Total Synthesis of Racemic and Optically Active Sarkomycin

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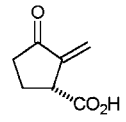
trans-3-Carboxy-2-diethoxyphosphorylcyclopentanone **(11)**, a key precursor of sarkomycin **1**, has been synthesized in the rhodium(II) acetate promoted cyclization of diethyl 1-diazo-2-oxohept-6-ene-phosphonate **(9)**, followed by transformation of the 3-vinyl moiety into the 3-carboxylic group. Racemic **11** has been resolved into enantiomers via diastereoisomeric enamine-type derivatives **13** resulting from its reaction with (−)-(*S*)-1-(1-naphthyl)ethylamine. The structure and absolute configuration of **13** have been determined by X-ray crystal structure analysis. The enantiomerically enriched (up to 77.6% ee) acid **11** has also been obtained in the enzyme-promoted hydrolysis of racemic 2-diethoxyphosphoryl-3-methoxycarbonylcyclopentanone **(12)**. The Horner-Wittig reaction of **11** with gaseous formaldehyde has been applied to introduce the exocyclic α-methylene moiety into the cyclopentanone system and thus to complete the synthesis of the racemate and, for the first time, each enantiomer of sarkomycin **1**. A phenomenon of enantiomer self-discrimination has been observed in ^{31}P NMR spectra of the nonracemic acid **11** and explained in terms of the formation of the hydrogen bonded homo- and hetero-dimers. The existence of dimeric structures has been confirmed by X-ray analysis of the structurally closely related *trans*-3-carboxy-2-diphenylphosphinoylcyclopentanone **(16)**.

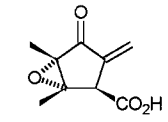
Introduction

Sarkomycin **1**, a member of the cyclopentanoid class of antibiotics, was first isolated by Umezawa et al.[1] in 1953 and its structure established in 1955.[2] Sarkomycin **1** possesses a stereogenic centre at carbon atom 3 of the cyclopentanone ring and the soil microorganisms (*Streptomyces erythrochromogenes, Shygelle* species and *Streptomyces neyagawaensis*) produce the levorotatory enantiomer having the absolute configuration *R* as correctly assigned by Hill in 1967.[3] Like methylenomycins **2**, **3** and **4**, closely related cyclopentanoid antibiotics, sarkomycin **1** shows not only antibacterial and antiphage properties but also displays antitumor activity.[4] For instance, sarkomycin **1** has inhibitory effects on Ehrlich ascites tumors in mice, Yoshida sarcoma, Sarcoma-180 and Hela human carcinoma cell lines. However, it is not active against solid tumors. The pharmacological studies of sarkomycin has resulted in its clinical use as an antitumor agent in Russia, Japan and USA.

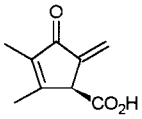
Although sarkomycin **1** is one of the simplest antitumor compounds known, its total synthesis has been a formidable challenge and elicited considerable interest in the synthetic community. This is because of a high chemical instability of this deceptively simple structure which is sensitive to acids and bases, very reactive toward dimerization and polymerization and not extremely stable toward storage. Among the numerous reported syntheses of sarkomycin **1**,[5−40] the majority are directed at the racemic compound. Moreover, many of them are so-called formal syntheses because they are completed at the stage of the sarkomycin precursors such as cyclosarkomycin[15,20,21,26] or sarkomycin esters (methyl,[12,16,17,22,27,28,30] ethyl,[13,31] isopropyl,[23] *tert*-butyl[31]). The latter are also unstable and cannot be easily converted to **1**. Similarly, a few recent syntheses aimed at the preparation of optically active sarkomycin **1** are formal and describe (−)-(*R*)- and (+)-(*S*)-sarkomycin methyl ester **5**[29] and (−)-cyclosarkomycin **6**[32,38−40] and its (+)-enantiomer[37] as the final products.



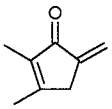
Sarkomycin, (-)-**1**



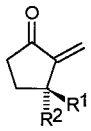
Methylenomycin A, (+)-**2**



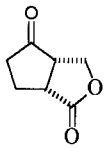
Desepoxy-4,5-didehydro-methylenomycin A, (+)-**3**



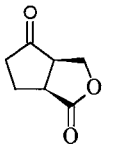
Methylenomycin B, **4**



(-)-(*R*)-**5**, R^1=H; R^2=CO_2Me
(+)-(*S*)-**5**, R^1=CO_2Me; R^2=H



(2*S*, 3*R*)-(-)-**6**



(2*R*, 3*S*)-(+)-**6**

As part of our program aimed at the efficient and versatile total synthesis of biologically active cyclopentanones and cyclopentenones using phosphorus and sulfur reagents,[41] we became interested in the preparation of sarkomycin **1**. In this paper we would like to disclose the details of our approach to the racemic compound as well as to describe the first preparation of both enantiopure forms of this target.

Synthesis of Racemic Sarkomycin (±)-1

Since sarkomycin **1** contains the reactive exocyclic α-methylene moiety and is a highly unstable compound, our strategy based on the experience with the synthesis of methylenomycin B **4**[42] was to synthesize 3-carboxy-2-diethoxyphosphorylcyclopentan-1-one as a key intermediate which should be converted into sarkomycin **1** via the Horner–Wittig reaction in the last step of the synthetic sequence. Moreover, we decided to utilize the intramolecular carbenoid cyclization for the construction of the suitably substituted cyclopentanone ring. A total synthesis of (±)-**1** starting from the readily available diethyl 2-oxopropanephosphonate (**7**) is shown in Scheme 1 and briefly discussed below.[43]

In the first step, the dianion generated from the β-oxophosphonate **7**[44] upon subsequent treatment with sodium hydride and butyllithium was alkylated with homoallyl bromide to give the β-oxophosphonate **8** which, under typical diazo-transfer reaction conditions,[45] was transformed into the α-diazophosphonate **9**. Decomposition of this intermediate in the presence of rhodium(II) acetate afforded *trans*-2-diethoxyphosphoryl-3-vinylcyclopenta-

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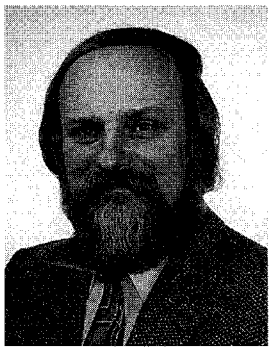
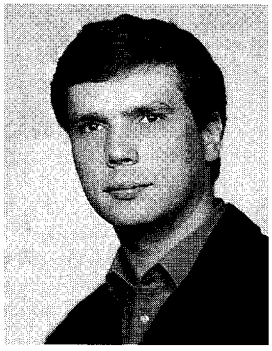
Biographical Sketches

