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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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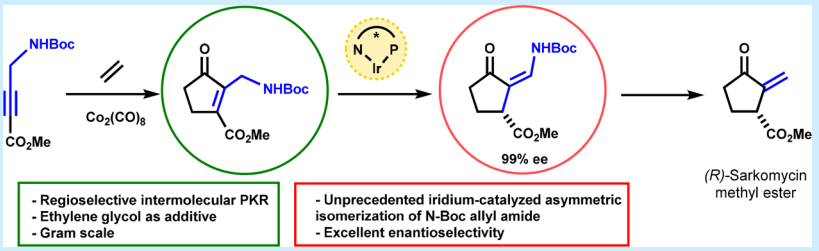
Supporting Information



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 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*)-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.)

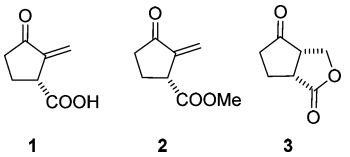


Figure 1. Natural sarkomycin **1** and stable derivatives.

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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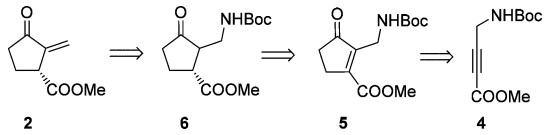
asymmetric hydrogenation would lead to cyclopentanone (**6**), which after hydrolysis and elimination, would afford (*R*)-sarkomycin methyl ester **2** (see Scheme 1).

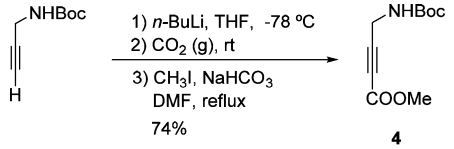
Scheme 1. Retrosynthetic Analysis of Sarkomycin Methyl Ester 2



Here, we report a total five-step synthesis of (*R*)-sarkomycin methyl ester from acyclic precursors, using a regioselective intermolecular PKR. During our search for appropriate asymmetric hydrogenation conditions, we uncovered an unprecedented iridium-catalyzed asymmetric isomerization of allylcarbamate **5** that allowed us to obtain (*R*)-sarkomycin methyl ester in excellent enantiomeric excess. The iridium-catalyzed isomerization of allyl amides[18] has received very little attention, in comparison to other substrates, such as allyl alcohols and allyl amines.[19−22] Moreover, to the best of our knowledge, this is the first example of an asymmetric isomerization of allyl carbamates to date.

The starting material **4**, according to our retrosynthetic analysis, was prepared in a straightforward manner in multigram scale by carboxylation of *N*-Boc-propargyl amine with CO_2, followed by esterification in 74% overall yield (Scheme 2).

Scheme 2. Synthesis of Internal Alkyne 4 from *N*-Boc-Propargyl Amine

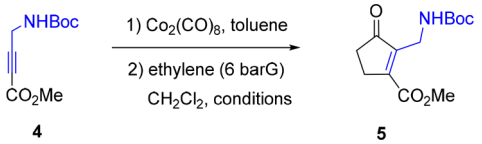


With alkyne **4** in hand, its cobalt hexacarbonyl complex was quantitatively prepared by treatment with $Co_2(CO)_8$ in toluene. After concentration in vacuo, the complex was submitted to several PKR conditions (Table 1). Although the standard thermal conditions under 6 barG pressure of ethylene gave only trace amounts of the product, we were pleased to see that, by using *N*-methylmorpholine *N*-oxide (NMO) as a promoter, it was obtained in 60%−75% yields with complete regioselectivity (Table 1, entry 1). Inspired by Baran's work,[15b] we recently reported a new synthetic protocol for intermolecular PKR using ethylene glycol (MEG) as an additive.[23] Adding 15% (v/v) of ethylene glycol to the reaction mixture, the yield increased up to 85% (Table 1, entry 2). Moreover, the crude material was cleaner and the workup much easier. We believe that the ethylene glycol behaves as a chelating agent reducing the activating effect of NMO and allowing coordination of the alkene before decomposition of the complex.

