JOC The Journal of Organic Chemistry

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# Total Synthesis of (*R*)-Sarkomycin via Asymmetric Rhodium-Catalyzed Conjugate Addition

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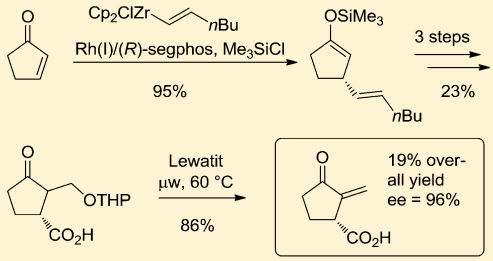
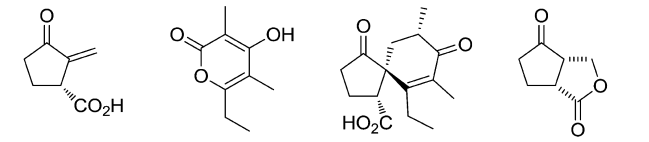
Supporting Information

**ABSTRACT:** (*R*)-Sarkomycin was prepared using a five-step total synthesis. Key steps in the enantioselective construction of the targeted scaffold were a rhodium-catalyzed asymmetric conjugate alkenyl addition with subsequent silyl trapping and a Mukaiyama aldol reaction with aqueous formaldehyde. Protection of the hydroxy group as a THP acetal and oxidative cleavage of the C,C-double bond provided a stable direct precursor to the natural product. The final liberation was carried out under slightly acidic conditions in a microwave-assisted reaction, resulting in a high yield of the "deceptive" sarkomycin. This represents the shortest enantioselective synthesis of this rather unstable compound to date and the first to employ asymmetric catalysis to introduce the stereogenic center.




## INTRODUCTION

Isolated from *Streptomyces erythrochromogenes* in 1953,[1] the secondary metabolite (*R*)-sarkomycin (**1**) was quickly garnering significant interest for several reasons. Not only does it show antibiotic activity, but, more importantly, it also demonstrates a strong anticancer activity against various carcinoma cell lines, including Ehrlich ascite tumors. As a result, in the 1950s and 1960s, it was used as a prescription drug for cancer treatments in Japan,[2] as well as in clinical studies in the US.[3] Even though sarkomycin contains only one stereogenic center, its configuration was initially inaccurately assigned[4] and only later corrected by Hill et al.[5] In 2007, Grond, Zezschwitz et al. reported on spirodionic acid (**3**), another metabolite from *Streptomyces*, whose biosynthesis most likely features a Diels–Alder type reaction of pyranone **2** with sarkomycin (**1**) as formal dienophile.[6] Over the years, more than 30 synthetic approaches have been published,[7,8] so sarkomycin might seem to be an already solved synthetic problem.




**1** Sarkomycin | **2** | **3** Spirodionic acid | **4** Cyclosarkomycin

Yet the plain structure of the natural product is misleading. Its sensitivity to acids and bases and its tendency to undergo dimerization and polymerization cause some major difficulties.[9] For example, they result in a very short shelf life and in the substance's attribution as the "deceptive" sarkomycin.[7b,c,e,f,8b] Consequently, most approaches to its formation are formal total syntheses that yield either sarkomycin esters[8a,h,i,10] or cyclosarkomycin (**4**).[7d,8a,c−g,11] However, it is quite difficult to liberate the natural product from these precursors, and yields for ester cleavages are 33% at best,[7b] while opening of cyclosarkomycin (**4**) was reported in a maximum yield of 43%.[7e]

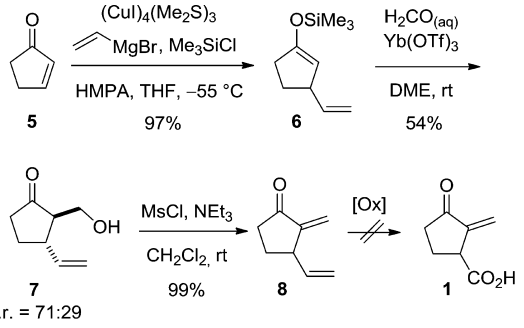
In addition to a number of racemic syntheses, enantiopure precursors to sarkomycin have been obtained through (kinetic) resolution,[8a−e] a chiral pool approach,[8f] and chiral auxiliary-based strategies.[8g−i] Surprisingly, synthesis using asymmetric catalysis has not been reported to date, even though this is generally considered the most elegant and state-of-the-art method for introducing stereogenic centers. To prove that spirodionic acid (**3**) is biosynthesized through a Diels–Alder reaction of sarkomycin, we pursued a total synthesis that could be adapted to prepare $^{13}$C-labeled material cost efficiently. This paper presents the first enantioselective preparation of sarkomycin using asymmetric catalysis.