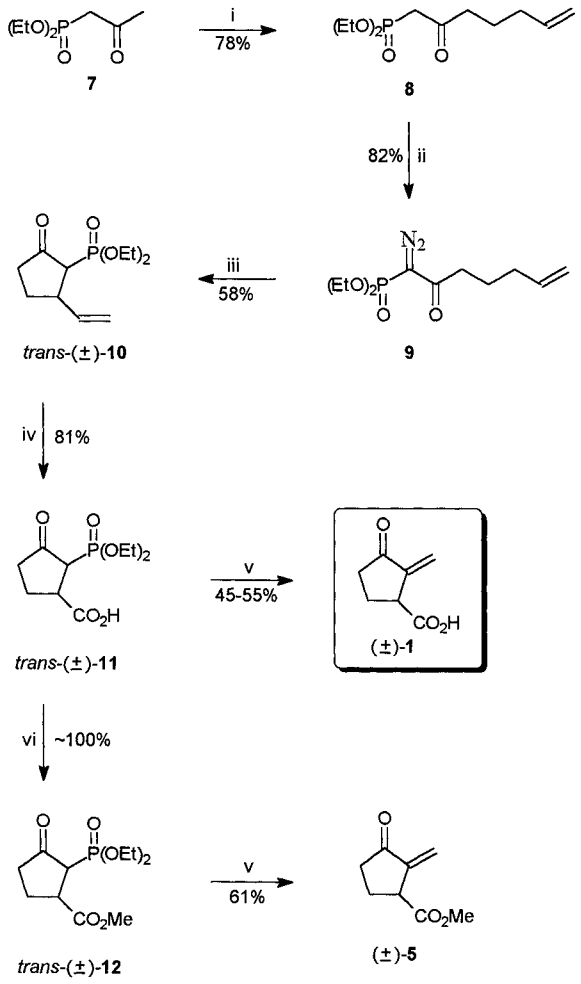
Marian Mikołajczyk, currently Professor of Organic Chemistry and Director of the Center of Molecular and Macromolecular Studies of the Polish Academy of Sciences in Łódź, was born in 1937 in Kłodawa, Poland. He received his M.S. degree in 1959 and Ph.D. in 1963 (under supervision of Professor Jan Michalski) from the Technical University of Łódź. From 1960 to 1963 he worked in the Institute of Organic Synthesis of the Technical University of Łódź. In 1964 he moved to the Institute of Organic Chemistry of the Polish Academy of Sciences in Łódź. In 1967 he did habilitation. In 1968–1969 he was at the Max-Planck Institute of Experimental Medicine where he worked with Professor F. Cramer. Since 1974 he has been Professor of Organic Chemistry and Head of the Department of Organic Sulfur Compounds in the Center of Molecular and Macromolecular Studies of PAS and since 1991 director of the Center. Among the awards he has received are the State Award for achievements in the field of phosphorus stereochemistry (1968), the Maria Skłodowska-Curie Award of PAS for creative research in organosulfur chemistry (1978) and Fellowship of the Japan Society for Promotion of Science (1993). In 1990 he was elected a member of the Deutsche Akademie der Naturforscher, Leopoldina and in 1991 a member of the Polish Academy of Sciences. He has been a visiting Professor at the University of Hamburg, University of Paris-Orsay, University of Utah in Salt Lake City, Ben-Gurion University of the Negev in Beer-Sheva, University of Sao Paulo, P. Sabatier University in Toulouse and Technical University in Braunschweig. His research interests are in the area of phosphorus and sulfur chemistry, chemo-enzymatic synthesis, stereochemistry, and conformational analysis.



Piotr Kiełbasiński was born in 1948 in Łódź. He graduated from the Technical University of Łódź in 1970. Then he joined the staff of the Center of Molecular and Macromolecular Studies, Polish Academy of Sciences where he has been employed till now, and where he received his PhD in 1977 under Professor M. Mikołajczyk with a thesis on the chemistry of carbodiimides. In 1977/78 he spent one year as a postdoctoral fellow with Professor B. Zwanenburg at the University of Nijmegen (The Netherlands). Later on, he visited several other universities as a guest-researcher Berlin, Halle (Germany), Caen, Toulouse (France), Milan (Italy), Nijmegen, and as an invited professor (Toulouse 1989). His main areas of research are the chemistry and stereochemistry of organosulfur and organophosphorus compounds, organic synthesis and enzyme-promoted transformations of organic compounds.



Remigiusz Żurawiński was born in 1961 in Łódź. He graduated from the Technical University of Łódź in 1985. He then joined the staff of the Center of Molecular and Macromolecular Studies, Polish Academy of Sciences where he has been employed till now. His main areas of research are organic synthesis and enzyme-promoted transformations of organic compounds.



Reagents and conditions: i - NaH, THF, r.t., n-BuLi, 0°C, CH_2=$CHCH_2CH_2Br$, r.t., H_3O^+; ii - NaH, TsN_3, C_6H_6-THF, 0°C to r.t.; iii - $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 2h; iv - O_3, MeOH, -70°C, Me_2S, -30°C to r.t., CrO_3, H_2SO_4, acetone, 0°C; v - NaH, THF, 0-5°C, CH_2O-gas r.t. to 40°C 1hr; vi - CH_2N_2, Et_2O, 0°C

Scheme 1

none **(10)** as a result of the carbenoid insertion into the C–H bond. Ozonolysis of the vinyl moiety in **10** gave the corresponding aldehyde (isolated for characterization purposes, see experimental section) which in this reaction sequence, without isolation, was subsequently oxidized with Jones reagent to *trans*-3-carboxy-2-diethoxyphosphorylcyclopentanone **(11)** – a desired sarkomycin precursor. In the last step, the Horner–Wittig reaction of the latter with gaseous formaldehyde was carried out. After the usual workup and column chromatography (±)-sarkomycin **1** was obtained in 16% overall yield. The spectral data of the product obtained were fully consistent with those reported in the literature.[27]

Additionally, the carboxyl group in **11** was reacted with diazomethane and the corresponding ester **12** formed was subjected to the Horner–Wittig reaction with formaldehyde to give the sarkomycin methyl ester **5** in 18% overall yield from the phosphonate **7**.

Resolution of (±)-3-Carboxy-2-diethoxyphosphorylcyclopentanone (11)

Having successfully prepared racemic sarkomycin **1**, we turned our attention to a prime goal of this work i.e. the synthesis of enantiomers of **1**. We found out that the sarkomycin precursor **11**, in contrast to sarkomycin itself, is fairly stable and contains the carboxyl group which may be used for its resolution via diastereoisomeric salts with optically active amines. To this end, a solution of the acid (±)-**11** in benzene was treated with (−)-(*S*)-1-(1-naphthyl)ethylamine and stirred for half an hour. After removal of the solvent, the crude mixture of the diastereoisomeric species obtained (^{31}P NMR assay; δ_P = 22.86 and 23.04 ppm) was separated into pure components by flash column chromatography (C_6H_6, *i*-PrOH, 100:8) and recrystallized from benzene. To our surprise, however, all the spectral data, particularly HRMS spectra, indicated that we had obtained not the diastereoisomerically pure salts but neutral compounds formed from the acid **11** and amine by water elimination. The X-ray crystal structure determination carried out on a single crystal of the diastereoisomer having $[\alpha]_D^{20}$ = + 308.9 and δ_P = 22.86 ppm, (see Fig. 1), revealed that it was the case and that the isolated diastereoisomers have the structure of the 1-amino-3-carboxy-2-phosphoryl substituted cyclopent-1-ene **13**. The formation of the latter is a result of the addition of amine to the carbonyl group followed by water elimination from the adduct formed.

The X-ray analysis of the diastereoisomer **13** mentioned above indicated unequivocally that the absolute configuration of the stereogenic carbon atom 3 in the cyclopentene ring is *S*. Consequently, the second diastereoisomer of **13** having $[\alpha]_D^{20}$ = +185.2 and δ_P = 23.04 ppm has the *R*-configuration at C3. Another interesting feature of the structure of (+)-(*S*)-**13** is that the phosphoryl oxygen forms an intramolecular hydrogen bond with the NH group of 2.227Å. The molecules of this compound are

