Stereochemically Complex and Structurally Diverse Small Molecules from Pleuromutilin: Synthesis, Structural Evaluation, and Biological Activity

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Complex natural products are often considered the end-point of synthetic endeavors, but they represent an advantageous starting point for the synthesis of novel structures of biological and theoretical interest. Many natural products containing complex ring systems, multiple stereogenic centers, and diverse functional groups are readily available to synthetic chemists via commercial sources or isolation. From such complex starting materials, dramatic structural alterations can be accessed rapidly through manipulation of core ring systems via ring distortion reactions (ring formation, cleavage, expansion, contraction, and rearrangement). The structurally diverse molecules thus created retain the molecular complexity inherent in the initial natural products and are highly valuable for probing biological processes and investigating unusual structural phenomena. To demonstrate the utility of complex natural products as feedstocks for complex molecule synthesis, we have transformed the commercially available natural product pleuromutilin into five highly diverse scaffolds that are dramatically different from each other and the parent natural product. One of these molecules was identified as a novel type of fenestrane, a strained polycyclic compound possessing a highly planarized four-coordinate carbon atom. The degree of planarization and the effects of peripheral substituents on scaffold geometry were investigated by chemical derivatization and X-ray crystallography. Biological evaluation of the compounds derived from pleuromutilin led to the identification of a compound with potent cytotoxicity in multiple cancer cell lines. Structure-activity relationship studies have provided insight into the possible mode of action for this scaffold and have led to the identification of more active derivatives.