## RESULTS AND DISCUSSION

The synthetic strategy is based on the asymmetric 1,4-addition of alkenyl zirconocenes with subsequent silyl trapping (a method we presented in a recent paper[12]) and on the total synthesis of spirodionic acid (**3**), in which an ethenyl group was used as a masked precursor to a carboxy moiety.[6b] First, a racemic synthesis was developed: Cyclopentenone (**5**) was transformed using a Cu-catalyzed, chlorotrimethylsilane-accelerated 1,4-addition of ethenylmagnesium bromide to yield silyl enol ether **6** (Scheme 1). Next, a Yb(OTf)$_3$-catalyzed Mukaiyama aldol reaction with aqueous formaldehyde (30 equiv) produced alcohol **7** in a *trans*/*cis* ratio of 71:29,[13] and mesylation and concomitant elimination were performed

**Received:** August 2, 2013
**Published:** September 30, 2013

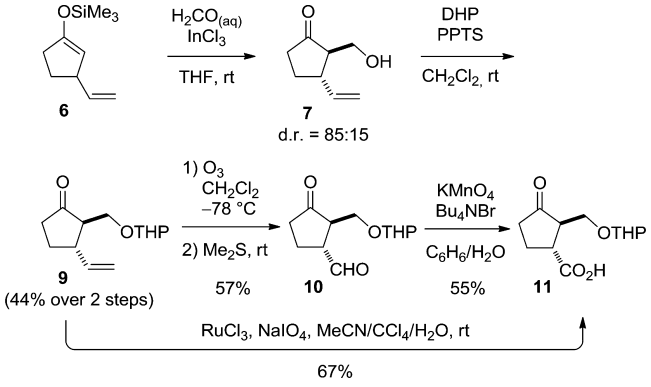
**Scheme 1. First Approach to Sarkomycin via Diene 8**




with MsCl and $NEt_3$[10e] to yield diene **8** in a quantitative yield.[14] The final step aimed to achieve a regioselective oxidative cleavage of the more electron-rich isolated double bond. To avoid racemization of the adjacent stereogenic center, this required that special precautions be taken. Unfortunately, all attempts with oxidants such as $OsO_4$/Oxone, ozone with subsequent oxidative or reductive workup, or $RuCl_3/NaIO_4$ failed to yield either the desired, or any other identifiable, product. Similar problems have been noted in previous syntheses of **1**[7c,8i,10f] and may be ascribed to the fast decomposition of the intermediate aldehyde or related structures.

An alternative approach consisted of performing the Mukaiyama aldol reaction with 50 mol% of $InCl_3$[15] and only 1 equiv of aqueous formaldehyde. The subsequent protection led to THP acetal **9** in a 44% yield over two steps (Scheme 2).

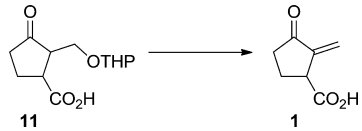
**Scheme 2. Racemic Synthesis of Precursor 11**




In addition to the desired product, significant amounts of 3-ethenylcyclopentanone arising from hydrolysis of silyl enol ether **6** were also isolated. The aldol reaction was then repeated with an excess of formaldehyde in the hope of favoring hydroxymethylation over protonation, but this led to products with oligomeric acetal chains in the 2-position. The amount of aldehyde was thus limited to 1 equiv, which is especially useful in view of preparing $^{13}C$-labeled material. Further protocols for hydroxymethylation,[16,17] as well as the introduction of other precursors[18,19] to a methylene group, were also explored but produced inferior results. The oxidative degradation of compound **9** required neutral conditions to avoid both the premature cleavage of the THP group that occurs under acidic conditions, as well as the epimerization at C-3 observed under alkaline conditions. Unlike diene **8**, ozonolysis of THP acetal **9** and a reductive workup with dimethyl sulfide worked well, delivering the aldehyde **10** in 57% yield, while transformation to acid **11** was achieved with $KMnO_4$ in a benzene/water biphasic mixture.[20] A more efficient one-step cleavage from **9** to **11** was performed with $RuCl_3/NaIO_4$.[21] This required carefully adjusted conditions: For an optimum yield, precisely 4 equiv of $NaIO_4$ and a rather high dilution (a 0.03 M concentration of **9**) were used. Because acid **11** can be stored at −18 °C over several months without decomposition, it is a remarkably stable precursor to sarkomycin.

Crucial for the overall efficiency of the total synthesis of sarkomycin (**1**) was its liberation from acid **11**, which, due to the instability of the natural product, had to be performed under the mildest possible conditions. A similar conversion of the dioxolane analogue of **11** has already been described by Argade et al.[7a] and Marx et al.[7e] with 0.5 M HCl (30−33% yield). Based on these results, a number of experiments were carried out in deuterated solvents. This made it possible to monitor the reaction by $^1H$ NMR spectroscopy; Table 1 provides the maximum yields and respective reaction times.

