room temperature over 75 min. The solution was poured into saturated NH_4Cl solution, stirred for 10 min, and then extracted with EtOAc. The extract was dried and the solvents were removed. The residue (30.16 g) was chromatographed on Florisil. Elution with hexane–benzene (4:1) provided the epoxide product (13.81 g), while further elution with benzene gave recovered starting ketone (10.20 g). The product was dissolved in THF (130 mL) and 15 mL of water; then the solution was cooled in ice and 8 mL of 70% $HClO_4$ was added dropwise. Stirring was continued at 0 °C for 5 min, and the solution was allowed to warm to room temperature for 6 h. It was then poured on ice and worked up conventionally to afford the crude product (11.56 g), which was purified by chromatography on Florisil. Elution with hexane–benzene (2:1) gave the pure aldehyde (5.76 g), which failed to crystallize.

A solution of this aldehyde (5 g) in 200 mL of methanesulfonic acid was stirred at 70 °C for 5 h under N_2. The solution was poured on ice and worked up in the usual manner followed by chromatography on Florisil to provide hexahydro-**26** (75%). Dehydrogenation of this mixture over a 10% Pd/C catalyst in refluxing triglyme furnished **26** (36%), mp 120.5–121 °C (acetone–hexane) (lit.[9] mp 123 °C); the NMR spectrum of **26** was in good agreement with that of an authentic sample; UV λ_{max} (EtOH) 306 (ϵ 7730), 289 (48100), 282 (44900), 271 (36220), 258 (37320), 221 (32310), 205 (27670). Anal. Calcd for $C_{19}H_{12}$: C, 94.96; H, 5.04. Found: C, 94.72; H, 5.00.

4*H*-Cyclopenta[*def*]chrysene (28). Reaction of 7-(bromomethyl)acenaphthene (620 mg, 2.51 mmol) with 40% excess **19** was carried out by the standard procedure (50 h). The usual workup followed by chromatography on silica gel furnished the alkylated ketone (300 mg, 68% based on conversion of the starting compound) as an oil along with 210 mg of the unreacted alkyl bromide. To a solution of 300 mg of the ketone in 12 mL of CH_2Cl_2 in an ice bath was added 4.5 mL of methanesulfonic acid. This solution was maintained at 0 °C for 30 min; then the reaction was worked up in the usual way to afford hexahydro-**28** (270 mg, 94%). Dehydrogenation of this mixture over a 10% Pd/C catalyst in refluxing triglyme (30 min) furnished **28** (58% based on the ketone), mp 172.5–173.5 °C (hexane) (lit.[26] mp 172.4–172.9 °C): IR (KBr) 1400, 765, 751 cm^{-1}; NMR δ 8.66 (d, 1, H_{10}, J = 8.06 Hz), 8.49 (d, 1, H_9, J = 8.83 Hz), 8.04 (d, 1, Ar, J = 7.52 Hz), 8.01 (d, 1, Ar, J = 8.48 Hz), 7.97 (s, 1 H_5), 7.92 (t, 1, Ar), 7.2–7.8 (m, 4, Ar), 4.40 (s, 2, CH_2); UV λ_{max} (EtOH) 326 (ϵ 12600), 312 (10900), 300 (11800), 269 (87300), 217 (28000).

Acknowledgment. This research was supported by grants from the National Institute of Environmental Health Sciences (ES 04266) and the National Cancer Institute (CA 36097 and CA 14599).

(26) Fieser, L. F.; Cason, J. *J. Am. Chem. Soc.* **1940**, *62*, 1293–1298.

Methylenomycin B: New Syntheses Based on β- and γ-Keto Phosphonates and γ-Keto Phosphine Oxides†

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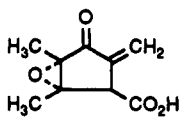
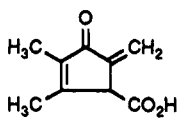
Methylenomycin B has been synthesized from diethyl 2-oxobutanephosphonate (**4**) in three steps in 39% overall yield. Starting from diethyl 3-oxobutanephosphonate (**10**) and diphenyl(3-oxobutyl)phosphine oxide (**13**), methylenomycin B has been obtained in 34% and 27% overall yield, respectively. A characteristic feature of these syntheses of methylenomycin B is that the *exo*-methylene function is introduced via the Horner–Wittig reaction of formaldehyde (36% aqueous solution) with the corresponding α-phosphorylcyclopentenones **6** and **20**. The latter were obtained from phosphorylated 1,4-diketones by intramolecular base-catalyzed cyclization. A brief discussion of some mechanistic aspects of the Conant reaction is also given.

Introduction

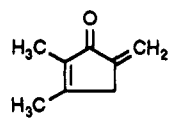
Methylenomycin A (**1**), desepoxy-4,5-didehydromethylenomycin A (**2**), and methylenomycin B (**3**) have recently been isolated[1] from the culture broth of *Streptomyces* species and belong to a family of cyclopentanoid antibiotics.[2]



1



2



3

Although the structure of methylenomycin B is deceptively simple, its synthesis is not trivial. Due to the presence of the two α,β-unsaturated ketone moieties, methylenomycin B is an unstable compound that undergoes easy decomposition under acidic or basic conditions. Since the first total synthesis,[3] which led to the revision of the original structure proposed by Haneishi et al.,[1] methylenomycin B has attracted considerable attention of many research groups as a synthetic target.[4]

In the course of our studies on the application of organic phosphorus and sulfur compounds for the synthesis of 1,4-dicarbonyl compounds and functionalized cyclo-

† Dedicated to the memory of the late David Ginsburg.

(1) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *24*, 386. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *J. Antibiot.* **1974**, *27*, 393. Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977.

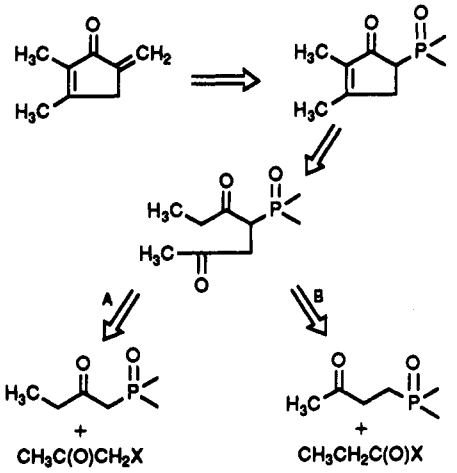
(2) For list of references on this class of compounds see: Smith, A. B. III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1297.