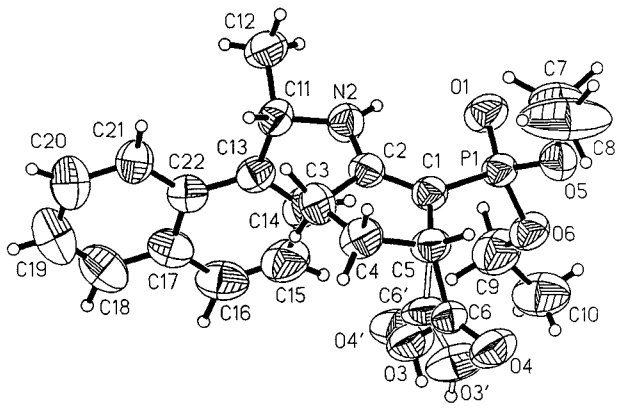
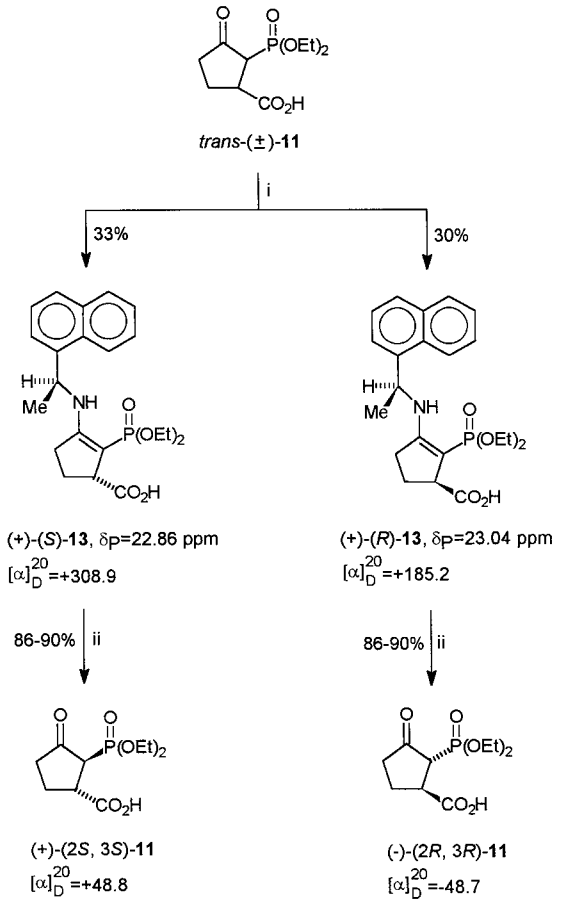


Figure 1. Thermal ellipsoidal view of the molecule of (+)-(*S*)-**13** with the atom numbering scheme. Selected bond lengths [Å] and angles [°]: P1–O1 1.476 (2), P1–O5 1.565 (2), P1–O6 1.567 (2), P1–C1 1.743 (2), C1–C2 1.364 (3), C1–C5 1.5818 (3), C2–C3 1.512 (3), C3–C4 1.512 (4), C4–C5 1.539 (3), C2–N2 1.350 (3); O1–P1–O5 114.96 (12), O1–P1–O6 112.99 (11), O5–P1–O6 97.21 (10), O1–P1–C1 111.40 (10), O6–P1–C1 108.72 (10), C2–C1–C5 111.3 (2), C1–C2–C3 110.9 (2), C2–C3–C4 103.7 (2), C3–C4–C5 107.0 (2), C1–C5–C4 102.6 (2).

held together in the crystal by a short intermolecular hydrogen bond between the phosphoryl oxygen and the carboxylic hydroxy group of 1.747Å and form linear hydrogen-bonded arrays.

The pure diastereoisomers of **13** obtained as above were dissolved in a methanol/water (10:1) mixture and passed through a column containing a weak-acid cation exchanger. Under these conditions, hydrolysis of the enamino function in **13** to carbonyl group took place affording the precursors **11**. The chemically and enantiomerically pure (+)-(2*S*,3*S*)-**11** and (−)-(2*R*,3*R*)-**11** were obtained after evaporation of methanol, lyophilization and column chromatography. Scheme 2 shows some details of the resolution of racemic **11** discussed above.



Reagents and conditions: i -(-)-(*S*)-1-(1-naphthyl) ethylamine, C_6H_6, r.t. 0.5h; ii - MeOH : H_2O (10 : 1), chromatography on ion exchanger IV Merck, eluent: MeOH : H_2O (10 : 5 to 1 : 1)

Scheme 2

Enzymatic Resolution of (±)-2-Diethoxyphosphoryl-3-methoxycarbonylcyclopentanone (12)

In an extension of our work aimed at the preparation of optically active sarkomycin precursor **11**, we found another, simple approach to this acid. It is based on enzymatic, kinetic resolution of racemic *trans*-2-diethoxyphosphoryl-3-methoxycarbonylcyclopentanone **(12)**. This reaction, when carried out to ca. 50% conversion, furnished the desired optically active acid **11** and the unreacted ester **12** having opposite configurations at the stereogenic carbon atoms 2 and 3. Among many enzymes tested, the best kinetic enzymatic resolution was observed with α-chymotrypsin (α-CT). In this case, enzymatic hydrolysis gave the acid (−)-**11** with 77% ee. The experimental results of hydrolysis of (±)-**12** mediated by this and other enzymes are collected in Table 1.

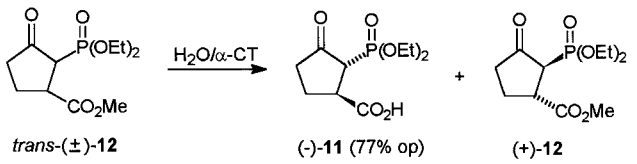


Table 1. Preparation of Optically Active Acid **11** by Enzymatic Hydrolysis of (±)-**12**

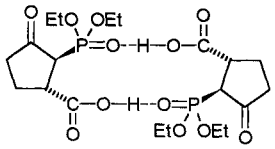
Enzyme	pH	Conversion (%)	Acid **11**		
			Yield (%)	$[\alpha]_D^{20}$	op (%)[g]
PLE[a]	7	47	38	+ 5.6	11.5
PLE	8	47	40	+ 7.2	14.7
α-CT[b]	8	50	42	− 37.4	76.6
SGP[c]	8	55	46	− 8.1	16.6
BSP[d]	8	50	46	− 16.8	34.4
MJL[e,f]	8	45	38	− 1.2	2.5

[a] Pig liver esterase.
[b] α-Chymotrypsin.
[c] Pronase from *Streptomyces Griseus*.
[d] Pronase from *Bacillus Subtilus*.
[e] Lipase from *Mucor Javanicus*.
[f] No reaction was observed with lipase from *Pseudomonas Fluorescens*.
[g] Calculated based on the value of $[\alpha]_D^{20} = +48.8$ for the optically pure acid **11**.

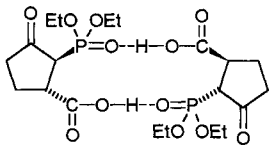
Enantiomer Self-discrimination in ^{31}P NMR Spectra of Nonracemic Acid 11

Following the progress of chemical and enzymatic resolution of the acid **11** by the $^{31}P\{^1H\}$ NMR spectra we found that chloroform solutions of partially resolved samples of this acid displayed two signals. Moreover, the ratios of intensities of these signals corresponded to the molar ratios of enantiomers present in the sample. On the other hand, the completely resolved enantiomeric acids **11** having $[\alpha]_D^{20} = +48.8$ and -48.7 as well as the racemic mixture showed only one signal but the chemical shift of the latter was different from that of a single enantiomer. These preliminary observations strongly suggested that we have encountered a new example of self-discrimination of enantiomers. Since enantiomer discrimination in solution, although known,[46] is still not very common,[47] we decided to look somewhat closer at the origin of this phenomenon in the acid **11**. First of all, the ^{31}P NMR chemical shifts and the magnitude of magnetic nonequivalence, $\Delta\delta$, for different mixtures of the (*S*,*S*)- and (*R*,*R*)-enantiomers of **11** were determined

(Table 2). Then, the influence of temperature on the magnitude of $\Delta\delta$ was briefly investigated (Table 3). An inspection of the data in Tables 2 and 3 allows the following conclusions to be drawn: (i) the chemical shift difference, $\Delta\delta$, for nonracemic mixtures of the enantiomeric acids **11** depends on their composition and decreases as the enantiomers approach equimolarity, (ii) the minor enantiomer resonates always at higher field regardless of its configuration, (iii) the magnitude of $\Delta\delta$ increases with the concentration of the acid investigated and decreases when temperature is raised. Finally, it was found that in less polar solvents such as CCl_4 and C_6H_6 the signal differences are greater than in $CDCl_3$, and strongly solvating polar solvents (MeOH, DMSO) destroy completely the observed magnetic nonequivalence of the enantiomeric acids **11**. The observed spectral behaviour of the enantiomeric acids **11** may be best rationalized in terms of the formation of the short-lived, diastereoisomeric homo- and hetero-dimers, **14** and **15**, (see below) which should display different chemical shifts.