**Table 1. Optimization of the Liberation of Sarkomycin**




| entry | solvent | acid | $T$ (°C) | $t$ (h) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | MeOH-$d_4$ | 0.03 M DCl | 85 | 1 | 25 |
| 2 | DMSO-$d_6$ | 0.03 M DCl | 85 | 4 | 40 |
| 3 | acetone-$d_6$ | 0.03 M DCl | 45 | 10 | 41 |
| 4 | acetone-$d_6$ | Lewatit | 45 | 24 | 58 |
| 5 | acetone-$d_6$ | Lewatit | 60[b] | 1 | 84 |
| 6 | acetone-$d_6$ | Lewatit | 80[b] | 0.75 | 66 |
| 7 | acetone-$d_6$ | Lewatit | 100[b] | 0.5 | 29 |
| 8 | acetone-$d_6$[c] | Lewatit | 60[b] | 2 | 63 |
| 9 | benzene-$d_6$ | Lewatit | 60[b] | 0.1 | 16 |

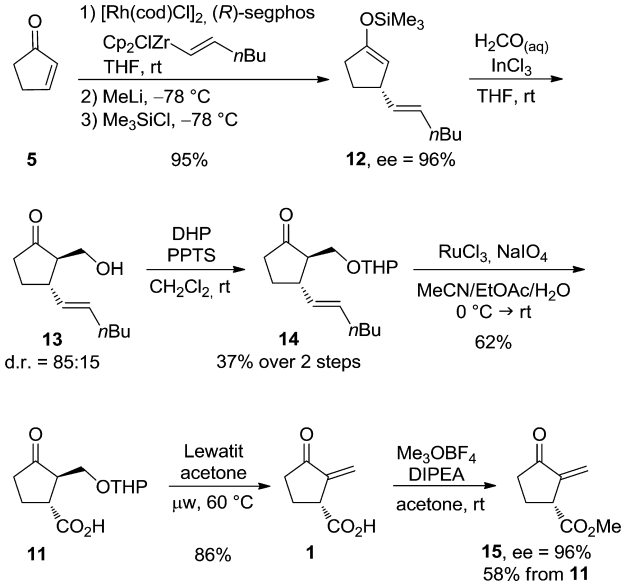
[a]Yields determined by $^1H$ NMR spectroscopy with mesitylene or benzene as internal standard. [b]Performed in a microwave reactor. [c]10:1 mixture of acetone-$d_6$/$D_2O$.

While a 0.03 M concentration of DCl in methanol was sufficient to achieve the intended elimination at 85 °C, it resulted in a substantial decomposition of **1** (entry 1). DMSO proved to be more suitable, with no significant decrease in yield noted even after prolonged reaction times (entry 2). With acetone, a more easily removable solvent, the temperature was lowered to 45 °C, resulting in an almost identical yield (entry 3). To facilitate removal of the acid, the ion-exchange resin Lewatit K 2611 was used instead of DCl, providing sarkomycin in 58% yield (entry 4). Further improvements were achieved by microwave-assisted synthesis which, in particular, caused tremendous rate acceleration. After a reaction time of only 1 h at 60 °C, a maximum yield of 84% was observed (entry 5), while reactions at 80 °C and 100 °C led to significant decomposition and inferior results (entries 6, 7). Mechanistically, the cleavage occurs as a two step-process: an initial acetal hydrolysis, followed by the elimination of water. In an attempt to speed up acetal cleavage and shorten the overall reaction time, another experiment was performed in a 10:1 acetone-$d_6$/$D_2O$ mixture, but, surprisingly this led to a longer reaction time and a lower yield (entry 8). Finally, very rapid conversion was observed in benzene, but decomposition of **1** prevented its synthetic use (entry 9).


dx.doi.org/10.1021/jo4016979 | J. Org. Chem. 2013, 78, 10718−10723

For an enantioselective approach, an asymmetric conjugate alkenyl addition with subsequent silyl trapping was performed.[12] The required hex-1-enyl zirconocene was prepared by hydrozirconation of hex-1-yne and underwent a 1,4-addition catalyzed by a rhodium/(*R*)-segphos complex (Scheme 3).

**Scheme 3. Asymmetric Synthesis of Sarkomycin**




Transmetalation of the enolate from zirconium to lithium was then achieved with 2 equiv of MeLi before $Me_3SiCl$ was added. This resulted in the formation of silyl enol ether **12** in 95% yield with an excellent ee of 96%. Hydroxymethylation to alcohol **13** and the subsequent conversion to the THP acetal **14** were then performed according to the racemic synthesis, furnishing an only slightly lower yield. For the oxidative cleavage of the hexenyl substituent, a modified solvent mixture containing EtOAc instead of $CCl_4$ was applied. By carrying out the reaction at 0 °C it was possible to improve the preparation of **11**. Finally, while microwave-assisted elimination to (*R*)-sarkomycin (**1**) succeeded just as well as with *rac*-**11**, isolation of the natural product turned out to be problematic. While sarkomycin is quite stable in acetone or chloroform solutions and can thus be stored at −18 °C for at least two weeks without decomposition, polymerization starts immediately upon removal of the solvent, causing an insoluble film to form in the flask.[22] Quantification and analysis of product **1** were therefore achieved using an unusual procedure: Sarkomycin was purified by extraction of the reaction mixture with an alkaline aqueous solution, and the reacidified phase was then extracted with diethyl ether. After removal of the solvent at temperatures below −40 °C, the residue was dissolved in $CDCl_3$. NMR spectra showed sarkomycin to be the sole product. Afterward, the $CDCl_3$ solution was thoroughly concentrated, and an 86% yield was calculated, which is consistent with the yield determined by NMR (Table 1, entry 5). To analyze the optical rotation, the diethyl ether extract of the reacidified aqueous solution was diluted with methanol, and the ether and majority of methanol were removed under reduced pressure. The remaining concentrated solution was used to determine the optical rotation, and its concentration was calculated by removing the solvent afterward. The specific rotation $[\alpha]_D^{20}$ was determined to be −53.2. On the basis of 96% ee, the pure (*R*)-enantiomer would thus have a value $[\alpha]_D^{20}$ of −55.4, which is significantly higher than the previously reported values of −34.7 for the synthetic material[8b] and −45 for sarkomycin isolated from natural sources.[22] As stated in the literature, this difference may be the result of the presence of degradation products in previous measurements.[8b] In contrast, sarkomycin prepared using the new approach described above appears to be of very high purity: Storage in diethyl ether at −65 °C resulted in the separation of solid product **1** (mp approximately −14 °C), though unfortunately no crystals suitable for X-ray analysis could be grown.

