

## Efficient Macrocyclization of Small Peptides

Category

Peptide Chemistry

Key words

cyclic peptides

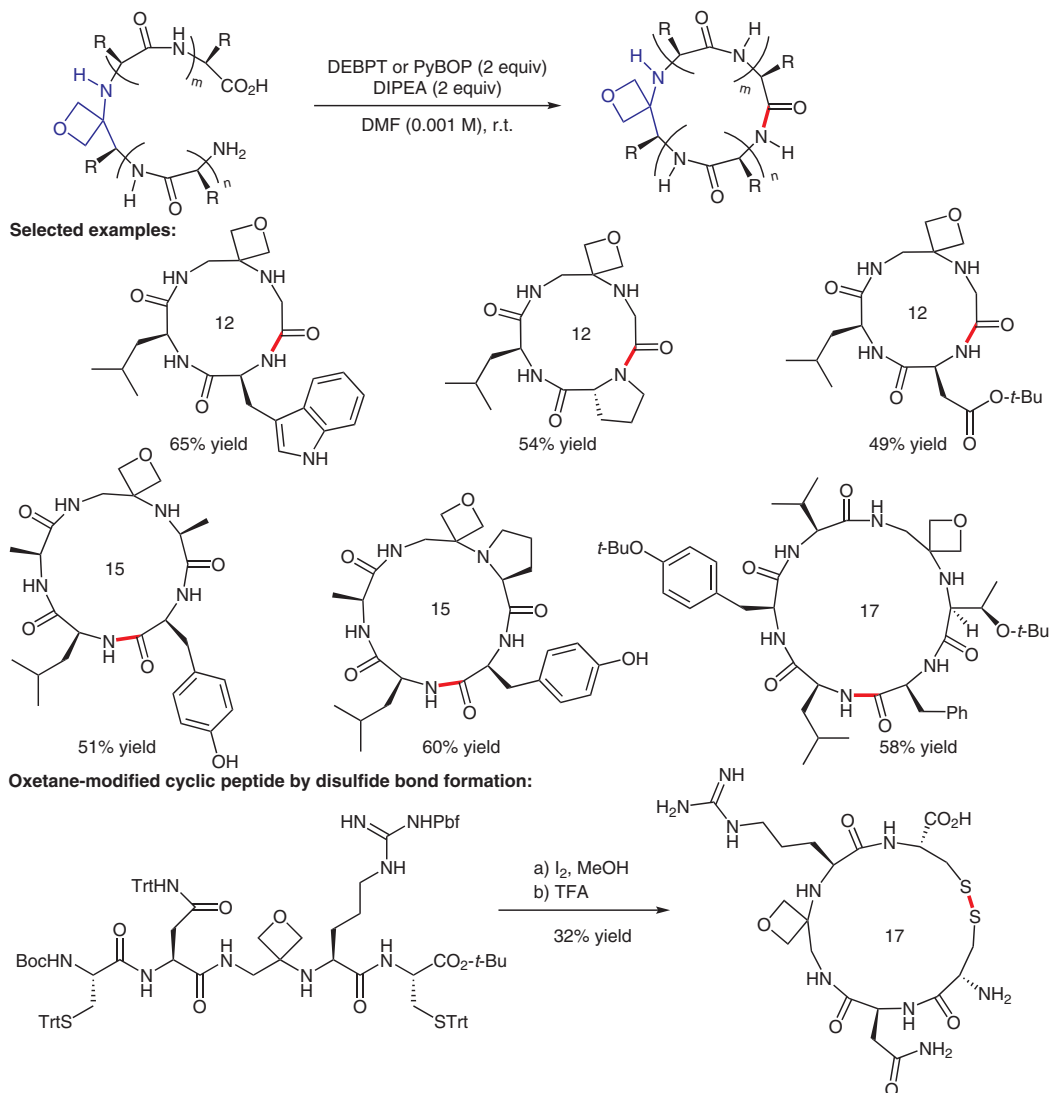
macrocyclization

oxetane

disulfide bond

amino acids

Synfact  
of the  
Month



**Significance:** Cyclic peptides have recently emerged as a new source of drug molecules, but very few in clinical use are derived from natural sources. The main problem is associated with their synthesis, which often suffers from C-terminal epimerization, cyclooligomerization, and byproduct formation during macrocyclization. Shipman and co-workers have developed a simple, mild, and efficient macrocyclization strategy, which involves the incorporation of an oxetane ring, for synthesizing cyclic peptides in good yields by using an appropriate coupling reagent.

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 Synfacts 2019, 15(05), 0569 Published online: 15.04.2019  
 DOI: 10.1055/s-0037-1612447; Reg-No.: H02319SF

**Comment:** Cyclic peptide drugs are more useful than the linear peptides, but their synthesis is quite challenging. The present approach shows that macrocyclization of head-to-tail peptide can be improved by substituting one of the backbone amide C=O bonds with a simple oxetane ring. In addition, a variety of cyclic peptides with challenging ring sizes (tetra-, penta-, or hexapeptides) were synthesized. Further study showed that the bioactivity does not change upon replacing the amide C=O bond with an oxetane ring.