With the Pauson−Khand adduct (**5**) in hand, we then studied its hydrogenation into the corresponding cyclopentanone **6**. Catalytic hydrogenation using Pd/C afforded the racemic methyl ester (**6**) (see Table 2, entry 1). Somewhat surprisingly for a tetrasubstituted olefin, the hydrogenation took place in quantitative yield at 3 barG or even with a hydrogen balloon. The stereochemistry of the hydrogenated product was determined to be *trans* by two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy. In some occasions, we have observed the presence of a mixture of *cis* and *trans* stereoisomers. However, the former equilibrates to the more stable *trans* under acid catalysis and even on standing in chloroform solution.

With pure **5** in hand, we performed a catalyst screening for the corresponding asymmetric hydrogenation. We chose the following as standard conditions: 50 barG of hydrogen, 5 mol % catalyst loading, and stirring overnight at room temperature. Rh[(*R*,*R*)EtDuPhos (COD)]CF_3SO_3 (**8**), which is the standard Rh catalyst for asymmetric hydrogenation, afforded poor conversion (53%) with moderate enantiomeric excess (49% ee) (see Table 2, entry 2). Using [Rh(COD)(*R*-MaxPHOS)]-BF_4 (**9**),[24] full conversion was achieved, but with moderate enantiomeric excess (51% ee) (Table 2, entry 3). We then selected the iridium complexes of the P,N-ligands MaxPHOX developed by our group (see Scheme 3), which are highly active for the asymmetric hydrogenation of cyclic enamides and imines, giving excellent yields and enantioselectivities.[25] These modular P,N-ligands have three stereogenic centers, thus allowing the optimization of the stereoselectivity by playing with the four possible diastereoisomers. We started our hydrogenation study with the four diastereomers **10**−**13a** with isopropyl substituents as catalysts. Two of them (**10a** and **11a**) showed very low (15%−21%) conversion. However, unexpectedly, the hydrogenation of **5** using **12a** and **13a** afforded substantial conversion (70%−55%) into exocyclic enamine **7** with no traces of the hydrogenation product **6**. This observation indicates that an unprecedented isomerization process had occurred.[18] Enamine **7** was hydrogenated using Pd/C to the desired cyclopentanone **6**, which showed remarkable enantiomeric excess. Comparing the two best catalysts, **12a** (Table 2, entry 6) outperformed **13a** (Table 2, entry 7), both in terms of conversion and enantioselectivity . An increase of hydrogen pressure to 50 barG produced only traces of hydrogenated product; enamine **7** was still the major product without erosion of the enantioselectivity (Table 2, entry 8). We concluded that the *cis* configuration of the two

Table 1. Synthesis of Cyclopentenone 5 Using Pauson−Khand Reaction with Ethylene



entry	conditions	additives	isolated yield (%)
1	NMO (10 equiv), room temperature, 4 h		60−75
2	NMO (6 equiv), room temperature, 4 h	4 Å MS, MEG	85

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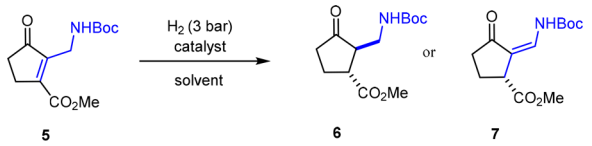
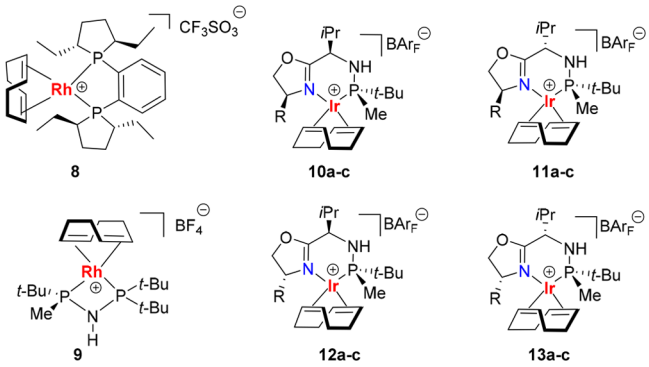
Table 2. Hydrogenation/Isomerization of 6



