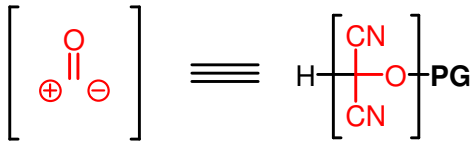
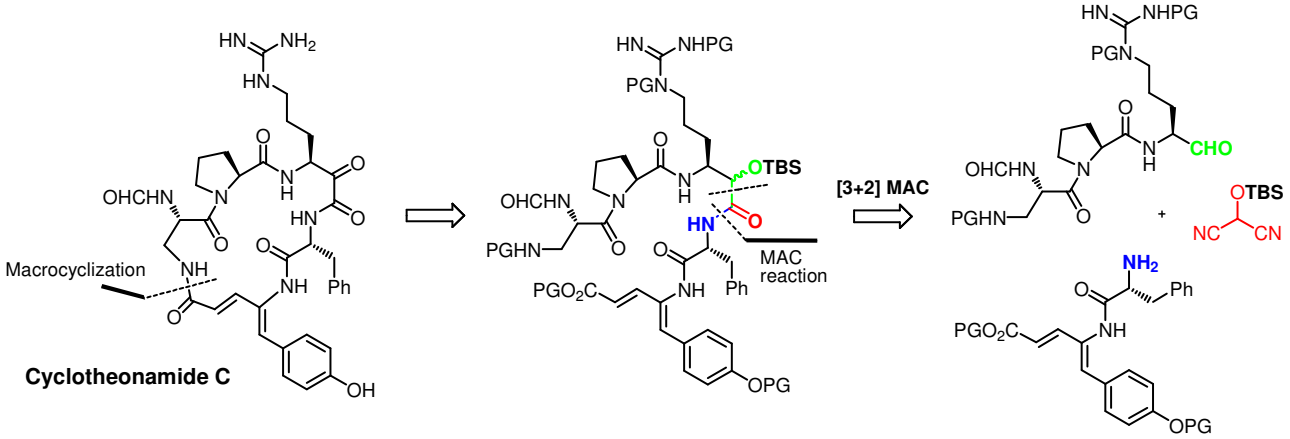
One-pot multicomponent MAC methodology

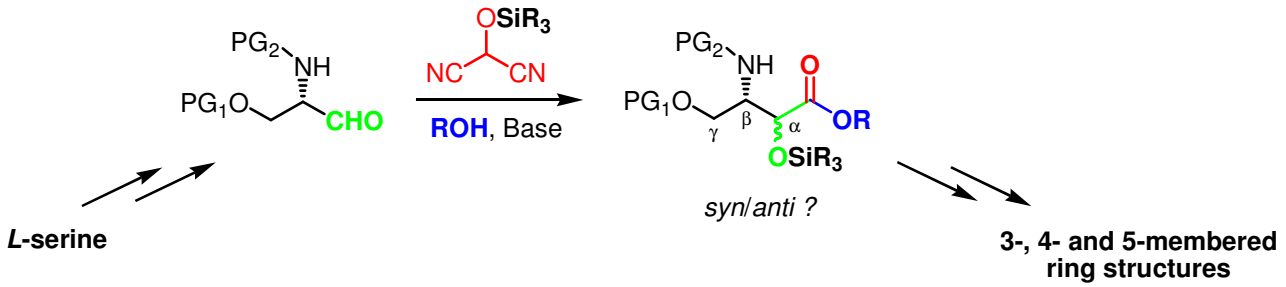
Protected α-hydroxymalononitriles, known as masked acyl cyanide (MAC) reagents, are shown to be effective umpolung synthons as carbon monoxide equivalents with both nucleophilic and electrophilic reactivity.



These Nemoto and co-workers' MAC reagents[1] are employed in sequential or in one-pot multicomponent methodology involving an electrophile (aldehyde, ketone or imine), a nucleophile (alcohol or amine) to afford simple or complex structures under mild basic condition. Aitken's group[2] has developed an original [3+2] MAC reaction between an arginal derivative, a dipeptide and α-(*tert*-butyldimethylsilyloxy)malononitrile as H-MAC-TBS reagent. Because of the *in situ* migration of the TBS group, cyanide anion is eliminated from the oxymalononitrile moiety to generate the acyl cyanide, which is condensed with the amine as nucleophile. This tandem backbone-extension-coupling procedure allowed the creation of a masked α-keto-β-amino acid within a cyclic pentapeptide chain during the total synthesis of Cyclotheonamide C, a potent inhibitor of thrombin.



We currently study this one-pot three-component procedure for the synthesis of a multi-functional four-carbon synthetic intermediate, an α,γ-dihydroxy-β-aminobutyric acid ester, starting from a protected L-serinal derivative, various alcohols as nucleophiles and a silylated hydroxymalononitrile. Depending on the protecting group suite and the applied reaction conditions, up to four different cyclisation modes can be anticipated from this single intermediate, leading to 3-, 4-, or 5-membered ring structures.



References :

[1] H. Nemoto, Y. Kubota, Y. Yamamoto *J. Org. Chem*. **1990**, *55,* 4515-4516 ; H. Nemoto, R. Ma, I. Suzuki, M. Shibuya *Org. Lett.* **2000**, *2,* 4245-4247.

[2] S.P. Roche, S. Faure, D.J. Aitken *Angew. Chem. Int. Ed*. **2008**, *47*, 6840-6842.