(3) Jernow, J.; Tautz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4212.

(4) Newton, R. F.; Newton, D. R.; Reynolds, D.; Eyre, T. *Synth. Commun.* **1981**, *11*, 527. Tonari, K.; Machiya, K.; Jochimoto, I.; Ueda, U. *Agric. Biol. Chem.* **1981**, *95*, 61561. Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 588. Struntz, G. M.; Lal, G. S. *Can. J. Chem.* **1982**, *60*, 2528. Takahashi, Y.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 496. Billington, D. C.; Pauson, D. L. *Organometallics* **1982**, *1*, 1560. Ho, T.-L. *Synth. Commun.* **1985**, *13*, 435. Doutheau, A.; Sartoretti, J.; Gore, J. *Tetrahedron* **1983**, *39*, 3059. Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. Stetter, M.; Haese, W. *Chem. Ber.* **1984**, *117*, 682. Cameron, A. G.; Hewson, A. T.; Osammor, M. I. *Tetrahedron Lett.* **1984**, *25*, 2267. Pohmakotr, M.; Chancharunee, S. *Tetrahedron Lett.* **1984**, *25*, 4141. Koller, M.; Karp, M.; Dreiding, A. S. *Tetrahedron Lett.* **1986**, *27*, 19. Tius, M. A.; Astrab, D. P.; Fang, A. H.; Ousset, J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438. Welch, S. C.; Asserq, J.-M.; Loh, J. P.; Glase, S. A. *J. Org. Chem.* **1987**, *52*, 1440; Rizzo, J. C.; Dunlap, N. K.; Smith, A. B. III *J. Org. Chem.* **1987**, *52*, 5280.

0022-3263/91/1956-1217$02.50/0

Scheme I



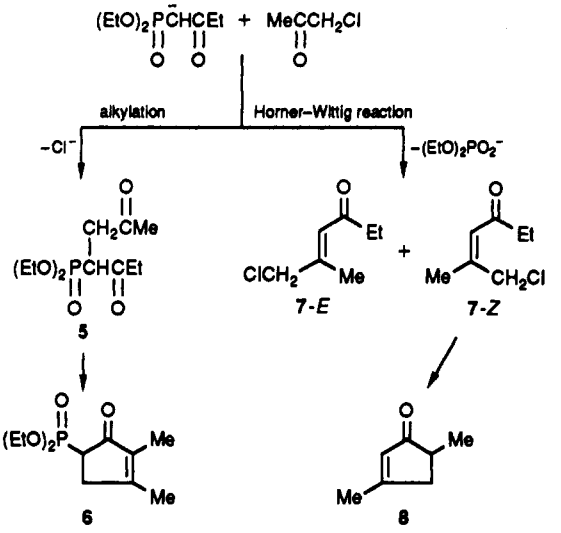
pentenones and cyclopentanones,[5] we have also devised new approaches to the synthesis of methylenomycin B using α-phosphoryl sulfides[6] and β-keto phosphonates[7] as substrates. In these syntheses the α-*exo*-methylene group in **3** was generated from the appropriate α-(hydroxymethylene)- or α-((methylthio)methylene)cyclopentenone derivatives. Since the introduction of such moieties into the cyclopentenone ring as well as their conversion into the α-*exo*-methylene function was not very efficient and influenced strongly the overall yield of **3**, we were searching for a new way to introduce such a function into the cyclopentenone ring. Therefore, we turned our attention to the Horner–Wittig reaction which is a well-established method for the olefinic bond formation[8] and was utilized very often in our previous studies.[9] It was expected that this reaction should also be suitable for the introduction of the exocyclic methylene group into the cyclopentenone skeleton. According to retrosynthetic analysis (Scheme I), such a strategy requires the synthesis of α-phosphorylcyclopentenone and its precursor (i.e., suitably phosphorylated 1,4-diketone). The synthesis of the latter may be accomplished in two ways. The first (A) involves ketomethylation of α-phosphoryl ketone (β-keto phosphonate), whereas the second, alternative route (B) consists in acylation of the α-phosphonate carbon atom in β-phosphoryl ketone (γ-keto phosphonate)

In this paper we would like to disclose the details of this approach to methylenomycin B.[10]

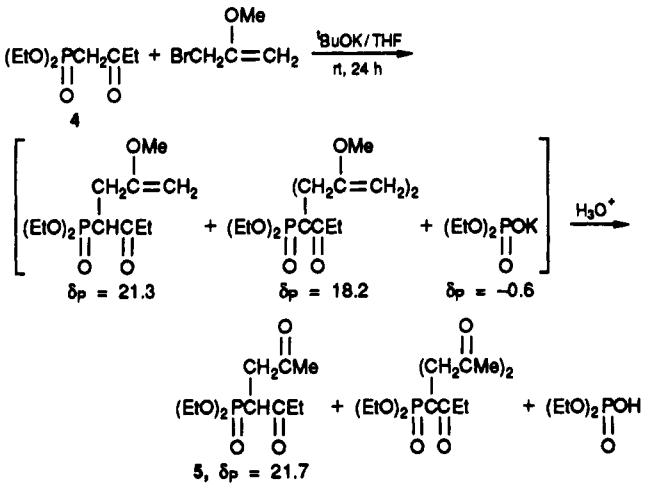
Results and Discussion

Synthesis of Methylenomycin B from Diethyl 2-Oxobutanephosphonate (4). The starting β-keto phosphonate **4** was prepared as described by us earlier.[7a] In order to obtain 4-(diethoxyphosphoryl)heptane-2,5-dione (**5**) according to route A, the α-phosphonate carbanion

Scheme II



Scheme III



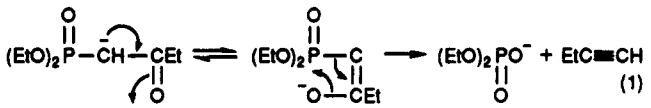
generated from **4** was treated first with chloroacetone. This reaction gave, however, a mixture of products. By means of GC–MS technique it was found to contain small amounts of 5-(diethoxyphosphoryl)-2,3-dimethylcyclopent-2-en-1-one (**6**) (M^+, 246), 1-chloro-2-methylhex-2-en-3-one (**7**) (M^+, 146), and 2,4-dimethylcyclopent-4-en-1-one (**8**) (M^+, 110) as major products. The formation of **7** and **8** in this reaction may be easily rationalized by assuming that α-phosphonate carbanion preferentially attacks the carbonyl group in chloroacetone to give, after diethyl phosphate anion elimination, a mixture of *E* and *Z* isomers of α,β-unsaturated ketone **7** (Horner–Wittig reaction). The *Z* isomer of the latter undergoes cyclization to cyclopentenone **8** under basic reaction conditions. Similarly, minor amounts of diketone **5** formed as a result of the α-phosphonate carbanion alkylation cyclize to the desired 5-phosphorylcyclopentenone **6** (see Scheme II).

