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Total Synthesis of (*R*)-Sarkomycin Methyl Ester via Regioselective Intermolecular Pauson−Khand Reaction and Iridium-Catalyzed Asymmetric Isomerization

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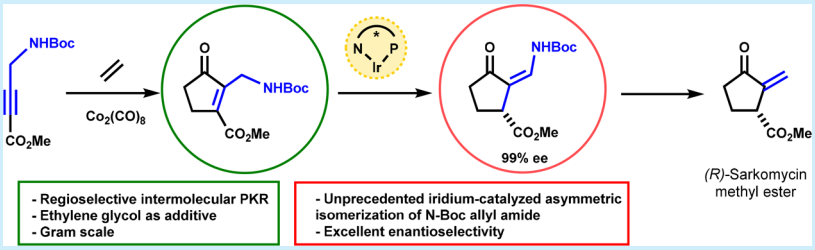
Supporting Information



ABSTRACT: A new five-step enantioselective synthesis of (*R*)-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 exocylic 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*)-Sarkomycin **1**, first isolated in 1953 from the soil microorganism *Streptomyces erythrochromogenes*,[1] 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.[2,3] Because of its chemical instability,[4] several stable derivatives such as its methyl ester[5] (**2**) or the cyclic lactone (**3**), so-called cyclosarkomycin,[6] have been developed. (See Figure 1.)

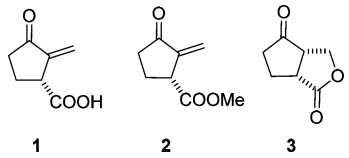


Figure 1. Natural sarkomycin **1** and stable derivatives.

Although its structure is relatively simple, with only one stereogenic center,[7] 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.[8] In other cases, the desired enantiopurity was obtained via (a) kinetic resolution,[9] (b) the chiral auxiliary approach,[10] or (c) classical racemic resolution.[11] However, most of these processes gave low overall yields. A recent report by Von Zezschwitz and co-workers[12] 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),[13] which is a textbook method for the construction of cyclopentanic compounds.[14] In most cases, they used cyclopentanic starting material. We envisioned that the cyclopentane ring of (*R*)-sarkomycin could be rapidly assembled by an intermolecular PKR[15] using an appropriate internal alkyne and ethylene. The regioselectivity of internal alkynes in the PKR has been widely studied[16] and has proven useful in the synthesis of natural compounds such as prostaglandins and phytoprostanes B1.[17]

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 alkynes with similar steric hindrance for each substituent, regioselectivity is influenced mostly by electronic factors.[16] According to previous studies, the most electron-withdrawing group (the methoxycarbonyl, in this case) should go to the *β*-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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