P. E. MALIGRES*, Z. J. SONG*, N. A. STROTMAN, J. YIN, T. PEI, H. R. STROTMAN, T. ITOH, E. C. SHERER, G. R. HUMPHREY (MERCK & CO., INC., KENILWORTH, USA)

Synthesis of Fused Oxepane HIV integrase Inhibitor MK-1376

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Synthesis of HIV Integrase Inhibitor MK-1376

Category

Synthesis of Natural Products and Potential Drugs

Key words

MK-1376

HIV integrase inhibitor

π -allyl alkylation

palladium catalysis

quinone methide

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Significance: MK-1376 is an HIV integrase inhibitor that is of interest for the treatment of AIDS. The key step in the synthesis of MK-1376 is the Trost palladium-catalyzed asymmetric π -allylation reaction that installed the stereogenic center at C-6 in the 1,4-oxazepane ring of **C**. Prolonged reaction times led to erosion of ee from reversible ring closure. This is the first example of reversibility in a π -allylation reaction. The epimerization processes were suppressed by addition of 1.5 mol% palladium acetate prior to workup.

Comment: Introduction of the stereogenic center at C-10 was accomplished by reaction of methylamine with the amides **Ha,b** ($\text{syn/anti} = 1:1$) that gave the *syn*-isomer **J** ($\text{syn/anti} = 97:3$), independent of the original stereochemistry at C-10, consistent with the diastereoselective addition of methylamine to quinone methide intermediate **I**.

SYNFACTS Contributors: Philip Kocienski
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