These preliminary, rather unsatisfactory results prompted us to use instead of chloroacetone its synthetic equivalent 1-bromo-2-methoxyprop-2-ene exhibiting typical alkylating properties.[11] It was gratifying to find that the reaction of the α-phosphonate carbanion derived from **4** with this reagent results in the formation of the monoalkylation product (73.3%, ^{31}P NMR assay) that upon acidic hydrolysis gave the desired phosphorylated 1,4-di-

(5) For a recent summary, see: Mikołajczyk, M. *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; Myu: Tokyo, 1989; Vol. 2, p 19.
(6) Mikołajczyk, M.; Grzejszczak, S.; Łyżwa, P. *Tetrahedron Lett.* **1982**, *23*, 2237.
(7) (a) Mikołajczyk, M.; Bałczewski, P. *Synthesis* **1984**, 691. (b) Mikołajczyk, M.; Bałczewski, P. *Synthesis* **1987**, 659.
(8) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(9) Mikołajczyk, M. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983; p 347.
(10) Preliminary results were presented at the IXth Int. conference on Phosphorus Chemistry, Nice, France, 1983, and the III Int. Conference on Chemistry and Biotechnology of Biologically Active Natural Products, Sofia, Bulgaria, 1985. Mikołajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Phosphorus Sulfur* **1983**, *18*, 175. Mikołajczyk, M. In *Proceedings of the Third Int. Conf. on Chemistry and Biotechnology of Biologically Active Natural Products*; Vlahov, R., Ed.; Sofia, 1985; Vol. 2, p 254. Mikołajczyk, M.; Zatorski, A. Polish Patent 141948, 15 Jan. 1988, Appl. 247247, 13 Apr. 1984.
(11) Jacobson, R. M.; Raths, R. A.; Mc Donald, J. H. III *J. Org. Chem.* **1977**, *42*, 2545.

ketone 5 (Scheme III) isolated in a pure state by column chromatography in 64% yield. However, apart from the monoalkylation product, dialkylated β-keto phosphonate and diethyl phosphate were formed in 11.1 and 15.5% yield.

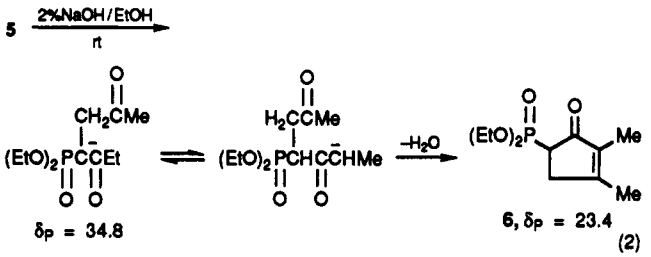
The formation of diethyl phosphate in this reaction is most probably due to the internal decomposition of the starting α-phosphonate carbanion as shown in eq 1.[12]



(1)

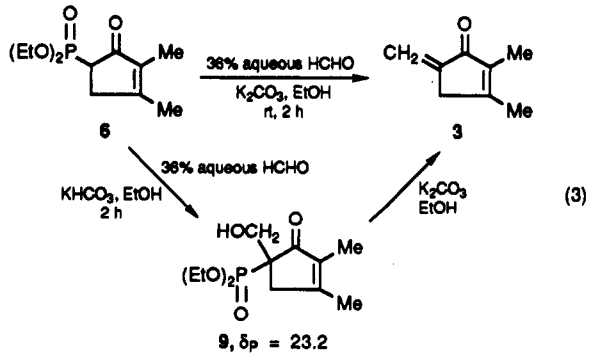
It is also worth noting that the alkylation of the phosphonate 4 is very sensitive to steric hindrance. The use of 1-bromo-2-ethoxyprop-2-ene[13] instead of the methoxy derivative completely failed. After 6 days the reaction mixture was found to contain diethyl phosphate anion only as a result of the "self Horner–Wittig reaction" depicted above.

As expected, the base-catalyzed cyclization of the 1,4-diketone 5 gave 5-(diethoxyphosphoryl)-2,3-dimethylcyclopent-2-en-1-one (6) in 75% yield. Monitoring the reaction course by ^{31}P NMR spectra revealed that also in this case small amounts of sodium diethyl phosphate are formed.



(2)

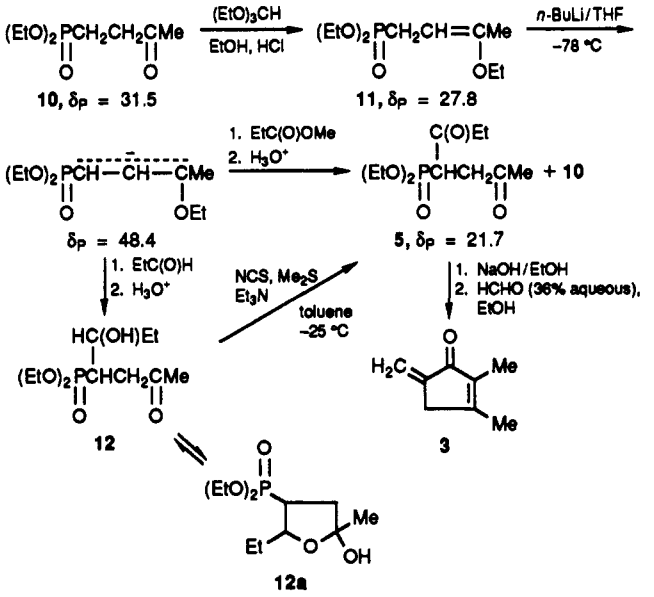
With the readily available phosphorylated cyclopentenone 6 in hand, the last and crucial step of the synthesis of methylenomycin B could now be studied. Since methylenomycin B as well as other cyclopentanoid antibiotics are chemically unstable and decompose in the presence of stronger bases, it was necessary to perform the Horner–Wittig reaction under very mild conditions. We found that 6 reacts smoothly at room temperature with formaldehyde (36% water solution) in ethanol solution in the presence of potassium carbonate as a base to give methylenomycin B 3 in 82% yield. It is interesting to note that the use of hydrogen potassium carbonate allows one to stop the Horner–Wittig reaction at the addition step. The addition product 9, which was characterized by ^{31}P NMR and mass spectra, may be decomposed to 3 in the presence of potassium carbonate.