Homo-dimer, **14**



Hetero-dimer, **15**

Table 2. ^{31}P NMR Chemical Shifts of Enantiomers of **11** and Their Mixtures[a]

Acid **11**		δ^{31}P (ppm)		$\Delta\delta$	Enantiomeric
$[\alpha]_D^{20}$	Opt. purity	(*S,S*)-**11**	(*R,R*)-**11**	ppm/Hz	excess
−48.7	100	–	23.260	0	100
−37.4	76.6	22.982	23.289	0.247/29.9	78
−16.8	34.4	23.082	23.184	0.102/12.3	32
0	0	23.170	23.170	0	0
+ 7.2	14.8	23.180	23.114	0.066/ 8.7	14
+24.8	50.8	23.220	23.020	0.200/24.2	52
+48.8	100	23.258	–	0	100

[a] C_6D_6 solution; concentration 9.5×10^{-2} M; temperature 20 °C; measured at 121 MHz.

Table 3. Temperature Dependence of $\Delta\delta$ of Enantiomer Self-Discrimination in Acid **11**,[a,b] in ^{31}P NMR Spectra[c]

T (°C)	−65	−40	−20	0	+20	+45
$\Delta\delta$ (Hz)	18.79	14.92	14.07	12.36	10.59	9.22

[a] $[\alpha]_D^{21} = +24.8$.
[b] Concentration 9.5×10^{-2} M.
[c] $CDCl_3$ solution; measured at 121 MHz.

Although carboxylic acids form dimers via a double hydrogen bond, the well-known ability of the phosphoryl group to act as hydrogen-bond acceptor[48] and the pronounced manifestation of enantiomer self-discrimination in ^{31}P NMR spectra of nonracemic acid **11** prompted us to assume participation of the P=O group in the formation of the hydrogen-bonded dimers **14** and **15**. In full agreement with this postulate are the results of X-ray structure determination of the structurally closely related, racemic *trans*-3-carboxy-2-diphenylphosphinoylcyclopentanone **(16)** which, in contrast to the investigated acid **11**, is crystalline. Figure 2 shows the molecules of **16** in the crystal lattice. It is clearly seen that they form the cyclic, hydrogen-bonded dimers in which, exactly as predicted, the phosphoryl groups are involved in intermolecular hydrogen bonds with the carboxylic hydroxy groups with the O(1)...H–O(3) distance and angle of 1.82(2) Å and 152(2)°, respectively. Interestingly, the dimers consist of two molecules of **16** having opposite

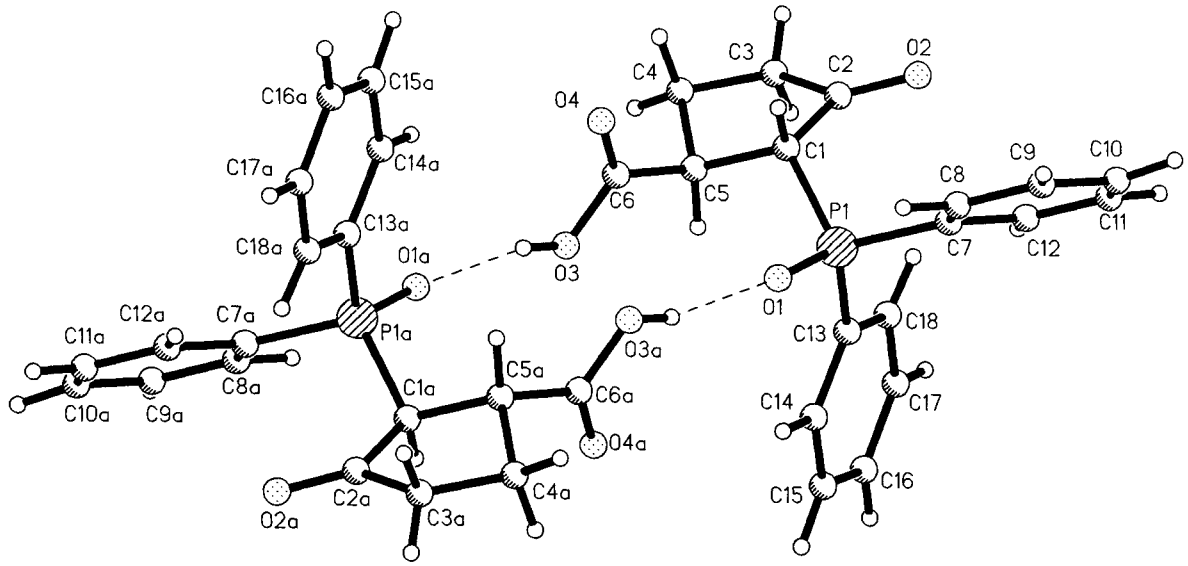


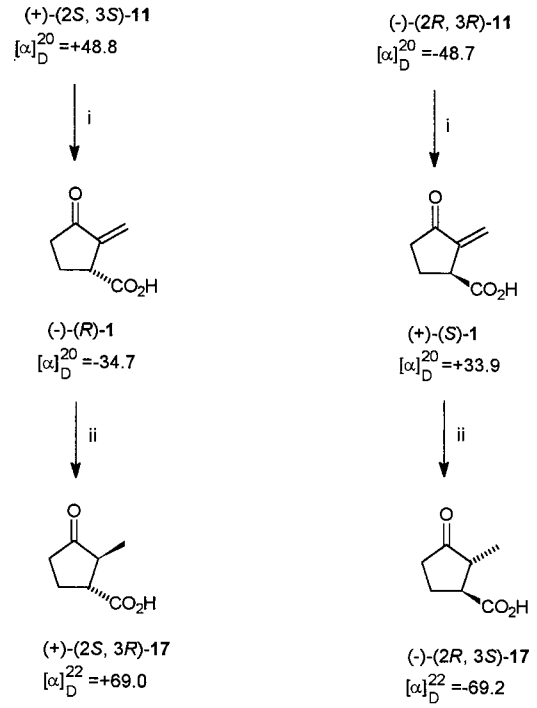
Figure 2. The hydrogen bonding system in the crystal lattice of two molecules of (±)-**16** and the atom numbering system. The dotted lines indicate the short intermolecular H–O contacts. Selected bond lengths [Å] and angles [°]: P1–O1 1.4876 (11), P1–C1 1.8240 (15), P1–C7 1.8020 (15), P1–C13 1.797 (2), C1–C2 1.530 (2), C1–C5 1.543 (2), C2–C3 1.502 (2), C3–C4 1.519 (2), C4–C5 1.538 (2), C6–O3 1.315 (2), C6–O4 1.196 (2), C2–O2 1.209 (2), O1–P1–C13 111.62 (7), O1–P1–C7 110.23 (7), O1–P1–C1 108.98 (7), C2–C1–C5 104.40 (7), C3–C2–C1 108.92 (12), C2–C3–C4 105.40 (13), C3–C4–C5 104.33 (12), C4–C5–C1 103.98 (11).

configurations at the stereogenic chiral atoms i.e. they are hetero-dimers.