The subsequent esterification into methyl ester **15** also confirmed the yield and purity of **1** prepared in this manner. To do so, the ion-exchange resin was simply filtered off after complete conversion to **1**, followed by the addition of $Me_3OBF_4$ and diisopropylethylamine (DIPEA).[23] Though compound **15** also undergoes decomposition in neat form,[8h] it was possible to use rapid column chromatography to purify it, furnishing a 58% yield over the two steps from (*R*)-**11**. Moreover, this material showed 96% ee, proving the integrity of the stereogenic center throughout the total synthesis.

## CONCLUSION

For the first time, asymmetric catalysis was used in the synthesis of (*R*)-sarkomycin. While diene **8** turned out to be an inappropriate precursor, acid **11** enabled a fast, efficient liberation of the natural product. On the basis of the NMR spectra and high value of the specific rotation, the material obtained in this manner appears to be exceptionally pure. Moreover, this approach can be used to prepare $^{13}C$-labeled sarkomycin because it only requires the use of 1 equiv of reasonably priced aqueous $^{13}C$-formaldehyde. Preparation of this material and feeding experiments are currently in progress. As a whole, this five-step synthesis is not only the shortest way known to date for preparing enantiopure sarkomycin but is also that with the highest overall yield of 19%.

## EXPERIMENTAL SECTION

**General.** Microwave reactions were carried out in a CEM Discover LabMate microwave reactor in sealed 10 mL microwave synthesis vessels. Microwave power was controlled internally and limited to 60 W; the temperature was measured using an external IR-sensor. The reaction temperature and time are given with the respective preparations. $^1H$ NMR spectra were recorded at 250, 300, or 500 MHz. Chemical shifts are reported as $\delta$ values relative to the residual proton signal ($CHCl_3$: $\delta$ = 7.26 ppm) as internal reference. $^{13}C$ NMR spectra were recorded at 62.5, 75.5, or 125 MHz. Chemical shifts are reported as $\delta$ values relative to $CDCl_3$ ($\delta$ = 77.16 ppm) as internal reference. IR spectra were recorded on a FT-IR spectrometer. MS and HRMS spectra were acquired on a linear ion-trap Fourier transform mass-analyzer. Optical rotations were measured with concentrations in g/100 mL. Column chromatography was carried out on MN Kieselgel 60 M (Machery-Nagel, 0.04−0.063 mm). TLC analysis was carried out on precoated sheets (Merck DC Kieselgel 60 $F_{254}$). Solvents used for extraction and chromatography were of technical grade and distilled prior to use. All moisture-sensitive reactions were carried out under dry nitrogen or argon in oven- and/or flame-dried glassware. THF was distilled from sodium benzophenone ketyl. HMPA was distilled from sodium. DIPEA, triethylamine, acetonitrile, and dichloromethane were distilled from calcium hydride. All other chemicals are of commercial origin and used as received.

**3-Ethenyl-1-trimethylsiloxycyclopent-1-ene (6).** A solution of ethenyl magnesium bromide (18 mL, 18 mmol, 1.0 M in THF) and HMPA (6.3 mL, 36 mmol) in THF (25 mL) was cooled to −55 °C, $(CuI)_4(DMS)_3$ (319 mg, 336 $\mu$mol) was added, and the resulting


dx.doi.org/10.1021/jo4016979 | J. Org. Chem. 2013, 78, 10718−10723

suspension was stirred at this temperature for 20 min. A solution of cyclopent-2-enone (**5**, 1.01 mL, 12.0 mmol) and $Me_3SiCl$ (3.6 mL, 28 mmol) in THF (10 mL) was added dropwise over 15 min, and stirring was continued for 30 min. The solution was warmed to rt, and $NEt_3$ (3.3 mL, 24 mmol) was added. The reaction mixture was poured into *n*-pentane (500 mL) and washed with water (3 × 150 mL), and the organic phase was dried over $Na_2SO_4$. Filtration over Celite/activated charcoal and evaporation of the solvents yielded 2.14 g (97%) of the title compound **6** as a colorless oil. Analytical data were in accordance with those in the literature.[24]