(3)

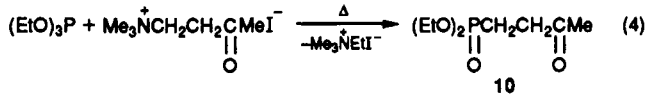
(12) Gough, S. T. D.; Trippett, S. *J. Chem. Soc.* **1962**, 2333.
(13) Hornig, D. E.; Kavadias, G.; Muchowski, J. M. *Can. J. Chem.* **1970**, *48*, 975.

Scheme IV



The total synthesis of methylenomycin B described above requires three steps from β-keto phosphonate 4 and proceeds in 39% overall yield.

Synthesis of Methylenomycin B from Diethyl 3-oxobutanephosphonate (10). According to retrosynthetic analysis outlined in Scheme I an alternative approach to 3 would utilize β-phosphoryl methyl ethyl ketone as a substrate. Since straightforward and efficient preparation of diethyl 3-oxobutanephosphonate (10) has been described by Myers et al.[14] as early as 1955, this compound was selected for our studies. In our hands the reaction of triethyl phosphite with trimethyl(2-(3-oxobutyl))ammonium iodide carried out under the typical Arbusov reaction conditions gave the γ-keto phosphonate 10 in 75% yield.



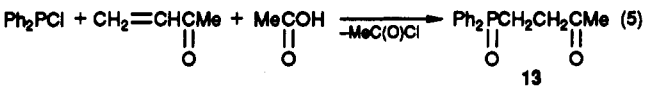
(4)

After some unsuccessful attempts to protect the carbonyl group in 10 as ethylene ketal (ethylene glycol, benzene, *p*-toluenesulfonic acid, reflux) we found that treatment of 10 with triethyl orthoformate in anhydrous ethanol at room temperature at pH 2 (HCl added) results in the formation of the phosphonate 11 (96% yield) in which the carbonyl group is protected as an enol–ether. Most probably the initially formed diethyl ketal of 10 undergoes elimination of ethanol to give 11. Although the carbanion generated from 11 with *n*-butyllithium has ambident character, it was found to react with methyl propionate at the desired α-position giving, after hydrolysis of the enol–ether moiety, 4-(diethylphosphoryl)heptane-2,5-dione (5). The only drawback of this reaction is that 5 is formed in 40% yield together with the starting phosphonate 10, which requires chromatographic separation of both compounds. The formation of the latter in this reaction is due to a fast proton exchange between 5 and the starting phosphonate anion. To complete the synthesis of methylenomycin B the dione 5 was cyclized to cyclopentenone 6, which was then subjected to the Horner–Wittig reaction with formaldehyde under the conditions described above. This synthesis afforded methylenomycin B in 27% overall yield.

(14) Myers, T. C.; Harvey, R. G.; Jensen, E. V. *J. Am. Chem. Soc.* **1955**, *77*, 3101.

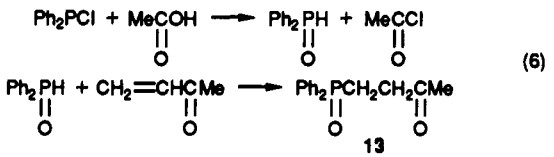
A moderate yield of the synthesis of 5 from 10 prompted us to improve this transformation. Thus, the anion derived from 11 was treated with propanal at low temperature, and the reaction mixture was quenched with a diluted hydrochloric acid before the addition product started to decompose. The hydroxy adduct 12, isolated from the reaction mixture in a crude state (88% yield), was oxidized with Corey's reagent[15] (*N*-chlorosuccinimide, dimethyl sulfide, triethylamine) to afford diketone 5 in 66% yield. The yield of the oxidation step is lower than usually observed because compound 12 exists as an equilibrium mixture with the hemiketal 12a being more resistant to oxidation. Taking into account this way of preparation of 5 we were able to complete the synthesis of 3 from 10 in 34% overall yield.

Synthesis of Methylenomycin B from Diphenyl(3-oxobutyl)phosphine Oxide (13). In an extension of the present study on the synthesis of methylenomycin B 3 from β- and γ-keto phosphonates 4 and 10, we turned our attention to diphenyl(3-oxobutyl)phosphine oxide (13) as a convenient starting material. It was prepared in a nearly quantitative yield from chlorodiphenylphosphine, methyl vinyl ketone, and acetic acid. The reaction was performed under different and much milder conditions than those described by Warren and co-workers.[16]



(5)

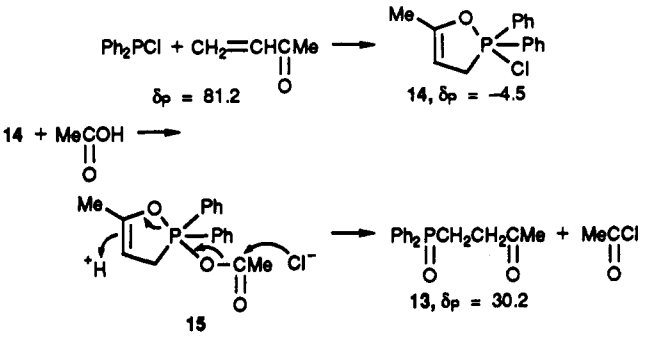
Before discussing the synthesis of methylenomycin B from 13, we would like to comment briefly on the mechanistic aspects of the reaction shown above which is called the Conant reaction.[17] According to Warren[16] the mechanism of this reaction involves formation of diphenylphosphine oxide and acetyl chloride in the first reaction step followed by Michael addition of the secondary phosphine oxide to enone.