The IR and Raman spectral studies of the acids **11** and **16** indicate that dimeric structures are present also in solution.[49]

Synthesis of Enantiopure Natural (−)-(*R*)- and Unnatural (+)-(*S*)-Sarkomycin 1

With the enantiomerically pure sarkomycin precursors, (+)-(2*S*,3*S*)-**11** and (−)-(2*R*,3*R*)-**11**, in hand, the last and crucial step of the synthesis of optically active sarkomycin **1** could now be studied. We found that the Horner–Wittig reaction of (+)-**11** and (−)-**11** with formaldehyde, carried out under the conditions elaborated earlier for the synthesis of racemic **1**, gave the corresponding enantiomeric sarkomycins (−)-(*R*)-**1** and (+)-(*S*)-**1** with $[\alpha]_D^{20} = -34.7$ and +33.9, respectively. It should be pointed out that both values of specific rotation of enantiomeric sarkomycins obtained in this way are slightly higher than that reported for the sarkomycin isolated from natural sources, $[[\alpha]_D^{15} = -32.5$ (MeOH)].[2,50] However, due to chemical instability of sarkomycin, the optical rotation cannot be measured very precisely and is not a good criterion of chemical and enantiomeric purity. Therefore, to check that the samples of (−)- and (+)-sarkomycin **1** prepared here are enantiomerically pure, they were hydrogenated and subsequently treated with diazomethane in a one-pot reaction. In both cases the *cis-trans* mixtures of the ester **17** were formed from which the pure *trans*-isomers, (+)-**17**, $[\alpha]_D^{22} = +69.0$ and (−)-**17**, $[\alpha]_D^{22} = -69.2$, were isolated by column chromatography. Their optical rotation values are almost the same (within the range of precision of measurement) as the ester (+)-**17**, $[\alpha]_D^{15} = +67.5$ (MeOH) obtained from natural sarkomycin.[50] Scheme 3 summarizes the transformations discussed above.



Reagents and conditions: (i) NaH, THF, 0-5°C, CH_2O-gas, r.t. to 40°C, 1hr; (ii) H_2/Pd/C, MeOH; CH_2N_2, Et_2O, 0°C; column chromatography

Scheme 3

Conclusions

We have developed a short synthesis of racemic sarkomycin from the easily available β-oxophosphonate. The key steps in this synthesis involve the intramolecular carbenoid cyclization leading to the cyclopentanone ring formation, and the Horner–Wittig reaction utilized for the introduction of the α-exocyclic methylene moiety. Our method compares favourably in terms of brevity and use of simple reagents with the majority of the previously reported syntheses. Another advantage of our approach is that the sarkomycin precursor, 3-carboxy-2-diethoxyphosphorylcyclopentanone, can be easily resolved into enantiomers. The latter in the Horner–Wittig reaction with formaldehyde were converted into natural (−)-(*R*)- and unnatural (+)-(*S*)-sarkomycin. This is the first synthesis of enantiopure forms of this target. Furthermore, the presence of phosphorus in all starting materials and intermediates allows the course of each synthetic step to be followed by means of ^{31}P NMR spectroscopy. Using this technique we were able to detect the phenomenon of enantiomer self-discrimination in the nonracemic sarkomycin precursor mentioned above.

Tetrahydrofuran was distilled from potassium/benzophenone and benzene was distilled from Na wire, both immediately prior to use. CH_2Cl_2 was distilled from P_2O_5 and stored over anhyd Na_2CO_3. All reactions in these solvents were conducted under a positive pressure of an inert gas. Oil-free NaH was prepared by washing mineral oil dispersion twice with hexane. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Melting points were determined on a Boethius PHMK 05 apparatus and were uncorrected. NMR spectra were recorded with a Bruker MSL-300 spectrometer at 300 MHz for ^1H, 75 MHz for ^{13}C and 121 MHz for ^{31}P with $CDCl_3$ as solvent, unless noted otherwise. Column chromatography was done on Merck $60F_{254}$ silica gel (70–230 mesh) and flash column chromatography was carried out on Merck $60F_{254}$ silica gel (230–400 mesh). Reaction mixtures were analyzed by TLC using Merck $60F_{254}$ TLC plates. All enzymes were purchased from Fluka. Rhodium(II) acetate dimer was a product of Aldrich.

Diethyl 2-Oxohept-6-enephosphonate (8):
To a magnetically stirred suspension of NaH (3.72 g, 0.155 mol) in THF (350 mL) at 0°C was added dropwise diethyl 2-oxopropylphosphonate (**7**) (30.0 g, 0.155 mol). After stirring for 1.5 h at r.t., BuLi (69.2 mL of 2.5 M; 0.17 mol) was added dropwise (0°C) and the resultant solution was stirred for 30 min. Then, 4-bromobut-1-ene (25.1 g, 0.186 mol) was added and the mixture stirred at r.t. for the next 30 min. The reaction was quenched by addition of 5% aq HCl and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extract was dried ($MgSO_4$), concentrated under reduced pressure and the residue distilled to yield the phosphonate **8**; 30.0 g, (78%), bp = 109–111°C/0.05 mmHg: $n_D^{22} = 1.4506$; $R_f = 0.34$ (EtOAc/hexane 4:1).

^{31}P NMR: $\delta = 20.54$.

^1H NMR: $\delta = 5.73$ (ddt, $J = 6.7, 10.2, 17.1$ Hz, 1H), 5.00–4.90 (m, 2H), 4.15–4.00 (m, 4H), 3.03 (d, $J = 22.8$ Hz, 2H), 2.60 (t, $J = 7.3$ Hz, 2H), 2.08–1.98 (m, 2H), 1.65 (quint., 2H, $J = 7.3$ Hz), 1.30 (t, $J = 7.0$ Hz, 6H).

^{13}C NMR: $\delta = 200.8$ (d, $J = 6.0$ Hz), 137.0, 114.4, 61.6 (d,

$J = 5.9$ Hz), 42.2, 41.5 (d, $J = 126.7$ Hz), 32.0, 21.6, 15.5 (d, $J = 5.6$ Hz).

MS (15 eV): m/z (%) = 249 ($M^+ + 1$, 3), 248 (M^+, 17), 207 (40), 194 (100), 179 (50), 167 (17), 166 (10), 152 (38), 151 (30), 125 (38), 124 (10), 123 (13), 109 (12), 97 (12).

Anal. Calcd for $C_{11}H_{21}O_4P$: C, 53.22; H, 8.53; P, 12.48. Found: C, 53.11; H, 8.60; P, 12.41.

Diethyl 1-Diazo-2-oxohept-6-enephosphonate (9):
To a magnetically stirred suspension of NaH (2.64 g; 0.11 mol) in THF (60 mL) and benzene (400 mL) at 0 °C was added dropwise β-oxophosphonate **8** (24.8 g; 0.1 mol) in benzene (100 mL). After stirring for 1.5 h, $TosN_3$ (21.7 g, 0.11) in benzene (50 mL) was added and the mixture was allowed to warm to r.t. After 3 h the mixture was filtered on a Celite pad, concentrated in vacuo and chromatographed on silica gel (EtOAc/hexane gradient as an eluent) affording **9**; 22.5 g; (82 %) as a light yellow liquid; $n_D^{22} = 1.4790$; $R_f = 0.31$ (EtOAc/hexane 1:1), $R_f = 0.53$ (EtOAc/hexane 4:1).

^{31}P NMR: $\delta = 11.78$.

^{1}H NMR: $\delta = 5.79$ (ddt, 1 H, $J = 6.7, 10.2, 17.0$ Hz), 5.10–4.95 (m, 2 H), 4.32–4.12 (m, 4 H), 2.58 (t, 2 H, $J = 7.4$ Hz), 2.11 (q, $J = 7.1$ Hz, 2 H), 1.76 (quint., $J = 7.4$ Hz, 2 H), 1.40 (t, $J = 7.1$ Hz, 6 H).

^{13}C NMR: $\delta = 191.7$ (d, $J = 11.8$ Hz), 137.1, 114.6, 63.1 (d, $J = 215.9$ Hz), 62.7 (d, $J = 5.0$ Hz), 37.9, 32.4, 22.6, 15.5 (d, $J = 6.5$ Hz).

MS (15 eV): m/z (%) = 275 ($M^+ + 1$, 4), 246 (8), 218 (27), 190 (76), 162 (98), 109 (100), 81 (88), 80 (87), 65 (47), 79 (41).

Anal. Calcd for $C_{11}H_{19}N_2O_4P$: C, 48.17; H, 6.98; P, 11.29; N, 10.21. Found: C, 48.11; H, 7.03; P, 11.21; N, 10.29.