entry	catalyst	mol %	solvent	conversion (%)	isolated yield	enantiomeric excess, ee[b] (%)
1	**Pd/C**	20	CH_2Cl_2	100	**6**, 100	
2[a]	**8**	5	CH_2Cl_2	53	**6**, nd	(*R*)-49
3[a]	**9**	5	CH_2Cl_2	100	**6**, nd	(*R*)-51
4	**10a**	7	THF	15	nd	nd
5	**11a**	7	THF	21	nd	nd
6	**12a**	7	THF	70	**7**, 56	(*R*)-93
7	**13a**	7	THF	55	**7**, 45	(*R*)-71
8[a]	**12a**	7	THF	68	**7**, 50	(*R*)-93
9	**12b**	7	THF	75	**7**, 64	(*R*)-95
10	**12c**	7	THF			
11	**12b**	12	THF	88	**7**, 70	(*R*)-95
12	**12b**	12	CH_2Cl_2	93	**7**, 73	(*R*)-99

[a]50 barG of H_2 were used. [b]Measured by HPLC Chiralpak IA on compound **6**.

Scheme 3. Catalysts Used in the Hydrogenation Screening: (a) R = *i*Pr; (b) R = Ph; (c) R = *t*-Bu



bulky groups (in the oxazoline and the P atom) was necessary for the isomerization to occur. Of the two catalysts with such a requirement, **12a**, gave the best enantioselectivity; therefore its configuration was considered optimum. We then modified the substituent in the oxazoline ring. An increase in steric hindrance by placing a *tert*-butyl group at the oxazoline fragment (catalyst **12c**) did not lead to conversion (Table 2, entry 10). However, when a phenyl group was placed at the oxazoline (catalyst **12b**), the conversion increased and, after conversion to **6**, the enantiomeric excess rose to 95% ee (Table 2, entry 9). Since the reaction was not complete, we increased the catalyst loading to 12 mol % (Table 2, entry 11). Finally, when performing the reaction in dichloromethane (Table 2, entry 12), **6** was obtained in an enantiopure form after hydrogenation of **7** with Pd/C (ee >99).

At first sight, there was no evident driving force for the reaction to occur, since the isomerization led to a seemingly less-conjugated product. In order to gain insight into the isomerization process, DFT calculations were performed (see the Supporting Information (SI) for details).[26] We found that the isomerization is, in fact, an exergonic process, $\Delta G = -5.4$ kcal mol^{-1}. The counterintuitive formation of product **7** can be rationalized by considering two key factors, namely, (i) conjugation and (ii) formation of a strong intramolecular hydrogen bond (see Figure 2).

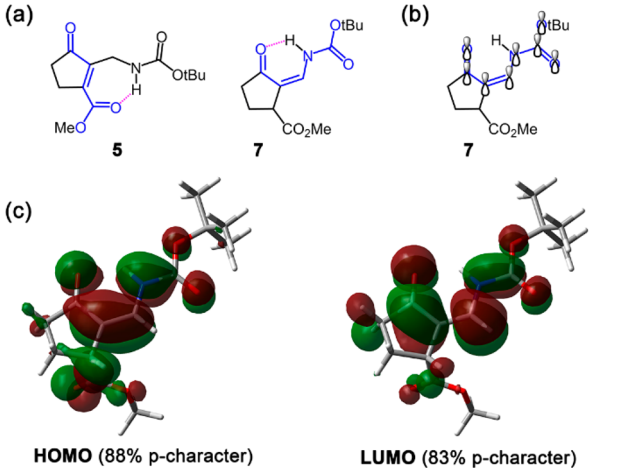


Figure 2. (a) Structures of the products before and after isomerization. The planar conjugated systems are depicted in blue. Hydrogen bonds are shown in magenta. (b) Schematic representation of the conjugated π-system of product **7**. (c) HOMO and LUMO of product **7** and major atomic contributions to the molecular orbitals.