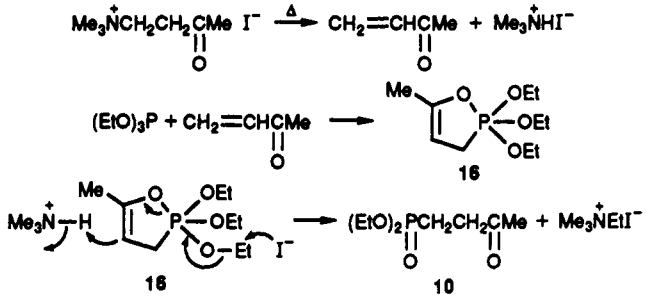
(6)

However, the results of Evans and co-workers[18] on the conjugate addition reaction of silicon phosphite esters to enones strongly suggest the involvement of pentacoordinate oxaphospholenes as intermediates. Our results are in favor of the latter possibility. Thus, in the ^{31}P NMR spectrum of a mixture of chlorodiphenylphosphine and methyl vinyl ketone we observed the phosphorus resonance signal at $\delta_P = -4.5$ ppm. This value of chemical shift is situated in the range characteristic for cyclic pentacoordinate phosphorus compounds and very close to the chemical shift values for other oxaphospholenes.[19,20]

Scheme V



Scheme VI

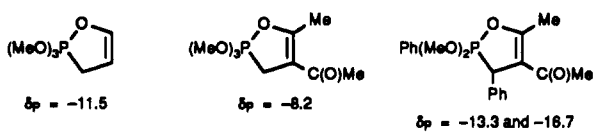


Addition of acetic acid caused disappearance of the signal at $\delta_P = -4.5$ ppm and appearance of the signal at $\delta_P = 30.2$ ppm ascribed to the phosphine oxide 13. Therefore, the most probable reaction pathway for the formation of 13 may be depicted as shown in Scheme V. The first reaction step is the formation of a pentacoordinate oxaphospholene 14. Its reaction with acetic acid leads to a new oxaphospholene 15 by the chloride–acetoxy exchange. The latter decomposes to the final reaction products, i.e. 13 and acetyl chloride.

In view of the fact that trivalent phosphorus compounds and enones easily form pentacoordinate oxaphospholenes[21] and taking into account a well-known tendency of quaternary γ-oxoammonium salts to decompose to α,β-unsaturated carbonyl compounds,[22] it is also quite reasonable to consider that the reaction leading to the γ-keto phosphonate 10 proceeds not according to the Arbusov reaction mechanism but instead by a Conant reaction that involves formation of the transient oxaphospholene 16 (see Scheme VI).

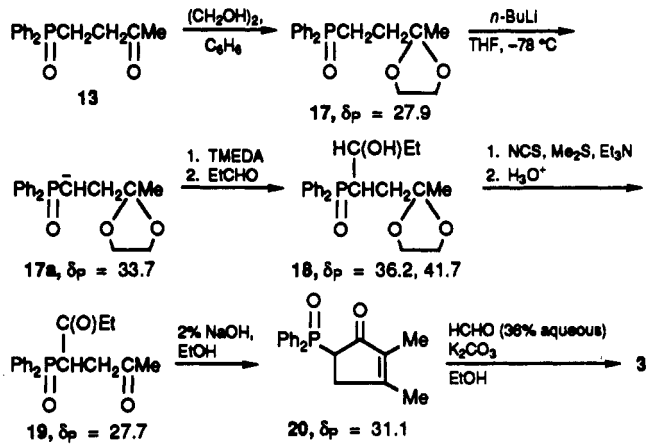
With γ-keto phosphine oxide 13 available in quantity, its suitability as substrate in the synthesis of methylenomycin B was examined. First of all, we found that, in contrast to the γ-keto phosphonate 10, ketalization of 13 using ethylene glycol under standard conditions (reflux in benzene solution containing catalytic amounts of *p*-toluenesulfonic acid) took place quantitatively, and the crude product 17 can be used without purification. In the next step, the lithio derivative 17a (generated from 17 by *n*-BuLi in THF at −78 °C) was treated with propanal. However, the β-hydroxy adduct 18 (a mixture of two diastereomers) was isolated in 40% yield only. The main reason for a low yield of this step is that the lithio deriv-

(15) Corey, E. J.; Kim, C. V. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
(16) Bell, A.; Davidson, A. H.; Earnshow, C.; Norrish, H. K.; Torr, R. S.; Trowbridge, D. B.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2879.
(17) Conant, J. B.; Braverman, J. B. S.; Hussey, R. E. *J. Am. Chem. Soc.* **1923**, *45*, 165.
(18) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467.
(19) Hellwinkel, D. In *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, 1972; Vol. 3, p 281. The chemical shifts of some selected oxaphospholenes are shown below.



(20) A small, negative value of the chemical shift observed for the intermediate oxaphospholene may be due to a substituent effect or to the fact that the pentaccordinate oxaphospholene formed may be in equilibrium with the phosphonium structure.
(21) Gorenstein, D.; Westheimer, F. *J. Am. Chem. Soc.* **1970**, *92*, 634. Ramirez, F. R.; Pilot, J. F.; Madan, O. P.; Smith, C. P. *J. Am. Chem. Soc.* **1968**, *90*, 1275.
(22) Houben-Weyl, *Methoden der Organischen Chemie*, Band VII/2c, 4. Auflage, 1977, p 2124.

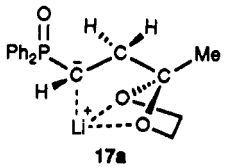
Scheme VII



ative **17a** behaves not only as a nucleophile but also as a strong base[23] that deprotonates an aldehyde to give back **17**. This reaction course was found by means of the ^{31}P NMR spectra to occur in ca. 30%. When the reaction of **17a** with propanal was carried out in the presence of a 2 molar equiv excess of tetramethylethylenediamine (TMEDA), the adduct **18** was obtained in 65% yield. However, also under these conditions ca. 25% of **17** was formed as a result of the propanal deprotonation.

Oxidation of **18** followed by deprotection of the keto function afforded 4-(diphenylphosphinyl)heptan-2,5-dione (**19**) in 79% yield. Its base-catalyzed cyclization gave 5-(diphenylphosphinyl)-2,3-dimethylcyclopent-2-en-1-one (**20**) in 82% yield. Finally, the Horner–Wittig reaction of **20** with formaldehyde (36% aqueous solution) in the presence of potassium carbonate in ethanol solution gave after 20 h methylenomycin B **3** in 59% yield. The overall yield of **3** starting from **13** was 25%.