***trans*-(±)-2-Diethoxyphosphoryl-3-vinylcyclopentanone (10):**
To a refluxing solution of the dirhodium(II) tetraacetate (0.194 g, 0.44 mmol) in CH_2Cl_2 (400 mL) was added slowly **9** (12.0 g, 44 mmol) in CH_2Cl_2 (20 mL). Reflux was continued until disappearance of the diazo compound **9** (about 2 h, monitored by TLC). After cooling, the resulting solution was washed with H_2O (2 × 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane gradient as an eluent) affording **10**; 6.28 g, (58 %) as a colorless liquid; $n_D^{22} = 1.4820$; $R_f = 0.29$ (EtOAc/hexane 4:1).

^{31}P NMR: $\delta = 22.33$.

^{1}H NMR: $\delta = 5.84$ (ddd, $J = 6.9, 10.3, 17.2$ Hz, 1 H), 5.12 (ddd, $J = 1.2, 1.2, 17.2$ Hz, 1 H), 5.06 (ddd, $J = 1.2, 1.2, 10.3$ Hz, 1 H), 4.21–4.00 (m, 4 H), 3.32–3.15 (m, 1 H), 2.52 (dd, $J = 8.1, 25.7$ Hz, 1 H), 2.38–2.20 (m, 3 H), 1.77–1.60 (m, 1 H), 1.29 (dt, $J = 0.4$, 7.1 Hz, 3 H), 1.28 (dt, $J = 0.3$, 7.1 Hz, 3 H).

^{13}C NMR: $\delta = 211.84$, 140.20 (d, $J = 5.8$ Hz), 115.79, 63.58 (d, $J = 6.5$ Hz), 62.98 (d, $J = 6.8$ Hz), 53.23 (d, $J = 137.3$ Hz), 42.82, 39.23 (d, $J = 3.4$ Hz), 28.76 (d, $J = 10.9$ Hz), 17.05 (d, $J = 5.4$ Hz), 16.98 (d, $J = 5.4$ Hz).

MS (15 eV): m/z (%) = 246 (M^+, 55), 218 (19), 191 (100), 190 (18), 163 (37), 139 (27), 138 (25), 135 (37), 111 (32), 99 (52), 98 (25).

Anal. Calcd for $C_{11}H_{19}O_4P$: C, 63.65; H, 7.78; P, 12.58. Found: C, 63.51; H, 7.71; P, 12.65.

***trans*-(±)-2-Diethoxyphosphoryl-3-formylcyclopentanone:**
A solution of **10** (6.3 g, 25.6 mmol) in anhyd MeOH (50 mL) was cooled to −70 °C and ozonized O_2 gas passed at the rate: 30L/h (1.5 g O_3/h) until one molar equivalent of ozone had been absorbed (colour changed to light blue). While still at −70 °C the system was flushed with N_2 and 3.2 g (51.2 mmol) of dimethyl sulfide was added. Then, the solution was stirred at −10 °C for 1 h and for an additional 2 h at r.t. The solvent and DMSO were removed under vacuum using a Kugelrohr apparatus (60 °C/0.05 mmHg). The remaining crude aldehyde was used without purification for the next reaction. Analytically pure sample was obtained by column chromatography using EtOAc/hexane gradient as an eluent; $n_D^{23} = 1.4728$; $R_f = 0.18$ (EtOAc).

^{31}P NMR: $\delta = 21.5$.

^{1}H NMR: $\delta = 9.74$ (t, $J = 1.0$ Hz, 1 H), 4.25–4.05 (m, 4 H), 3.72–3.40 (m, 1 H), 3.21 (dd, $J = 6.2, 25.7$ Hz), 2.52–2.05 (m, 4 H), 1.29 (t, $J = 7.0$ Hz, 6 H).

^{13}C NMR: $\delta = 208.7$ (d, $J = 4.0$ Hz), 198.9 (d, $J = 8.3$ Hz), 63.2 (d, $J = 6.7$ Hz), 62.7 (d, $J = 6.9$ Hz), 50.1, 46.4 (d, $J = 138.2$ Hz), 37.3, 22.0 (d, $J = 6.7$ Hz), 16.2.

MS (15 eV): m/z (%) = 248 (M^+, 4), 220 (80), 219 (99), 193 (34), 192 (18), 191 (76), 165 (11), 163 (100), 138 (92), 137 (14), 135 (12), 111 (42), 83 (30).

Anal. Calcd for $C_{10}H_{17}O_5P$: C, 48.39; H, 6.90; P, 12.48. Found: C, 48.11; H, 7.15; P, 12.55.

***trans*-(±)-2-Diethoxyphosphoryl-3-carboxycyclopentanone (11):**
To a magnetically stirred solution of the crude aldehyde prepared as above (0.6 g, 2.4 mmol) in acetone (15 mL) was added slowly 0.8 mL of 8 N Jones reagent (2.0 g CrO_3, 1.65 mL, H_2SO_4, H_2O up to 7.5 mL). Colour changed to orange-brown. The mixture was stirred for 0.5 h and the precipitate of the chronium salt separated. After removal of the solvent the mixture was diluted with brine (2 mL) and extracted with $CHCl_3$ (10 mL). The extract was dried (Na_2SO_4), concentrated under vacuum and the residue purified by column chromatography affording the acid **11**; 0.52 g (81 % for two steps from **10**); semisolid; $R_f = 0.18$ ($CHCl_3$/MeOH 10:3).

^{31}P NMR: $\delta = 21.4$.

^{1}H NMR: $\delta = 8.91$ (br signal, 1 H), 4.25–4.10 (m, 4 H), 3.55–3.40 (m, 1 H), 3.27 (dd, $J = 7.8, 25.5$ Hz, 1 H), 2.52–2.32 (m, 3 H), 2.14–2.02 (m, 1 H), 1.36 (dt, $J = 0.6$, 7.1 Hz, 3 H), 1.35 (dt, $J = 0.6$, 7.1 Hz).

^{13}C NMR: $\delta = 209.21$ (d, $J = 4.0$ Hz), 175.78 (d, $J = 5.9$ Hz), 64.17 (d, $J = 6.7$ Hz), 50.15 (d, $J = 139.6$ Hz), 43.96, 39.04 (d, $J = 3.9$ Hz), 26.50 (d, $J = 9.8$ Hz), 16.96 (d, $J = 4.9$ Hz), 16.90 (d, $J = 4.9$ Hz).

MS (15 eV): m/z (%) = 265 ($M^+ + 1$, 8), 264 (M^+, 52), 236 (10), 220 (30), 219 (80), 218 (49), 209 (100), 192 (27), 153 (32), 139 (14), 138 (64), 135 (27), 111 (36), 110 (14), 97 (12).

Anal. Calcd for $C_{10}H_{17}O_6P$: C, 45.46; H, 6.49; P, 11.72. Found: C, 45.31; H, 6.53; P, 11.64.

***trans*-(±)-2-Diethoxyphosphoryl-3-methoxycarbonylcyclopentanone (12):**
To a magnetically stirred solution of 3-carboxy-2-diethoxyphosphorylcyclopentanone **(11)** (1.50 g, 5.7 mmol) in Et_2O (10 mL) was added slowly ethereal solution of diazomethane at 0 °C. Addition of diazomethane was continued until a yellow colour persisted. The reaction mixture was stirred at r.t. for 0.5 h. The solvent was removed under reduced pressure and the crude **12** (1.58 g, 100 %) was used without purification for the next reaction; $n_D^{19} = 1.4595$; $R_f = 0.29$ (EtOAc).

^{31}P NMR: $\delta = 21.1$.

^{1}H NMR: $\delta = 4.25–4.00$ (m, 4 H), 3.72 (s, 3 H), 3.55–3.40 (m, 1 H), 3.20 (dd, $J = 7.1, 25.6$ Hz, 1 H), 2.50–2.34 (m, 3 H), 2.09–1.96 (m, 1 H), 1.30 (dt, 3 H, $J = 0.4$, 7.1 Hz), 1.29 (dt, 3 H, $J = 0.4$, 7.1 Hz).

