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STEREOCHEMICAL IDENTIFICATION OF AN INTERMEDIATE IN THE SYNTHESIS OF DOLUTEGRAVIR USING MOLECULAR ROTATIONAL RESONANCE SPECTROSCOPY

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Over half of pharmaceuticals, both among the top 100 drugs by prescription totals and new U.S. Food and Drug Administration (FDA) approvals, contain at least one chiral center. Moreover, most new chiral pharmaceuticals are synthesized as a single isomer. Therefore, it is important to be able to determine the primary isomer generated by a synthetic process as well as the presence of any other isomers - preferably directly on the intermediate compounds where each chiral center has been introduced. Molecular rotational spectroscopy, with its sensitivity to small changes in structure and ability to identify compounds directly from electronic structure theory, can be a powerful tool in this application.

The present study concerns dolutegravir, an HIV integrase inhibitor developed by GlaxoSmithKline and approved by the FDA in 2013. Efforts are ongoing at the Medicines for All institute in Richmond, Virginia to develop a stereoselective flow synthesis for dolutegravir to reduce its cost and increase availability.[a] As part of a new route development, an intermediate with two chiral centers was assessed by rotational spectroscopy to determine which diastereomer was the predominant one formed by the process. Notably, NMR was unable to conclusively determine this, but rotational spectroscopy unambiguously determined that the synthetic route produced the correct stereochemistry. This result suggests that rotational spectroscopy can be a useful complement to other analytical characterization methods in organic process development.

[a] R.E. Ziegler, B.K. Desai, J.-A. Jee, B.F. Gupton, T.D. Roper, and T.F. Jamison, *Angew. Chem. Int. Ed.*, **2018**, *130*, 7299-7303.