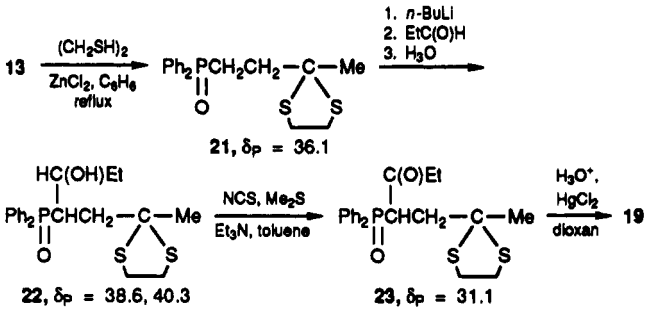
It is interesting to note that the ^{31}P NMR spectrum of **17a** in THF solution recorded at −78 °C shows only one resonance signal at δ_P = 33.7 ppm. When TMEDA is added to this solution one observes in the ^{31}P NMR spectrum two additional signals at δ_P = 35.9 and 41.3 ppm. These spectral observations and a strong influence of TMEDA on the course of addition of **17a** to propanal indicate that both oxygen atoms of the ethylene ketal moiety may play some role in solvation of lithium cation and formation of chelated structures like, for example **17a**. This type of solvation should decrease the reactivity of the carbanionic reagent **17a**. Addition of TMEDA results in the formation of new chelated structures exhibiting different chemical shifts.



17a

As the sulfur atom has a weaker tendency than oxygen to coordinate lithium cation, it was conceivable that the use of the ethylene dithioketal protection of the carbonyl group in **13** would result in a better yield of the addition step. This was found to be the case. Thus, the α-phosphinoxide carbanion generated from **21** reacted with propanal to give the β-hydroxy adduct **22** in 86% isolated yield. Scheme VIII shows this modification which allowed

Scheme VIII



us to synthesize methylenomycin B from **13** in 27% overall yield.

In summary, this study establishes straightforward syntheses of methylenomycin B **3** from the easily available β- and γ-keto phosphonates **4** and **10** and γ-keto phosphine oxide **13**. Our methods compare favorably in terms of brevity, use of simple reagents, and overall yields with the majority of the previously reported syntheses of **3**. Especially short, simple, and efficient is the synthesis of **3** from β-keto phosphonate **4** (three steps, 39% overall yield). Another advantage of our approach is that the presence of phosphorus atom in all starting materials and intermediates allows one to follow the course of each synthetic step by means of ^{31}P NMR spectra.

Finally, our work demonstrated that the Horner–Wittig reaction may be applied for the introduction of the exocyclic methylene moiety into the cyclopentenone rings which are sensitive to acid and bases.

Experimental Section

General. Melting points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use.

4-(Diethoxyphosphoryl)heptane-2,5-dione (5). A solution of 1-(diethoxyphosphoryl)butan-2-one (**4**) (1.04 g, 5 mmol) in THF (10 mL) was treated with potassium *tert*-butoxide (0.62 g, 5.5 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 15 min, and then a solution of 1-bromo-2-methoxyprop-2-ene[24] (1.8 g) in THF (5 mL) was added. After 20 h of stirring at room temperature, the reaction mixture contained three products a, b, and c (73.3, 11.1, and 15.5%, respectively), which were identified and characterized by the ^{31}P NMR and mass spectra. (a) 4-(Diethoxyphosphoryl)-2-methoxy-5-oxohept-1-ene: ^{31}P NMR (THF) δ 21.3 ppm; MS *m/z* (rel intensity), 278 (M^+, 8.0), 220 (100). (b) 4-(Diethoxyphosphoryl)-2-methoxy-5-oxo-4-(2-methoxyprop-2-eneyl)hept-1-ene: ^{31}P NMR (THF) δ 18.2 ppm; MS *m/z* (rel intensity) 348 (M^+, 1.7), 179 (100). (c) Potassium diethyl phosphate: ^{31}P NMR (THF) δ −0.6 ppm.

The reaction mixture was treated with 2 N hydrochloric acid (5 mL) and stirred at room temperature for 2 h. After removal of THF and water, the residue was dissolved in chloroform (20 mL). The organic layer was dried and evaporated to give the crude product **5**, which was purified by column chromatography on silica gel (Merck 70–230 mesh) using a mixture of benzene and acetone (12:1) as eluent: 0.85 g (64%); ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, $CH_3CH_2C(O)$), 1.31 (t, 6 H, CH_3CH_2OP), 2.15 (s, 3 H, $CH_3C(O)$), 2.77 (m, 2 H, $CH_2C(O)$), 3.24 (dd, 2 H, $CHCH_2C(O)$, J_{H-H} = 10.86 Hz, $^3J_{P-H}$ = 5.58 Hz), 3.62 (m, 1 H, CHP(O)), 4.11 (m, 4 H, CH_2OP); ^{31}P NMR (THF) δ 21.7; MS *m/z* (rel intensity) 264 (M^+, 2.2), 165 (100).

Anal. Calcd for $C_{11}H_{21}PO_5$: C, 50.00; H, 8.01; P, 11.72. Found: C, 49.66; H, 8.10; P, 11.74.

5-(Diethoxyphosphoryl)-2,3-dimethylcyclopent-2-en-1-one (6). The dione **5** (0.792 g, 3 mmol) in dry ethanol (12 mL) was added to 2% sodium hydroxide in ethanol (6 mL). The reaction

(23) A similar behavior of the α-phosphonate carbanions was recently observed in our laboratory: Mikołajczyk, M.; Bałczewski, P. *Synthesis* **1989**, 101.

(24) Actually, a mixture of 1-bromo-2-methoxyprop-2-ene (48%), 1-bromo-2-methoxyprop-1-ene (25%), and 1-bromo-2,2-dimethoxypropane (27%) was used in this reaction.

mixture was stirred at room temperature for 2 h. After acidification of the reaction mixture with concentrated hydrochloric acid to pH 7, ethanol was evaporated. The residue was treated with ether (20 mL), and potassium hydrogen carbonate (0.3 g) was added. This mixture was stirred for 6 h at room temperature, and the insoluble material was filtered off. Removal of ether gave the pure cyclopentenone **6**: 0.554 g (75%); ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.34 (dt, 6 H, CH_3CH_2OP), 1.71 (br s, 3 H, CH_3C=), 2.08 (br s, 3 H, CH_3C=), 2.70–3.14 (m, 3 H, $CHCH_2$), 4.16 (m, 4 H, CH_3CH_2OP); ^{31}P NMR ($CDCl_3$) δ 23.3; MS m/z (rel intensity) 246 (M^+, 70.0), 190 (100).

Anal. Calcd for $C_{11}H_{19}PO_4$: C, 53.65; H, 7.78; P, 12.58. Found: C, 53.37; H, 7.68; P, 12.54.