^{13}C NMR: $\delta = 209.88$ (d, $J = 3.9$ Hz), 174.58 (d, $J = 8.3$ Hz), 63.83 (d, $J = 6.3$ Hz), 63.25 (d, $J = 6.7$ Hz), 53.09, 50.84 (d, $J = 138.3$ Hz), 44.00, 38.72 (d, $J = 2.9$ Hz), 26.73 (d, $J = 8.4$ Hz), 16.99 (d, $J = 5.4$ Hz), 16.92 (d, $J = 5.4$ Hz).

MS (15 eV): m/z (%) = 279 ($M^+ + 1$, 7), 278 (M^+, 43), 247 (14), 223 (75), 220 (10), 219 (100), 218 (23), 191 (52), 190 (12), 167 (16), 163 (52), 149 (12), 138 (14), 135 (10), 111 (9), 83 (9).

Anal. Calcd for $C_{11}H_{19}O_6P$: C, 47.48; H, 6.88; P, 11.13. Found: C, 47.19; H, 6.94; P, 11.09.

Preparation of Racemic and Optically Active Sarkomycin (1); General Procedure:
To a magnetically stirred cold (0–5 °C) suspension of NaH (2 mmol) in THF (25 mL) was added slowly **11** (1 mmol) in THF (2 mL). After stirring for 1.5 h at r.t., formaldehyde formed by thermal depolymerization of paraformaldehyde (4 mmol) was carried over into the reaction vessel by a slow current of dry N_2 (paraformaldehyde has been previously dried for two days in a vacuum desic-

cator over P_2O_5). The mixture was heated at about 40 °C for 1 h. After cooling to r.t. the reaction was acidified by addition of 5% aqueous HCl and the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to flash column chromatography ($CHCl_3$/MeOH 100:3) affording sarkomycin **1** in 55% yield; $R_f = 0.17$ ($CHCl_3$/MeOH 10:1).

^{1}H NMR: $\delta = 9.8$ (br signal, 1 H), 6.23 (d, $J = 2.5$ Hz, 1 H), 5.71 (d, $J = 2.5$ Hz, 1 H), 3.90–3.65 (m, 1 H), 2.70–2.03 (m, 4 H).

^{13}C NMR: ($CDCl_3$, 50 MHz): $\delta = 204.62$, 177.81, 141.77, 121.11, 45.61, 36.56, 22.84.

MS (15 eV): m/z (%) = 140 (M^+, 15), 112 (100), 95 (29), 84 (41), 67 (26).

Sarkomycin Methyl Ester (5):

The title compound was obtained in 61% yield from the cyclopentanone **12** according to the experimental procedure described for the synthesis of sarkomycin **(1)** using stoichiometric amount of NaH and a mixture of hexane/EtOAc as an eluent; $R_f = 0.68$ (EtOAc/hexane 4:1).

^{1}H NMR: $\delta = 6.17$ (d, $J = 2.7$ Hz, 1 H), 5.60 (dd, $J = 0.6$, 2.4 Hz, 1 H), 3.76 (s, 3 H), 3.85–3.65 (m, 1 H), 2.65–2.50 (m, 1 H), 2.45–2.10 (m, 3 H).

Resolution of *trans*-(±)-3-Carboxy-2-diethoxyphosphorylcyclopentanone (11):

To a magnetically stirred solution of racemic 3-carboxy-2-diethoxyphosphorylcyclopentanone **(11)** (2.0 g, 7.6 mmol) in benzene (50 mL) was added (*S*)-(−)-1-(1-naphthyl)ethylamine (1.3 g, 7.6 mmol) in benzene (2 mL). After stirring for 0.5 h at r.t. the solvent was removed under reduced pressure and the diastereoisomers were separated by flash column chromatography (benzene/*i*-PrOH 100:8) and then crystallized from benzene.

(+)-(*S*)-**13**; 1.09 g (33%); $[\alpha]_D^{20} = +308.0$ ($c = 1.8$, MeOH); mp 183–184 °C; $R_f = 0.59$ (acetone).

^{31}P NMR ($CDCl_3$, 81 MHz): $\delta = 22.86$.

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 9.82$ (br s, 1 H), 8.00–7.20 (m, 7 H), 5.38–5.19 (m, 1 H), 4.19–3.90 (m, 4 H), 3.50–3.43 (m, 1 H), 2.56–1.80 (m, 5 H), 1.59 (d, $J = 6.7$ Hz, 3 H), 1.31 (t, $J = 7.1$ Hz, 3 H), 1.26 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 180.14$, 167.95 (d, $J = 15.8$ Hz), 140.56, 133.84, 129.92, 129.09, 127.56, 126.18, 125.76, 125.52, 122.36, 122.08, 81.83 (d, $J = 201.6$ Hz), 61.22 (d, $J = 3.9$ Hz), 50.56, 48.86 (d, $J = 12.9$ Hz), 32.19 (d, $J = 18.1$ Hz), 27.08 (d, $J = 12.3$ Hz), 23.91, 16.28 (d, $J = 7.4$ Hz), 16.11 (d, $J = 9.5$ Hz).

MS (70 eV): m/z (%) = 417 (M^+, 1), 372 (12), 344 (3), 234 (2), 218 (100), 155 (58).

HRMS (EI) calcd for $C_{22}H_{28}NO_5P$ 417.1705, obsd 417.1697.

(+)-(*R*)-**13**; 0.95 g (30%); $R_f = 0.53$ (acetone); $[\alpha]_D^{20} = +185.2$ ($c = 1.86$, MeOH); mp = 172–176 °C.

^{31}P NMR ($CDCl_3$, 81 MHz): $\delta = 23.04$.

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.12$–7.13 (m, 7 H), 5.33–5.14 (m, 1 H), 4.21–3.91 (m, 4 H), 3.46–3.40 (m, 1 H), 2.85–2.65 (m, 1 H), 2.16–1.68 (m, 5 H), 1.58 (d, $J = 6.7$ Hz, 3 H), 1.34 (t, $J = 7.1$ Hz, 3 H), 1.29 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 180.08$, 167.54 (d, $J = 15.5$ Hz), 141.14, 133.82, 129.87, 129.05, 128.29, 127.47, 126.28, 125.59, 122.22, 122.09, 82.57 (d, $J = 201.0$ Hz), 61.27 (d, $J = 3.9$ Hz), 50.63, 49.54 (d, $J = 13.3$ Hz), 32.24 (d, $J = 18.0$ Hz), 27.19 (d, $J = 12.2$ Hz), 23.95, 16.33 (d, $J = 6.3$ Hz), 16.20 (d, $J = 7.2$ Hz).

MS (70 eV): m/z (%) = 417 (M^+, 2), 372 (9), 344 (2), 234 (2), 218 (100), 155 (43).

HRMS (EI) calcd for $C_{22}H_{28}NO_5P$ 417.1705, obsd 417.1699.

A solution of each pure diastereoisomer **13** (1.2 mmol) in MeOH/H_2O (10:1) was introduced to the column packed with a weak acid cation exchanger (Ionenaustauscher IV Merck) and eluted with a MeOH/H_2O system (gradient from 2:1 to 1:1). MeOH was evaporated and the aqueous residue lyophilized to give the crude acid **11**, which was additionally purified by column chromatography (eluent $CHCl_3$/MeOH 10:3).

(+)-(2*S*,3*S*)-**11**: yield 86%, $[\alpha]_D^{20} = +48.8$ ($c = 2.9$, MeOH).

(−)-(2*R*,3*R*)-**11**: yield 90%, $[\alpha]_D^{20} = -48.7$ ($c = 1.8$, MeOH).

