Sir:

Our search for new protein farnesyltransferase inhibitors recently led to the isolation of kurasoins A (1) and B (2) from a fermentation broth of Paecilomyces sp. FO-3684. Kurasoins A (1) and B (2) proved to inhibit farnesyltransferase in a dose-dependent manner. The IC_{50} values of 1 and 2 against protein farnesyltransferase were 59.0 and 58.7 μM, respectively.

The structures of 1 and 2 were initially deduced via extensive spectroscopic analyses and total syntheses of the racemates. However, the absolute configurations of 1 and 2 remained unknown. Herein we describe a concise asymmetric construction of 1 and 2, as well as the elucidation of their natural absolute configurations.

Concerning the total synthesis of kurasoin A (1), as our point of departure, Doering-Parikh oxidation of 2-(4-hydroxyphenyl)ethanol (3) (pyridine-SO_3, DMSO, Et_3N) furnished hydroxy aldehyde 4 (Scheme 1), which in turn was added vinylmagnesium bromide to obtain the racemic allylic alcohol 5 (45% overall yield). Kinetic resolution of (±)-5 via Sharpless asymmetric epoxidation [1.2 equiv (+)-DIPT, 1.0 equiv Ti(O-i-Pr)_4, 0.5 equiv t-butyl hydroperoxide, CH_2Cl_2, -20°C, 2 days] gave the desired epoxy alcohol (−)-6 in 35% yield (70% of theory) and >90% ee, as determined by NMR analysis of the derived (+)-MTPA ester. Protection of (−)-6 by TBSCI and imidazole afforded (−)-7 in 71% yield. Stereospecific alkylation of epoxide (−)-7 with phenylmagnesium bromide in the presence of Cul afforded the (−)-8 in 75% yield. Moffat oxidation (DCC, TFA, pyridine, DMSO, benzene) of (−)-8 furnished (−)-9 (88%). Finally, removal of the TBS group (HF-pyridine) generated (+)-kurasoin A (1) (68%). The synthetic material was identical with natural 1 in all respects (TLC, ^1H and ^13C NMR, IR, HRMS and UV), furthermore, optical rotation of synthetic (+)-1, [x]_D^{22} +9° (c=1.0, MeOH); natural (+)-1, [x]_D^{22} +7° (c=0.1, MeOH). The synthesis established that the absolute configuration of kurasoin A is (3S).

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subsequently furnished the (−)-enantiomer of 1 \([\alpha]_{D}^{22} -6.0° (c=1.0, \text{MeOH})\). We next analyzed racemic kurasoin A \([±]-1\), synthetic (+)-1, (−)-1 and natural (+)-1 via HPLC with a chiral stationary phase. The antipodes were separated and individually characterized. The natural-1 was identical with synthetic (+)-1.\(^1\)

On the other hand, for the total synthesis of kurasoin B (2), as our point of departure, addition of vinylmagnesium bromide to phenylacetaldehyde (10) afforded the racemic allylic alcohol 11 (Scheme 2) in 68% yield. Kinetic resolution of (+)-11 via Sharpless asymmetric epoxidation4) \([1.2 \text{ equiv } (-)-\text{DIPT}, 1.0 \text{ equiv } \text{Ti(O-\text{Pr})}_4, 0.5 \text{ equiv } \text{f-butyl hydroperoxide, } \text{CH}_2\text{Cl}_2, -20°C, 2 \text{ days}]\) gave the desired epoxy alcohol (−)-12 in 38% yield (76% of theory) and >90% ee, as determined by NMR analysis of the derived (+)-MTPA ester,5) and recovered 11 in 45% yield. Then, (−)-12 was oxidized (CrO\(_3\), H\(_2\)SO\(_4\)) to furnish epoxy ketone (−)-13 in 82% yield. Stereospecific alkylation of indole (2.0 equiv) with epoxide (−)-13 (1.4 equiv SnCl\(_4\), CCl\(_4\), 0°C)\(^6\) afforded (+)-kurasoin B (2) in 27% yield. The synthetic material was identical with natural 2 in all respects (TLC, \(^1\)H and \(^13\)C NMR, IR, HRMS and UV), furthermore, optical rotation [synthetic (+)-2, \([\alpha]_{D}^{22} +31° (c=0.33, \text{chloroform}); \text{natural } (+)-2\(^{11})), \([\alpha]_{D}^{22} +22° (c=0.1, \text{chloroform})]\]. The synthesis also established that the absolute configuration of kurasoin B is (3S).

Use of (−)-DIPT for asymmetric epoxidation of (±)-11 subsequently furnish the (−)-enantiomer of 2 \([\alpha]_{D}^{22} -15° (c=0.4, \text{chloroform})\]. We also analyzed racemic kurasoin B \([±]-2\), synthetic (+)-2, (−)-2 and natural (+)-2 via HPLC with a chiral stationary phase. The antipodes were separated and individually characterized. The natural-2 was identical with synthetic (+)-2.

The completion of these syntheses supported that kurasoin A (1), and B (2) are (3S)-3-hydroxy-4-(\(\beta\)-hydroxyphenyl)-1-phenyl-2-butanone, and (3S)-3-hydroxy-4-(3-indolyl)-1-phenyl-2-butanone.\(^2\)

In summary, we have prepared (+) and (−)-kurasoin A (1) and (+) and (−)-kurasoin B (2) in sufficient quantities to permit more detail biological evaluation. Further studies of the kurasoins are in progress.

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TOSHIAKI SUNAZUKA
TOMOYASU HIROSE
TIAN ZHI-MING
RYUJI UCHIDA
KAZURO SHIOMI
YOSHIHIRO HARIGAYA
SATOSHI ÔMURA*

Research Center for Biological Function,
The Kitasato Institute and School of
Pharmaceutical Sciences, Kitasato University,
Shirokane, Tokyo 108, Japan
(Received February 12, 1997)

References


\(^{11}\) Chiralcel OJ i.d. 4.6 x 250 mm column; mobile phase, n-hexane - 2-propyl alcohol (85:15); Flow rate, 1.0 ml/minute; Detection, UV at 275 nm.