Methylenomycin B 3 from Cyclopentenone 6. To a solution of the cyclopentenone **6** (0.246 g, 1 mmol) in dry ethanol (5 mL) containing dry potassium carbonate (0.138 g, 1 mmol) was added a water solution of formaldehyde (36%, 0.15 mL). The reaction mixture was stirred at room temperature for 8 h. Ethanol was evaporated in vacuo at 5 °C, and ether (5 mL) was added to the residue. The insoluble materials were filtered off. The filtrate was concentrated to ca. 1 mL and subjected to column chromatography on silica gel (Merck 70–230 mesh) to afford methylenomycin B **3** (0.098 g, 80%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.76 (br s, 3 H, CH_3C=) 2.08 (br s, 3 H, CH_3C=), 3.08 (br s, 2 H, CH_2C=), 5.32 and 6.02 (ds, 2 H, CH_2=); MS m/z (rel intensity) 122 (M^+, 32), 31 (100).

5-(Diethoxyphosphoryl)-5-(hydroxymethylene)-2,3-dimethylcyclopent-2-en-1-one (9). To a solution of the cyclopentenone **6** (0.246 g, 1 mmol) in dry ethanol (5 mL) containing dry potassium hydrogen carbonate (0.1 g, 1 mmol) a water solution of formaldehyde (36%, 0.15 mL) was added. After stirring for 2 h at room temperature, the reaction mixture was evaporated, and ether (5 mL) was added to the residue. The ether layer was filtered, dried, and evaporated to give the practically pure cyclopentenone **9** (0.275 g, 100%); ^{31}P NMR ($CDCl_3$) 23.2; MS m/z (rel intensity) 276 (M^+, 9.5), 246 (94), 190 (100). This product was converted into methylenomycin B **3** (0.1 g, 82%) in the presence of potassium carbonate (see the procedure described above).

1-(Diethoxyphosphoryl)-3-ethoxybut-2-ene (11). To a solution of triethyl formate (5.92 g, 40 mmol) in dry ethanol (6 mL) the δ-keto phosphonate **10** (4.16 g, 20 mmol) was added. The resulting mixture was acidified with concentrated hydrochloric acid to pH 2. After 15 min the reaction was completed. Evaporation of ethanol and distillation of the residue gave the enol–ether **11**; 4.53 g (96%); bp 94 °C/0.01; ^{1}H NMR ($CDCl_3$/TMS int) δ 1.15 (t, 3 H, CH_3CH_2OC), 1.25 (t, 6 H, CH_3CH_2OP), 1.78 and 1.83 (two s for *E* and *Z* isomers, 3 H, CH_3C=), 2.11 and 2.78 (AB part of ABX system (X = P), 2 H, J_{AB} = 12 Hz, J_{AX} = 20.83 Hz, J_{BX} = 20.54 Hz, CH_2P), 3.44 and 3.69 (two q for *E* and *Z* isomers, 2 H, CH_2OC=), 4.10 (qt, 4 H, CH_3CH_2OP), 4.35 (m, 1 H, HC=); ^{31}P NMR ($CDCl_3$) δ 27.8; MS m/z (rel intensity) 263 (M^+, 9.2), 71 (100).

Anal. Calcd for $C_{10}H_{21}PO_4$: C, 50.84; H, 8.96; P, 13.11. Found: C, 50.01; H, 8.45; P, 13.37.

Reaction of 11 with Methyl Propionate. Synthesis of 4-(Diethoxyphosphoryl)heptane-2,5-dione (5). To a solution of the enol–ether **11** (2.36 g, 10 mmol) in THF (25 mL) was added at −78 °C a solution of *n*-butyllithium (10 mL, 11 mmol) in hexane. The reaction mixture was stirred for 15 min, and then a solution of methyl propionate (0.44 g, 5 mmol) in THF (5 mL) was added. Stirring at −78 °C was continued for 0.5 h. The reaction mixture was warmed slowly to −20 °C and acidified with concentrated hydrochloric acid to pH 4 and stirred at room temperature for 1 h. The solvents were evaporated, and the residue was extracted with chloroform (3 × 15 mL). The chloroform solution was dried and evaporated to give the crude product containing a 1:1 mixture of the dione **5** and δ-keto phosphonate **10**. The analytically pure dione **5** (1.06 g, 40%) was obtained by column chromatography on silica gel (Merck 70–230 mesh) using a mixture of benzene and acetone (12:1) as eluent.

Reaction of 11 with Propanal. Synthesis of 4-(Diethoxyphosphoryl)-5-hydroxyheptan-2-one (12) and Its Oxidation to 5. A solution of *n*-butyllithium (5 mL, 5.5 mmol) in hexane was added at −78 °C to a solution of the enol–ether **11** (1.18 g, 5 mmol) in THF (20 mL). The reaction mixture was stirred at this temperature for 10 min, and a solution of the freshly distilled propanal (0.29 g, 5 mmol) in THF (3 mL) was added. Stirring at −78 °C was continued for 0.5 h. The reaction mixture was warmed slowly to −20 °C and acidified with diluted hydrochloric acid (5%, 8 mL). After 1 h of stirring at room temperature the organic solvents and about half amount of water were evaporated under reduced pressure. The residue was extracted with chloroform (5 × 10 mL), dried, and evaporated to give the crude product. Its ^{31}P NMR spectrum showed five signals in the range 26.5–30.0 ppm; MS m/z (rel intensity) 265 (M^+ − 1, 2.5), 111 (100). This product was used without purification for oxidation.

Method A. To a solution of PCC (0.52 g, 2.4 mmol) in methylene chloride (5 mL) was added a solution of the crude **12** (0.532 g, 2 mmol) in methylene chloride. The reaction mixture was stirred for 6 h and left to stand overnight. The solvent was decanted, and a dark brown, sticky precipitate was extracted with methylene chloride (6 × 5 mL). The combined methylene chloride solutions were evaporated to give the crude product (0.56 g). The ^{31}P NMR spectrum (THF) of this product showed two groups of signals: the first signal at δ = 22.2 ppm (corresponding to **5**, 67%) and three broad signals at δ = 29.8, 31.8, and 33.7 ppm (33%). The analytically pure dione **5** was obtained by column chromatography, 0.28 g (52%).