Enzyme-Catalyzed Hydrolysis of 2-Diethoxyphosphoryl-3-methoxycarbonylcyclopentanone (12):

To a stirred solution of the cyclopentanone **12** (0.18 g, 0.65 mol) in phosphate buffer (pH 7.0 or 8.0, 15 mL) the relevant enzyme: PLE (100 μL), α-CT (25 mg), SGP (25 mg), BSP (20 mg), PFL (27 mg), MJL (30 mg) was added in one portion. The pH was maintained by addition of 0.2 N aqueous NaOH. When the desired degree of hydrolysis was achieved, the mixture was acidified with dilute aqueous H_2SO_4 to pH 2.8, and then MeOH (100 mL) was added. The mixture was kept in a refrigerator (−15 °C) for 1 h, and filtered through Celite. The filtrate was concentrated under vacuum at r.t., and the residue extracted with $CHCl_3$ (4 × 15 mL). The extract was dried (Na_2SO_4), concentrated under vacuum and the residue purified by silica gel chromatography ($CHCl_3$/MeOH gradient as eluent) affording the desired optically active acid **11** (yields given in Table 1).

3-Carboxy-2-diphenylphosphinoylcyclopentanone (16):

To a magnetically stirred solution of 2-diphenylphosphinoyl-3-methoxycarbonylcyclopentanone[51] (0.9 g, 2.6 mmol) in MeOH (20 mL) was added 6 M HCl (2.0 mL). The mixture was stirred at r.t. for 24 h, concentrated under reduced pressure, extracted with $CHCl_3$ (4 × 10 mL) and dried (Na_2SO_4). After removal of the solvent the residue was purified by crystallization from acetone yielding **16**; 0.77 g, (89%); mp = 197–198 °C; $R_f = 0.26$ (MeOH/$CHCl_3$ 3:10).

^{31}P NMR (DMSO-d_6, 81 MHz): $\delta = 31.6$.

^{1}H NMR (DMSO-d_6, 200 MHz): $\delta = 12.62$ (s, 1 H), 7.91–7.77 (m, 4 H), 7.65–7.45 (m, 6 H), 4.09 (dd, $J = 5.0$, 11.7 Hz, 1 H), 3.25–3.09 (m, 1 H), 2.41–1.93 (m, 4 H).

^{13}C NMR (DMSO-d_6, 50 MHz): $\delta = 211.0$ (d, $J = 3.7$ Hz), 174.7 (d, $J = 8.7$ Hz), 133.0–128.2 (several signals), 51.6 (d, $J = 62.0$ Hz), 42.5, 38.0, 25.6 (d, $J = 3.2$ Hz).

MS (15 eV): m/z (%) = 329 ($M^+ + 1$, 2), 328 (M^+, 10), 283 (26), 282 (100), 281 (56), 254 (32), 202 (72), 201 (77), 166 (30), 100 (48), 83 (48), 82 (46), 55 (41), 44 (51), 43 (36).

Chemical Correlation of the Absolute Configuration of the Sarkomycins Synthesized:

A solution of an optically active sarkomycin **1** (0.4 mmol) in MeOH (1.5 mL) was hydrogenated at atmospheric pressure over 10% Pd/C for ca 20 min. After filtration of the catalyst and evaporation of the solvent the residue was dissolved in Et_2O (1 mL) and the ethereal solution of diazomethane was slowly added at 0 °C. Addition of the diazomethane solution was continued until yellow colour persisted. The solvent was removed under reduced pressure and for analytical purposes only the *trans*-isomer of **17** was separated using column chromatography (EtOAc/hexane gradient); $R_f = 0.34$ (EtOAc/hexane 1:2), $R_f = 0.44$ (EtOAc/hexane 1:1); (+)-(2*S*,3*R*)-**17**: $[\alpha]_D^{22}$ +69.0 ($c = 1.0$, MeOH); (−)-(2*R*,3*S*)-**17**: $[\alpha]_D^{22}$ −69.2 ($c = 0.7$, MeOH).

^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 3.75$ (s, 3 H), 2.71–1.92 (m, 6 H), 1.15 (d, $J = 6.9$ Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 217.67$, 174.44, 52.02, 48.86, 47.53, 36.74, 24.38, 13.10;

MS (CI): m/z (%) = 157 ($M^+ + 1$, 100), 125 (10), 97 (21).

Crystal Structure Analysis of (±)-(*S*)-13:

Crystal Data: $C_{22}H_{28}NO_5P$, $M_r = 417.42$; monoclinic; space group $P2_1$; $a = 7.809$ (2); $b = 13.378$ (3); $c = 10.934$ (2) Å, $\beta = 104.95$ (3)°, $V = 1103.6$ (4) Å^3, $Z = 2$; $d_c = 1.256$ g/cm^3.

Data Collection and Structure Solution: The data collection was performed using a CAD4 diffractometer with graphite monochromatized CuKα radiation. The lattice constants were refined by least-squares fit of 25 reflections in θ range of 12.84°–29.31°. The decline in intensities of three standard reflections (3, −4, −2; −1, −5, 0; 4, −5, −1) was 0.3% during 65.1 h of exposure time. An empirical

absorption correction was applied by using of the EAC program. A total of 4435 reflections with $I > O$ were used to solve the structure by direct methods and to refine it by full-matrix least squares using F^2. The bond lengths for two positions (sof equal to 0.7 and 0.3, respectively) of the disordered carboxyl group were restrained to be equal. Hydrogen atoms at the ethylene groups were placed geometrically, and allowed to ride on the immediately preceding atom C and rotate about the C–C bond (for methyl groups) with C–H distance free to refine and fixed thermal parameters equal to 1.3 times of the equivalent isotropic thermal parameter of the parent-atom. Hydrogen atom at the disordered carboxyl group was placed geometrically at idealized position with C–O–H angle tetrahedral (the choice was based on forming the "best" hydrogen bond), and set as riding with O–H distance equal to 0.82Å, and the isotropic thermal parameters free to refine. All other hydrogen atoms were found in a difference Fourier map and refined isotropically. Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged to R = 0.0426 (for 4287 reflections with $F > 4\sigma(F)$) with weight $w^{-1} = \sigma^2(F_o^2) + (0.0913P)^2 + 0.0597P$, where $P = (F_o^2 + 2F_c^2)/3$, for 368 refined parameters. The absolute configuration of the chiral atoms C5 and C11 was established as *S*. The absolute structure was determined by the Flack method with results: $\chi = 0.01(2)$, $\chi_{inv} = -0.01(2)$.

Crystal Structure Analysis of (±)-16:

Crystal Data: $C_{18}H_{17}O_4P$, $M_r = 328.29$; monoclinic; space group *C2/c*; $a = 16.3446$ (9); $b = 6.9759$ (9); $c = 27.809$ (2)Å, $\beta = 94.456$ (5)°, $V = 3161.1$ (5)Å^3; $Z = 8$; $d_c = 1.380$ (2) g/cm^3.

Data Collection and Structure Solution: Crystal and molecular structure of **16** was determined using data collected at r.t. on a CAD4 diffractometer with graphite monochromatized CuKα radiation. Intensity data were collected at r.t. using graphite monochromatized CuKα radiation. The lattice constants were refined by least-squares fit of 25 reflections in θ range of 20.54°–29.22°. The decline in intensities of three standard reflections (−6,−2,8; 1,−1,15; −6,−2,−1) was 2.0% during 46.0 hours of exposure time. An empirical absorption correction was applied by using of the EAC program. A total of 3081 reflections with $I > 0$ were used to solve the structure by direct methods and to refine it by full-matrix least-squares using F^2. Hydrogen atoms were found in a difference Fourier map and refined isotropically. Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged to r = 0.0323 (for 2808 reflections with $F > 4\sigma(F)$) with weight $w^{-1} = \sigma^2(F_o^2) + (0.0412P)^2 + 2.0962P$, where $P = (F_o^2 + 2F_c^2)/3$, for 209 refined parameters.

Data correction for both structures **13** and **16** was carried out with the Enraf-Nonius SDP crystallographic computing package; structure solution and refinement with SHELX-93 program. Scattering factors were taken form International Tables for X-ray Crystallography. The authors have deposited atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles for these structures with the Cambridge Crystallographic Data Centre.

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