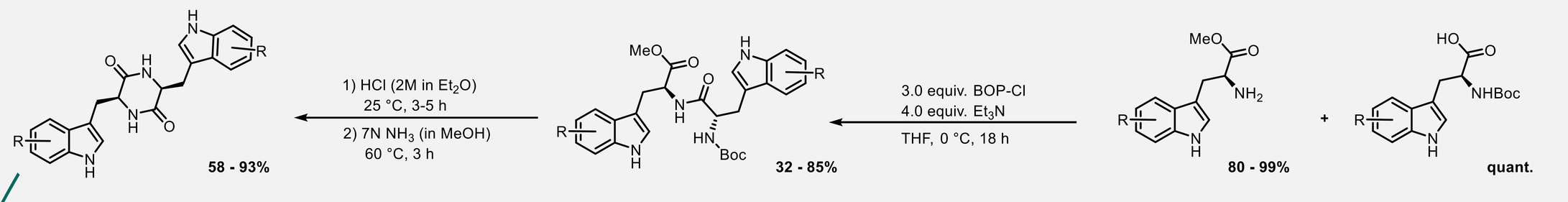
Within this project, we have developed an enantiomerically pure synthesis of the natural product Lansai B, utilizing two enzymes and additionally providing derivatives.



D. K. Romney et al., *J. Am. Chem. Soc.* 2017, 139, 10769-10776.

C. E. Boville et al., *Angew. Chem. Int. Ed.* 2018, 57, 14764-14768.

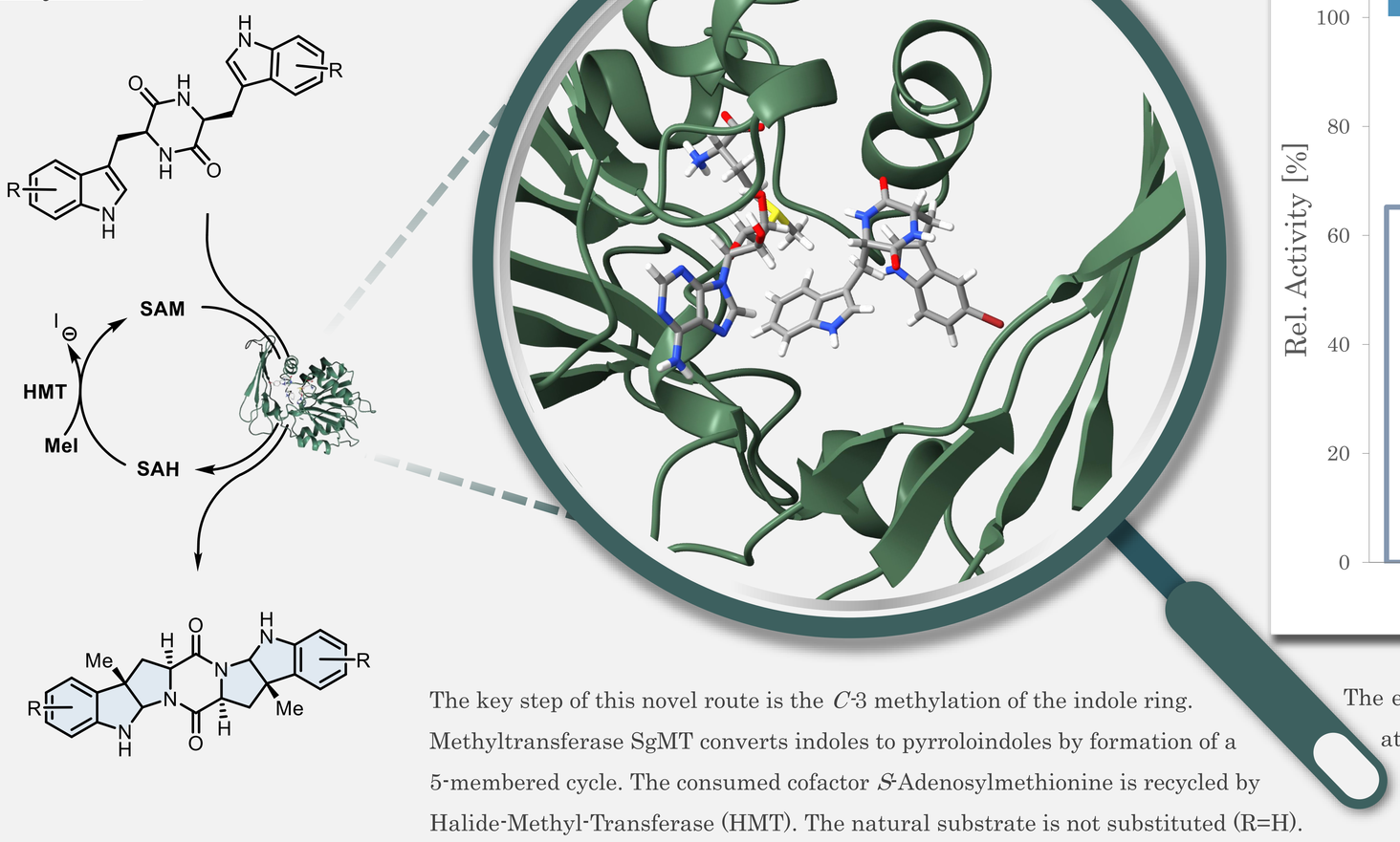
Enantioselective Synthesis of Diketopiperazine-Derivatives utilizing Trp-Synthase B