***trans*-3-Ethenyl-2-hydroxymethylcyclopentanone (7).** *With Yb(OTf)$_3$.* $Yb(OTf)_3$ (620 mg, 1.00 mmol) and 3-ethenyl-1-trimethylsiloxycyclopent-1-ene (**6**, 1.95 g, 10.7 mmol) were dissolved in a mixture of aqueous formaldehyde (25 mL, 37% in $H_2O$, 336 mmol) and dimethoxyethane (25 mL), and the solution was stirred for 24 h at rt. The reaction mixture was then concentrated under reduced pressure, diluted with water (100 mL), and extracted with $Et_2O$ (3 × 150 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by Kugelrohr distillation (80 °C, 0.01 mbar) afforded 808 mg, 54% of the title compound **7** with a *trans*/*cis* ratio of 71:29 (determined by $^1$H NMR) as colorless oil.

*With InCl$_3$.* To solution of 3-ethenyl-1-trimethylsiloxycyclopent-1-ene (**6**, 2.17 g, 11.9 mmol) and aqueous formaldehyde (0.89 mL, 37% in $H_2O$, 12 mmol) in THF (55 mL) was added $InCl_3$ (1.33 g, 6.01 mmol), and the reaction mixture was stirred for 22 h at rt. THF was removed under reduced pressure, and the reaction mixture was diluted with $CH_2Cl_2$ (10 mL) and washed with water (20 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL), and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield 1.93 g of crude product with a *trans*/*cis* ratio of 85:15 (determined by $^1$H NMR). ESI-HRMS calcd for $C_8H_{12}O_2Na$: 163.0730; found: 163.0729. Further analytical data were in accordance with those in the literature.[6b]

**3-Ethenyl-2-methylenecyclopentanone (8).** A solution of *trans*-3-ethenyl-2-hydroxymethylcyclopentanone (**7**, 95.0 mg, 0.678 mmol from the $Yb(OTf)_3$-catalyzed transformation) in $CH_2Cl_2$ (3.2 mL) was treated with $NEt_3$ (395 μL, 2.83 mmol) and MsCl (309 mg, 2.70 mmol), and the reaction mixture was stirred for 24 h at rt. Then, $H_2O$ (15 mL) was added, the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Column chromatography over silica gel (*n*-pentane/EtOAc 5:1) yielded 82.0 mg, 99% of the title compound **8** ($R_f$ = 0.70) as a viscous, colorless oil. ESI-HRMS calcd for $C_8H_{10}ONa$: 145.0624; found: 145.0627. Further analytical data were in accordance with those in the literature.[14]

***trans*-3-Ethenyl-2-(tetrahydropyran-2-yloxymethyl)-cyclopentanone (9).** Crude *trans*-3-ethenyl-2-hydroxymethylcyclopentanone (**7**, 1.93 g) from the $InCl_3$-mediated transformation was dissolved in $CH_2Cl_2$ (20 mL), and 3,4-dihydro-2*H*-pyran (3.3 mL, 36 mmol) and PPTS (301 mg, 1.20 mmol) were added subsequently at rt. The reaction mixture was stirred for 17 h, water (50 mL) was added, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography over silica gel (*n*-pentane/EtOAc 5:1) yielded 1.18 g of the title compound **9** ($R_f$ = 0.35) in 44% yield over the two steps from **6** as highly viscous, colorless oil. $^1$H NMR (300 MHz, $CDCl_3$, signals marked with "*" belong to just one diasteromer): $\delta$ = 5.81 (ddd, $^3J$ = 17.3, 10.0, 7.4 Hz, 1H), 5.16−5.01 (m, 2H), 4.54 (m, 1H), 4.08 (dd, $^2J$ = 9.9, $^3J$ = 3.6 Hz, 1H*), 3.83 (dd, $^2J$ = 9.8, $^3J$ = 3.2 Hz, 1H*), 3.81−3.75 (m, 1H), 3.72 (dd, $^2J$ = 9.9, $^3J$ = 3.2 Hz, 1H*), 3.49 ($m_c$, 1H), 3.42 (dd, $^2J$ = 9.9, $^3J$ = 3.5 Hz, 1H*), 2.96−2.80 (m, 1H), 2.42−2.34 (m, 1H), 2.17 ($m_c$, 2H), 2.04−1.95 (m, 1H), 1.82−1.42 (m, 7H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 217.9, 217.5, 140.3, 140.2, 115.3, 115.2, 99.1, 98.5, 63.5, 63.4, 61.9, 61.4, 55.0, 54.8, 43.2, 43.0, 38.5, 38.4, 31.0, 30.4, 27.5, 25.43, 25.41, 19.3, 19.0. IR (neat): $\nu$ = 2940, 1743, 1032, 1020, 907 cm$^{-1}$. MS (ESI, 70 eV), *m*/*z* (%): 246.9 (100) $[M + Na]^+$. ESI-HRMS calcd for $C_{13}H_{20}O_3Na$: 247.1316; found: 247.1308.

