Category

Chemistry in Medicine and Biology

Key words

oxytetracycline

terramycin

antibiotics

Diels–Alder reaction

thiazolone condensation

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Tetracyclines. 9. Total Synthesis of *dl*-Terramycin

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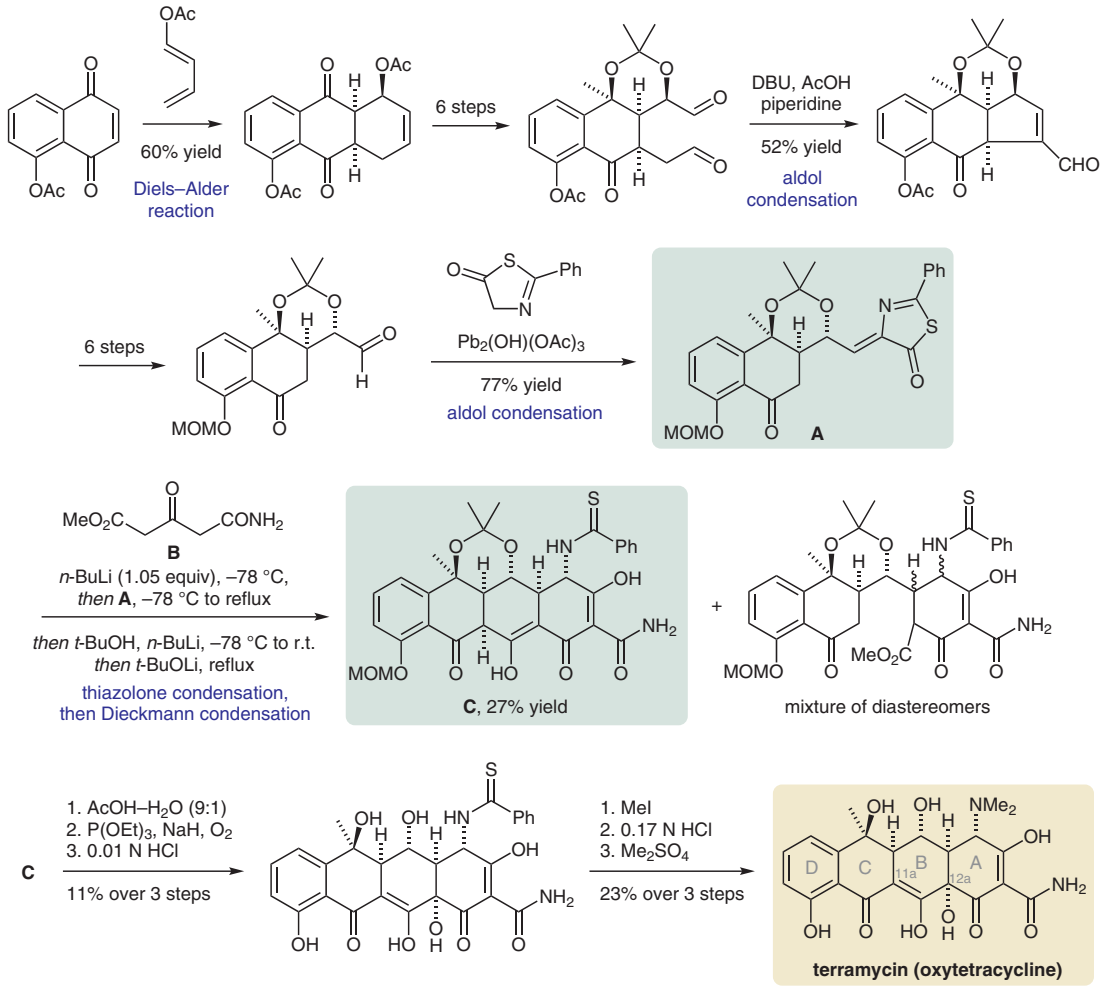
Muxfeldt's Synthetic Tetracycline Antibiotics



Significance: Tetracyclines are broad-spectrum antibiotics with potent activities against Gram-positive and Gram-negative pathogens. Since their discovery in the 1940s several members of this natural product family as well as semi-synthetic derivatives thereof have been used clinically. While the group of R. B. Woodward accomplished the total synthesis of simplified analogues earlier (*J. Am. Chem. Soc.* **1968**, *90*, 439), it was Hans Muxfeldt and his coworkers who first finished the racemic total synthesis of the structurally more challenging natural product terramycin (oxytetracyclin).

Comment: The opening step of their total synthesis was an *endo*-selective Diels–Alder reaction. Further transformations afforded the key thiazolone building block **A**. A subsequent elegant condensation with the 1,3-acetone dicarboxylate **B** then afforded the functionalized A/B-ring system in just a single step. While further diastereomers formed, the desired tetracyclic product readily crystallized from the mixture. Unfortunately, oxidative conditions mostly afforded the undesired C11a- over the desired C12a-hydroxylation product. The thioamide could be cleaved by methylation followed by treatment with dilute hydrochloric acid.

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