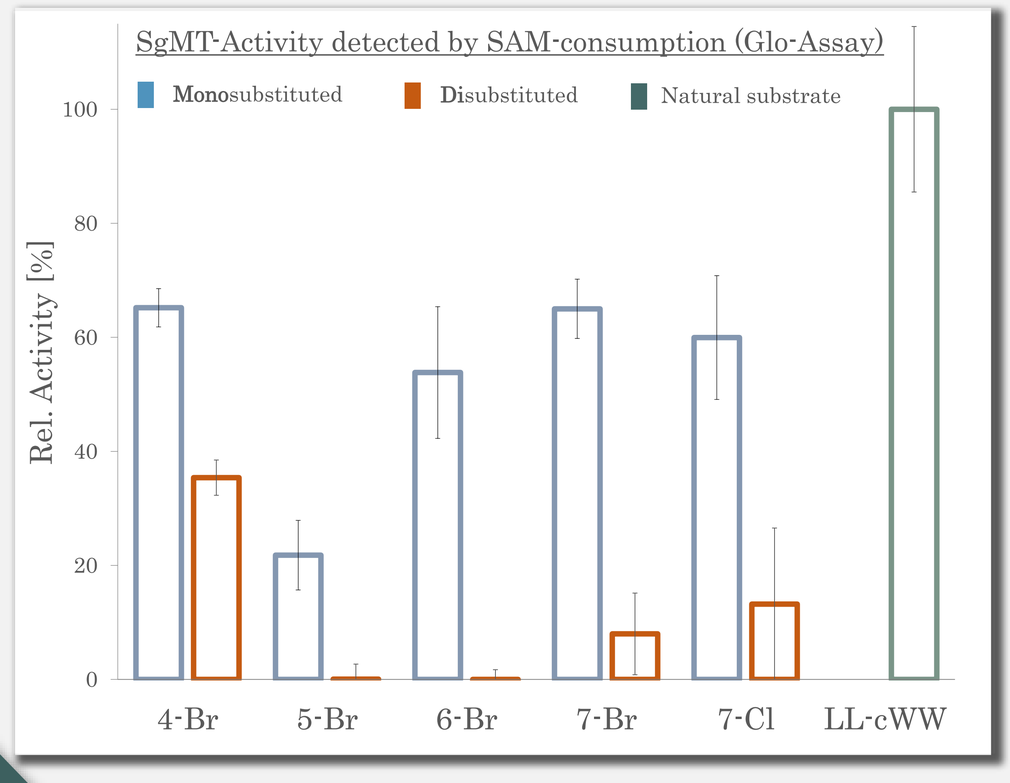
H.Wang, S.E. Reisman et al., *Angew. Chem. Int. Ed.* 2014, 53, 6206-6210.