***trans*-2-(Tetrahydropyran-2-yloxymethyl)cyclopentanone-3-carbaldehyde (10).** A solution of *trans*-3-ethenyl-2-(tetrahydropyran-2-yloxymethyl)cyclopentanone (**9**, 33 mg, 0.15 mmol) in $CH_2Cl_2$ (35 mL) was cooled to −78 °C. Ozone was introduced into the solution over 90 s until a slightly blue color persisted, followed by oxygen until the solution was colorless. Then, $Me_2S$ (66 μL, 0.90 mmol) was added, and the reaction mixture was allowed to warm to rt and stirred for additional 12 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography over aluminum oxide (Brockmann activity II, *n*-hexane/EtOAc 1:1) to yield 19 mg, 57% of the title compound **10** ($R_f$ = 0.36) as highly viscous, colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.77 ($m_c$, 1H), 4.57−4.46 (m, 1H), 4.00−3.38 (m, 4H), 3.27−3.14 (m, 1H), 2.69−2.59 (m, 1H), 2.44−1.88 (m, 3H), 1.84−1.36 (m, 7H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 215.5, 215.2, 201.4, 201.3, 99.5, 98.6, 65.4, 65.1, 62.5, 61.7, 52.0, 51.9, 49.9, 49.8, 37.64, 37.61, 30.4, 30.37, 25.4, 25.3, 21.54, 21.51, 19.5, 19.1. IR (neat): $\nu$ = 2941, 2872, 2725, 1739, 1723, 1121, 1012 cm$^{-1}$. ESI-HRMS calcd for $C_{12}H_{19}O_4$: 227.1278; found: 227.1260.

***trans*-2-(Tetrahydropyran-2-yloxymethyl)cyclopentanone-3-carboxylic Acid (11).** A solution of *trans*-3-ethenyl-2-(tetrahydropyran-2-yloxymethyl)cyclopentanone (**9**, 328 mg, 1.46 mmol) in a mixture of acetonitrile (21 mL), $CCl_4$ (14 mL), and $H_2O$ (14 mL) was treated with $RuCl_3$ (61.0 mg, 293 μmol) and $NaIO_4$ (625 mg, 2.92 mmol). Additional $NaIO_4$ (625 mg, 2.92 mmol) was added after 30 min, and stirring was continued for 1.5 h before the reaction mixture was filtered over activated charcoal/Celite. The filter cake was washed with EtOAc (20 mL), and the filtrate was extracted with aqueous $NaHCO_3$ (0.6 M, 3 × 30 mL). The combined aqueous phases were acidified with HCl (1 M) to pH 3 and extracted with EtOAc (5 × 15 mL), and the combined organic phases were dried over $Na_2SO_4$. The solvent was removed under reduced pressure to yield 239 mg, 67% of the title compound **11** as highly viscous, colorless oil. $^1$H NMR (300 MHz, $CDCl_3$, $RCO_2H$ not observed, signals marked with "*" belong to just one diasteromer): $\delta$ = 4.61−4.55 (m, 1H), 4.08 (dd, $^2J$ = 10.0, $^3J$ = 4.5 Hz, 1H*), 3.97 (dd, $^2J$ = 9.9, $^3J$ = 3.4 Hz, 1H*), 3.88−3.71 (m, 1H), 3.76 (dd, $^2J$ = 9.9, $^3J$ = 3.2 Hz, 1H*), 3.60 (dd, $^2J$ = 10.0, $^3J$ = 3.7 Hz, 1H*), 3.50 ($m_c$, 1H), 3.34−3.22 (m, 1H), 2.64 ($m_c$, 1H), 2.54−2.33 (m, 2H), 2.31−2.14 (m, 1H), 2.11−1.95 (m, 1H), 1.76−1.43 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 215.9, 215.6, 179.6, 179.4, 99.5, 98.7, 64.9, 64.7, 62.5, 61.7, 52.4, 52.1, 43.7, 43.6, 38.25, 38.22, 30.43, 30.37, 25.41, 25.35, 24.72, 24.67, 19.5, 19.1. IR (neat): $\nu$ = 2943, 2875, 1733, 1705 cm$^{-1}$. MS (ESI, 70 eV), *m*/*z* (%): 265 (100) $[M + Na]^+$, 141 (21) $[M - OTHP]^+$. ESI-HRMS calcd for $C_{12}H_{18}O_5Na$: 265.1046; found: 265.1048.

