ABSTRACT

Radical Fragmentation Towards the Synthesis of **FS-2**

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Radical fragmentation studies of cyclic thionocarbonates attached to five-membered rings aimed at the synthesis of sesquiterpene micotoxin FS-2 are presented. The synthetic strategy targeted the formation of a rigid tricycle [5.4.0.$0^{2,6}$]-undecane skeleton with well-defined geometry to take advantage of face-selective reactions to install the necessary functionality in a stereoselective manner. The final product could be unraveled at the last step of the synthesis *via* a radical fragmentation cascade. The rigid skeleton was assembled by an intramolecular [2+2] photoaddition to set the relative stereochemistry of the two adjacent quaternary centers characteristic of the trichothecene natural products. The fragmentation of a model system demonstrated the feasibility of this approach. The stereochemistry at the ring junction enabled the control of the selectivity of the fragmentation. The *cis* fused system leads to the formation of the secondary radical while the *trans* fused system gives a primary radical at a ratio greater than 20:1. Fragmentation of the cyclobutylcarbinyl radical derived from the thionocarbonate fragmentation selectively cleaved the exocyclic C-C bond to give the more stable radical resembling the trichothecene skeleton.

This methodology offers an entry for the preparation of the trichothecene family of compounds *via* control of the stereochemistry at the thionocarbonate ring junction. The radical fragmentation of the *cis*-fused system leads to the formation of trichothecenes

with the FS-2 type skeleton, while fragmentation of the *trans*-fused system leads to the formation of the tricyclic type trichothecene skeleton upon biomimetic cyclization.

Geometry *ab initio* calculations were conducted to better understand the origin of the observed selectivity in the fragmentation reactions. A series of differently substituted cyclic thionocarbonates were analyzed with respect to energy, charge distribution, geometry and an "offset-from-ideal-angle" quantity to gage angle-strain. Additionally, the intermediates and transition states involved in the radical fragmentation reactions were investigated in the context of the *cis* and *trans* ring junction. These calculations indicate that secondary radical is favored over primary unless the system is highly strained as represented by the offset-from-ideal-angle. For these highly strained molecules, release of strain may determine the preferred pathway of the reaction overcoming the natural thermodynamical tendencies of the system.

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For my parents.

And my family,

Jon and Clawed.

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