Total Synthesis of \((R)-\text{sarkomycin Methyl Ester via Regioselective Intermolecular Pauson--Khand Reaction and Iridium-Catalyzed Asymmetric Isomerization}

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Supporting Information

ABSTRACT: A new five-step enantioselective synthesis of \((R)-\text{sarkomycin methyl ester is described. The cyclopentane scaffold was built by a regioselective intermolecular Pauson--Khand reaction. Enantioselectivity was introduced by a novel Ir-catalyzed isomerization reaction. The last steps involved a catalytic hydrogenation of the exocyclic double bond, followed by the deprotection and elimination of the amino group. This route is the shortest enantioselective synthesis of this antibiotic reported to date.}

\((R)-\text{sarkomycin} \text{ 1, first isolated in 1953 from the soil microorganism} \text{ Streptomyces erythrozochromogenes,} \text{ is a cyclopentenone that has rapidly gained relevance not only for its antibiotic activity, but also for its strong inhibitory effect on several human tumors and carcinoma cell lines.} \text{ Because of its chemical instability, several stable derivatives such as its methyl ester} \text{ 2 or the cyclic lactone} \text{ 3, so-called cyclosarkomycin, have been developed. (See Figure 1.)}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Natural sarkomycin 1 and stable derivatives.}
\end{figure}

Although its structure is relatively simple, with only one stereogenic center, a large number of synthetic approaches toward sarkomycin (or sarkomycin derivatives) have been reported, often being used as a benchmark for new synthetic methodologies. Some of the syntheses addressed the racemic mixture and involve a relatively large number of steps. In other cases, the desired enantiopurity was obtained via (a) kinetic resolution, (b) the chiral auxiliary approach, or (c) classical racemic resolution. However, most of these processes gave low overall yields. A recent report by Von Zeechwitz and co-workers was the first to use asymmetric catalysis. They described a five-step sequence based on the Rh-catalyzed asymmetric conjugate addition of a hexenyl chain to cyclopentenone. However, none of the numerous syntheses of sarkomycin published so far have exploited the Pauson--Khand reaction (PKR), which is a textbook method for the construction of cyclopentanonic compounds. In most cases, they used cyclopentanic starting material. We envisioned that the cyclopentane ring of \((R)-\text{sarkomycin could be rapidly assembled by an intermolecular PKR using an appropriate internal alkyne and ethylene. The regioselectivity of internal alkylnes in the PKR has been widely studied and has proven useful in the synthesis of natural compounds such as prostaglandins and phytoprostanes B1. We hypothesized that the PKR of alkyne 4 with ethylene would afford adduct 5. The underlying challenge was the regioselective control of the reaction. In the PKR of internal alkylnes with similar steric hindrance for each substituent, regioselectivity is influenced mostly by electronic factors. According to previous studies, the most electron-withdrawing group (the methoxy carbonyl, in this case) should go to the \(\beta\)-position. Therefore, we assumed that, using 4 as an alkyne, the major isomer would be enone 5. We hypothesized that the

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