**(3*S*)-(Hex-1*E*-enyl)-1-trimethylsilyloxycyclopent-1-ene (12).** A solution of $[Rh(cod)Cl]_2$ (24.7 mg, 50.1 μmol) and (*R*)-segphos (73.3 mg, 120 μmol) in THF (4.0 mL) was stirred for 1 h at rt. In parallel, a suspension of $Cp_2ZrHCl$ (671 mg, 2.60 mmol) in THF (8.0 mL) was treated with hex-1-yne (274 μL, 2.40 mmol), and stirring was continued for 1 h at rt. Cyclopent-2-enone (**5**, 168 μL, 2.01 mmol) was added to the catalyst mixture followed by the alkenyl zirconocene solution. The reaction mixture was stirred for 1 h at rt and then cooled to −78 °C followed by addition of methyllithium (3.5 mL, 5.3 mmol, 1.5 M in $Et_2O$). After 1 h, $Me_3SiCl$ (0.76 mL, 6.0 mmol) was added, and stirring was continued for 1 h at −78 °C. Triethylamine (3.3 mL, 24 mmol) and urea hydrogen peroxide (1.13 g, 12.0 mmol) were added subsequently, and the reaction mixture was stirred for 24 h at rt. The reaction mixture was diluted with THF (10 mL), filtered over Celite, diluted with water (40 mL), and extracted with *n*-pentane (3 × 50 mL). The combined organic phases were dried over $Na_2SO_4$, suspended with activated charcoal (1 g), and filtered over Celite. The solvents were removed under reduced pressure to furnish 455 mg, 95% of the title compound **12**. 96% ee was determined by GC on a chiral stationary phase; analytical data were in accordance with those in the literature.[12]

**(3*S*)-(Hex-1*E*-enyl)-(2*R*)-(tetrahydropyran-2-yloxymethyl)-cyclopentanone (14).** To a solution of (3*S*)-(hex-1*E*-enyl)-1-


dx.doi.org/10.1021/jo4016979 | J. Org. Chem. 2013, 78, 10718−10723

trimethylsilyloxycyclopent-1-ene (**12**, 1.36 g, 5.70 mmol) in THF (30 mL) were added $InCl_3$ (630 mg, 2.84 mmol) and aqueous formaldehyde (424 μL, 37% in $H_2O$, 5.70 mmol). The reaction mixture was stirred for 40 h at rt, the solvent was removed under reduced pressure, and the residue was diluted with $Et_2O$ (20 mL) and water (20 mL). The aqueous phase was extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with brine (20 mL) and dried over $Na_2SO_4$, and the solvent was removed under reduced pressure to afford 1.29 g of crude (3*S*)-(hex-1*E*-enyl)-2-hydroxymethylcyclopentanone (**13**) as a yellowish oil with a *trans*/*cis* ratio of 85:15 (determined by $^1H$ NMR).

A solution of the crude alcohol **13** (866 mg) in $CH_2Cl_2$ (20 mL) was treated with 3,4-dihydro-2*H*-pyran (1.04 mL, 11.5 mmol) and PPTS (96 mg, 0.38 mmol), and the reaction mixture was stirred for 24 h at rt. Afterward, $H_2O$ (50 mL) was added, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Column chromatography over silica gel (*n*-pentane/EtOAc 10:1) yielded 395 mg of the title compound **14** ($R_f$ = 0.32) as a colorless oil. This corresponds to 37% yield over the two steps from compound **12**. $^1H$ NMR (300 MHz, $CDCl_3$, signals marked with "*" belong to just one diasteromer): δ = 5.61−5.46 (m, 1H), 5.45−5.34 (m, 1H), 4.56 ($m_c$, 1H), 4.05 (dd, $^2J$ = 9.9, $^3J$ = 3.5 Hz, 1H*), 3.82 (dd, $^2J$ = 9.9, $^3J$ = 3.2 Hz, 1H*), 3.79−3.72 (m, 1H), 3.68 (dd, $^2J$ = 9.8, $^3J$ = 3.2 Hz, 1H*), 3.48 ($m_c$, 1H), 3.39 (dd, $^2J$ = 9.9, $^3J$ = 3.5 Hz, 1H*), 2.83 ($m_c$, 1H), 2.39−2.29 (m, 1H), 2.20−2.06 (m, 2H), 2.06−1.96 (m, 2H), 1.96−1.87 (m, 1H), 1.77−1.41 (m, 7H), 1.39−1.23 (m, 4H), 0.87 (t, $^3J$ = 7.1 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 218.4, 218.0, 131.9, 131.8, 99.1, 98.6, 63.6, 63.4, 61.9, 61.4, 55.5, 55.3, 42.3, 42.2, 38.7, 38.6, 32.3, 31.8, 30.52, 30.49, 28.18, 28.16, 25.6, 25.5, 22.28, 22.26, 19.3, 19.1, 14.0. IR (neat): ν = 2927, 2870, 1744, 1124, 1032, 1020 $cm^{-1}$. MS (EI, 70 eV), *m*/*z* (%): 280 (1) $[M]^+$, 178 (15) $[M-HOTHP]^+$, 85 (100) $[THP]^+$. ESI-HRMS calcd for $C_{17}H_{28}O_3Na$: 303.1931; found: 303.1929.

