A. D. ALORATI, * A. D. GIBB, * P. R. MULLENS, G. W. STEWART (MERCK SHARP \& DOHME LTD., HODDESDON, UK)
An Efficient Process for the Large-Scale Synthesis of a 2,3,6-Trisubstituted Indole
Org. Process Res. Dev. 2012, 16, 1947-1952.

## Synthesis of the Indole Core of MK-3281



A


99\% (259 mol scale)


C



G

$$
\mathrm{K}_{2} \mathrm{CO}_{3} \text { (1.0 equiv) }
$$

DMF, $35^{\circ} \mathrm{C}, \mathrm{o} / \mathrm{n}$
Truce-Smiles
rearrangement


87\% from D


H
$\mathrm{H}_{2}$ (2.3 bar) $10 \% \mathrm{Pd} / \mathrm{C}$ THF-AcOH, $60^{\circ} \mathrm{C}, \mathrm{o} / \mathrm{n}$ $74 \%$ (149 mol scale)


I
mp not reported

Products and
Potential Drugs

## Key words

MK-3281
RNA polymerase NS5B inhibitor

## indole ring

synthesis
Truce-Smiles rearrangement

SYNFACher
of her mant

Significance: MK-3281 inhibits hepatitis C RNA polymerase NS5B. A synthesis starting from the indole fragment I was recently described: J. P. Scott et al. Org. Process Res. Dev. 2011, 15, 1116. In this paper a large scale synthesis of the MK-3281 fragment $\mathbf{I}$ is described that features a Truce-Smiles rearrangement.

Comment: The highly telescoped synthesis of the indole fragment I depicted was accomplished on a $>50 \mathrm{~kg}$ scale and delivered the target indole in $55 \%$ overall yield in five steps. All of the yields are assay yields. For the discovery synthesis of MK3281, see: F. Narjes et al. J. Med. Chem. 2011, 54, 289.

