

Synthesis of Kurasoin B Analogs Jason R Nielson, Merritt B. Andrus, and Michael A. Christiansen

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Background

Kurasoin B (1), isolated in 1996 by Uchida et al, selectively inhibits Farnesyltransferase (FTase), an enzyme responsible for activating human RAS proteins (ref. 1). When RAS proteins are mutated and then activated, they contribute 20 to 30 percent of all human tumors, including those of the pancreas, colon, small intestine, lung, prostate. liver, skin, and thyroid, as well as multiple myeloma and a number of leukemias (ref. 2). Kurasoin B, therefore, has great potential as a cancer drug lead.

Unfortunately, the natural abundance of 1 is small, and its FTase-inhibiting potency is only moderate (IC₅₀ = 59 μ M). Increased potency might be achieved by making and testing analogs of 1. Naturally, this can only be done through total synthesis.

Applying Phase-Transfer Catalysis (PTC) to Asymmetric Alkylation

Our group recently completed an enantioselective total synthesis of kurasoin B using asymmetric phase-transfer-catalyzed alkylation (ref. 3). This method follows the generic scheme below, in which a compound of type 2 is treated with a metal-hydroxide base under biphasic conditions, giving Z-enolate 3. This complexes electrostatically with a charged, chiral phase-transfer catalyst R*,N*. Electrophilic attack gives products with high enantioselectivity, and the catalyst is released to repeat the cycle.

Alkylating Substrate 5

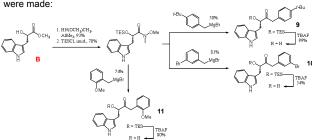
After screening multiple phase-transfer catalysts and conditions, this approach was applied to substrate 5 ("NAP" = 2-methylnaphthalene). made in three steps (73%) from 2-naphthalene methanol (ref. 4). Products 7 were accessed with high selectivities and yields and could be converted to methyl esters 8, which were deprotected (R = Bn only) to elucidate the absolute S configuration.

Kurasoin B Total Synthesis

A total synthesis of kurasoin B was envisioned from product 7 (where R = A), but the "NAP" group could not be removed. Fortunately. exchange for a benzyl protecting group smoothly facilitated the total synthesis, giving synthetic kurasoin B with a 43 percent yield over 10 steps (ref. 3)

Synthesizing Kurasoin B Analogs

Beginning with intermediate B (from the previous panel), analogs 9-11 were made:



In an effort to vary the compound's indolyl mojety, electrophile 12 was prepared, which is currently being used to access analogs 13-16:

These first-generation analogs will soon be tested for their FTase inhibiting potency and anti-cancer pharmaceutical potential.

Acknowledgments

- · Brigham Young University Department of Chemistry and Biochemistry
- · Office of Research and Creative Activities (ORCA)
- · National Institute of Health (NIH)
- BYU Cancer Research Center

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