**(2*R*)-(Tetrahydropyran-2-yloxymethyl)cyclopentanone-(3*R*)-carboxylic Acid (11).** A solution of (3*S*)-(hex-1*E*-enyl)-(2*R*)-(tetrahydropyran-2-yloxymethyl)cyclopentanone (**14**, 300 mg, 1.07 mmol) in a mixture of acetonitrile (18 mL), EtOAc (12 mL), and $H_2O$ (12 mL) was cooled to 0 °C and treated with $RuCl_3$ (44 mg, 0.21 mmol) and $NaIO_4$ (915 mg, 4.28 mmol). Stirring was continued for 30 min at 0 °C and for 15 min at rt. Activated charcoal (100 mg) was added, and the reaction mixture was filtered over Celite. The filter cake was washed with EtOAc (20 mL), and the filtrate was extracted with half saturated aqueous $NaHCO_3$ (3 × 36 mL). The combined aqueous phases were acidified with HCl (6 M) to pH 2 and extracted with EtOAc (3 × 75 mL), and the combined organic phases were dried over $Na_2SO_4$. The solvents and valeric acid were removed under reduced pressure to yield 161 mg, 62% of the title compound as highly viscous, yellowish oil.

**2-Methylenecyclopentanone-(3*R*)-carboxylic Acid (Sarkomycin, 1).** A 10 mL CEM microwave synthesis vessel was charged with a solution of (2*R*)-(tetrahydropyran-2-yloxymethyl)-cyclopentanone-(3*R*)-carboxylic acid (**11**, 54.0 mg, 223 μmol) in acetone (2 mL), and ion-exchange resin Lewatit K2611 (200 mg) was added. The vessel was sealed, and the reaction was carried out in the microwave reactor (60 °C, 1 h, 60 W max.). Afterward, the ion-exchange resin was filtered off, EtOAc (10 mL) was added, and acetone was removed under reduced pressure. The organic phase was extracted with aqueous $NaHCO_3$ solution (5%, 3 × 10 mL), and the combined aqueous phases were extracted with EtOAc (10 mL), acidified with aqueous HCl (6 M) to pH 2, and then extracted with $Et_2O$ (4 × 15 mL). After being dried over $Na_2SO_4$, the solvent was evaporated at a pressure of 0.02 mbar at −40 °C to −50 °C. The residue was dissolved in $CDCl_3$ for NMR analysis, and thorough concentration of the NMR sample after the measurements yielded 27 mg, 86% of the title compound **1** as a rapidly polymerizing oil. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 7.39 (bs, 1H), 6.21 (d, $^2J$ = 2.6 Hz, 1H), 5.68 (d, $^2J$ = 2.3 Hz, 1H), 3.80−3.72 (m, 1H), 2.65−2.16 (m, 4H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 204.4, 178.0, 141.9, 121.3, 45.7, 36.7, 23.0. ESI-HRMS calcd for $C_7H_7O_3$: 139.0401; found: 139.0405. $[\alpha]_D^{20}$ −53.2 (*c* 0.56, MeOH).

**Methyl 2-Methylenecyclopentanone-(3*R*)-carboxylate (15).** A 10 mL CEM microwave synthesis vessel was charged with a solution of (2*R*)-(tetrahydropyran-2-yloxymethyl)cyclopentanone-(3*R*)-carboxylic acid (**11**, 38.2 mg, 158 μmol) in acetone (1.5 mL), and ion-exchange resin Lewatit K2611 (200 mg) was added. The vessel was sealed, and the reaction was carried out in the microwave reactor (60 °C, 1 h, 60 W max.). Afterward, the ion-exchange resin was filtered off, the filtrate was treated with DIPEA (40.2 μL, 236 μmol) and $Me_3OBF_4$ (35.1 mg, 237 μmol), and the reaction mixture was stirred for 1 h at rt. Then, $H_2O$ (10 mL) was added, the aqueous phase was extracted with $Et_2O$ (4 × 5 mL), the combined organic phases were dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Column chromatography over silica gel (*n*-pentane/$Et_2O$ 1:1) afforded 14.0 mg, 58% of the title compound **15** ($R_f$ = 0.46) as colorless oil. 96% ee was determined by HPLC analysis on a chiral stationary phase. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 6.16 (d, $^2J$ = 2.6 Hz, 1H), 5.58 (d, $^2J$ = 2.4 Hz, 1H), 3.76−3.72 (m, 1H), 3.74 (s, 3 H), 2.59−2.52 (m, 1H), 2.39−2.31 (m, 1H), 2.31−2.24 (m, 1H), 2.21−2.13 (m, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 204.7, 173.0, 142.5, 120.5, 52.5, 45.9, 36.8, 23.1. ESI-HRMS calcd for $C_8H_{10}O_3Na$: 177.0522; found: 177.0529.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1H$ and $^{13}C$ NMR spectra of all compounds as well as chromatograms for the determination of the enantiomeric excesses of compounds **12** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

J.W. is indebted to the Konrad-Adenauer-Stiftung for a doctoral scholarship. The authors are indebted to Sophie Schlondorff for careful proofreading of the manuscript.

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dx.doi.org/10.1021/jo4016979 | *J. Org. Chem.* 2013, 78, 10718−10723