N. Alqahtani et al., *Org. Biomol. Chem.* 2015, 13, 7177-7192.

Formation of the Pyrroloindole-Ring by C-Methylation

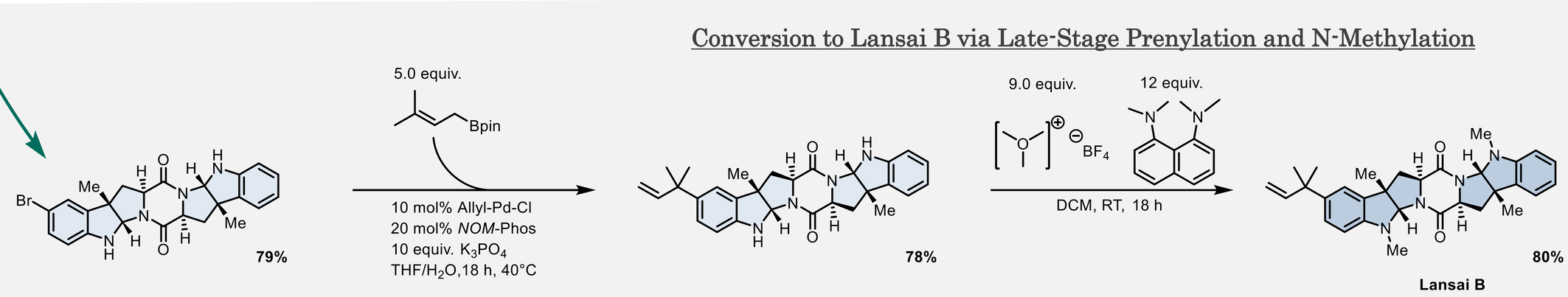


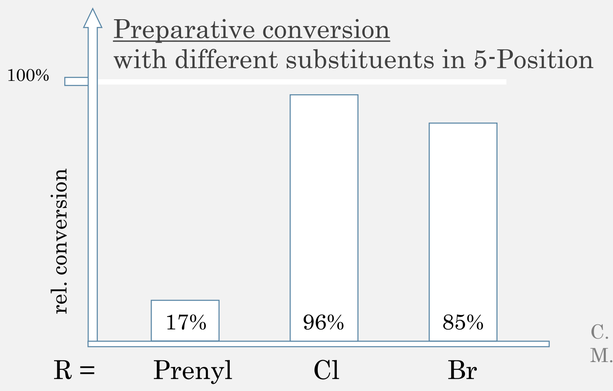
The key step of this novel route is the *C*-3 methylation of the indole ring. Methyltransferase SgMT converts indoles to pyrroloindoles by formation of a 5-membered cycle. The consumed cofactor *S*-Adenosylmethionine is recycled by Halide-Methyl-Transferase (HMT). The natural substrate is not substituted (R=H).

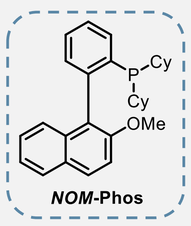


The enzyme performs C3-methylation on both tryptophan moieties, however the attached substituents reduce the enzyme activity due to their steric demand. This effect is particularly pronounced when both sides of the molecule contain halogen-substituents.

Conversion to Lansai B via Late-Stage Prenylation and N-Methylation







Since the 5-prenyl group is sterically demanding and thus barely accepted by the enzyme, the brominated compound is favoured enabling late-stage Suzuki-cross-coupling. In the final step the former indole-*N* is methylated. While Eschweiler-Clarke conditions seemed to harsh, methylation performs in good yields using an excess of Meerwein's salt and proton-sponge as base.

Therefore, the synthesis is completed in **8 linear steps** from small building blocks with an **overall yield of 34%.**

C. Liao et al., *Nat. Catal.* 2019, 2, 696–701.
M. Haase, J. Pietruszka et al., *ACS Catal.* 2024, 14, 227–236.

Y. Yang et al., *J. Am. Chem. Soc.* 2013, 135, 10642–10645.

J. R. Harding et al., *Tetrahedron. Lett.* 2002, 43, 9487-9488.

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