In contrast with product **5**, in which the nitrogen atom had a slightly pyramidalized geometry, the N atom in product **7** was completely planar. This implies that the N p-orbital can overlap with the π-orbitals of the double bond. Therefore, there is no actual loss of conjugation upon isomerization, since the fragment that goes from the carbonyl of the cyclopentanone ring to the carbonyl of the Boc group is a completely planar, conjugated π-system. Inspection of the frontier molecular orbitals clearly illustrates this point, with the HOMO and LUMO being a combination of all the aforementioned p-orbitals forming an extended, conjugated π-system.

Intramolecular hydrogen bonds are also responsible for the stabilization of product **7**. The strong hydrogen bond explains the experimental observation of the Z-isomer of the enamide as the only product (see the SI). Although product **5** also has an intramolecular hydrogen bond, NBO calculations and NCI (noncovalent interactions) analysis showed that it is significantly weaker than the hydrogen bond in product **7**. This could also be observed by IR: the NH frequency of **7** (3301 cm^{-1})

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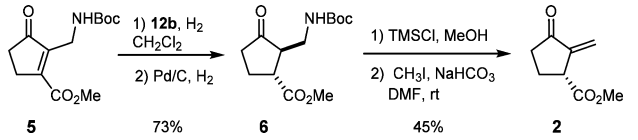
appears at a shorter wavelength than **5** (3401 cm^{-1}) and **6** (3439 cm^{-1}) (see the SI).

With the enantiopure compound **6** in hand, we then proceeded to perform the last steps (see Scheme 4). Boc-

Scheme 4. Final Steps To Afford (*R*)-sarkomycin Methyl Ester



deprotection was first attempted using TFA or HCl in MeOH. However, a considerable amount of base was then required to neutralize the solution. We realized that the chiral position was easily racemized in basic media and that neutral conditions were required. After much experimentation, we found that TMSCl in MeOH were the best reaction conditions for the cleavage of the Boc protecting group. After evaporation of the solvent, the crude product was dissolved in DMF, and $NaHCO_3$ (4.0 equiv) and MeI (4.0 equiv) were added to form the quaternary ammonium salt, which was eliminated spontaneously. When the reaction was completed by TLC, it was treated with water and extracted with diethyl ether. Because of the volatility of **2**, great care had to be taken to evaporate the solvent. The desired (*R*)-sarkomycin methyl ester (**2**) was obtained in 45% yield. An enantiomeric excess of 98% was determined by HPLC analysis.

In summary, we have described an innovative, short, and enantioselective synthetic route to the antibiotic (*R*)-sarkomycin methyl ester. We were able to concisely build a significant degree of molecular complexity using a novel approach based on high-yielding and remarkably selective steps. Starting from acyclic precursors, the regioselective intermolecular PKR afforded the tetrasubsituted enone in excellent yields. The use of ethylene glycol as an additive improved the yield significantly. The PKR adduct was then subjected to an unprecedented asymmetric isomerization catalyzed by an Ir-MaxPHOX complex. The resulting exocyclic enamine was subsequently hydrogenated and deprotected. Spontaneous elimination of the quaternary ammonium salt afforded the desired natural product as a methyl ester. The unexpected isomerization process catalyzed by a P,N-iridium complex is unprecedented and paves the way for new catalytic isomerization methodologies. The scope of this new transformation is currently being addressed by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01525.

Detailed experimental procedures, details of the theoretical calculations and characterization data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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