Method B. To a solution of *N*-chlorosuccinimide (0.405 g, 3 mmol) in toluene (10 mL) was added dimethyl sulfide (0.3 mL, 4.1 mmol) at 0 °C under argon. The resulting solution was cooled to −25 °C (CCl_4–dry ice), and the crude **12** (0.532 g, 2 mmol) in toluene (2 mL) was added dropwise. The reaction mixture was stirred at −25 °C for 2 h, and then a solution of triethylamine (0.303 g, 3 mmol) in toluene (1 mL) was added dropwise. After 5 min a cooling bath was removed and ether (20 mL) was added. The organic phase was washed with diluted hydrochloric acid (5%, 2 mL) and water (2 mL), dried, and evaporated to give the crude product (0.62 g). Its ^{31}P NMR spectrum ($CHCl_3$) showed two groups of signals: one signal at δ = 21.9 ppm (corresponding to **5**, 68%) and three broad signals at δ = 29.5, 31.5, and 32.9 ppm (32%). The analytically pure dione **5** was obtained by column chromatography, 0.35 g (66%).

1-(Diphenylphosphinyl)butan-3-one (13). A solution of the freshly distilled acetic acid (0.66 g, 11 mmol) in dry benzene (10 mL) was added to a stirred solution of the freshly distilled chlorodiphenylphosphine (2.20 g, 10 mmol) and methyl vinyl ketone (0.77 g, 11 mmol) in dry benzene (10 mL). The reaction mixture was left to stand for 42 h at room temperature in the dark. The solvent was evaporated, and chloroform (20 mL) was added to the residue. The organic phase was washed with saturated aqueous sodium bicarbonate (2 × 5 mL) and water (2 × 5 mL). After drying and removal of chloroform, the pure ketone **13** (2.71 g, 99.6%) was obtained as a pale yellow sticky oil: ^{31}P NMR (C_6H_6) δ 30.2; ^{13}C NMR ($CDCl_3$) δ 23.6 (d, CH_2P, J_{PC} = 73.5 Hz), 29.51 ($CH_3C(O)$), 35.3 (d, $CH_2(O)$, J_{PC} = 2.94 Hz), 128.45–135.21 (aromatic C), 205.54 (d, C(O), $^3J_{PC}$ = 11.77 Hz); MS m/z (rel intensity) 273 (M^+ + 1, 3.2) 272 (M^+ − 1, 2.6), 202 (100).

Anal. Calcd for $C_{16}H_{17}PO_2$: C, 70.58; H, 6.29; P, 11.38. Found: C, 70.26: H, 6.35; P, 11.16.

1-(Diphenylphosphinyl)butan-3-one Ethylene Ketal (17). The phosphine oxide **13** (14.5 g, 0.05 mol) prepared as above was heated under reflux in dry benzene (100 mL) in a Dean–Stark apparatus with an excess of ethylene glycol (4.65 g, 0.075 mol) and catalytic amounts of *p*-toluenesulfonic acid (100 mg) for 6 h. The reaction solution was cooled and washed with saturated aqueous solution of sodium bicarbonate (3 × 5 mL) and water (2 × 10 mL), dried, and evaporated in vacuo to afford the analytically pure product **17**: 15.8 g (100%); mp 102–3 °C; ^{31}P NMR ($CHCl_3$) δ 27.9; ^{13}C NMR ($CDCl_3$) δ 23.53 ($CH_3C(OCH_2)_2$), 24.25 (d, CH_2P, J_{PC} = 73.54 Hz), 30.55 ($CH_2C(OCH_2)_2$), 64.55 (OCH_2CH_2O), 109.14 (d, $C(OCH_2)_2$, $^3J_{PC}$ = 14.71 Hz), 128.19–135.27 (aromatic C); MS m/z (rel intensity) 316 (M^+, 0.5), 87 (100).

Anal. Calcd for $C_{18}H_{21}PO_3$: C, 68.34; H, 6.69; P, 9.79. Found: C, 68.14; H, 6.43; P, 9.52.

4-(Diphenylphosphinyl)-5-hydroxyheptan-2-one Ethylene Ketal (18). To a solution of **17** (7.9 g, 25 mmol) in THF (50 mL) was added at −78 °C a solution of *n*-butyllithium (25 mL, 26 mmol) in hexane. After 5 min a solution of TMEDA (5.8 g, 50 mmol) in THF (20 mL) was added at −78 °C, and the reaction mixture was stirred at this temperature for 0.5 h. Then, a solution of the

freshly distilled *n*-propanal (1.45 g, 25 mmol) in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 0.6 h, warmed slowly to −20 °C, and acidified with saturated aqueous solution of ammonium chloride. The organic solvents were evaporated and the residue was extracted with chloroform (3 × 20 mL). The chloroform solution was washed with 2 N hydrochloric acid (3 × 10 mL) and then with water (3 × 5 mL) and dried. Evaporation of chloroform afforded the crude product **18** (9.2 g) as a mixture of two diastereomers (δ ^{31}P = 41.7 and 36.2 ppm) in a 2:1 ratio. The analytically pure adduct **18** (6.08 g, 65%) was obtained by column chromatography on silica gel (Merck 70–230 mesh) using a mixture of benzene and acetone (10:1) as eluent. Anal. Calcd for $C_{21}H_{27}PO_4$: C, 67.37; H, 7.27; P, 8.27. Found: C, 67.26; H, 7.34; P, 8.20.

Small amounts (0.53 g) of the major diastereomer of **18** (δ ^{31}P = 41.7 ppm, mp 114–116 °C) were isolated by column chromatography and characterized by ^{13}C NMR and MS: ^{13}C NMR ($CDCl_3$) δ 10.40 (CH_3CH_2), 23.99 ($CH_3C(OCH_2)_2$), 28.47 (d, $CH_2CH(OH)$, $^3J_{CP}$ = 11.77 Hz), 30.68 ($CH_2C(OCH_2)_2$), 37.05 (d, CHP, $^1J_{CP}$ = 70.60 Hz), 64.09 and 64.29 (OCH_2CH_2O), 71.63 (CHOH), 108.85 (d, $C(OCH_2)_2$, $^3J_{CP}$ = 7.35 Hz), 127.86–134.56 (aromatic C); MS *m/z* (rel intensity) 375 (M^+ + 1, 0.6), 83 (100).

Oxidation of 18. Synthesis of 4-(Diphenylphosphinyl)-5-oxoheptan-2-one (19). To a solution of NCS (0.27 g, 2 mmol) in toluene (7 mL) was added dimethyl sulfide (0.2 mL, 2.7 mmol) at 0 °C under argon. After cooling to −25 °C this solution was treated with **18** (0.497 g, 1.33 mmol) dissolved in toluene (1.5 mL). The reaction mixture was stirred at −25 °C for 2 h, and triethylamine (0.202 g, 2 mmol) in toluene (0.5 mL) was added dropwise. After 5 min the cooling bath was removed and toluene (15 mL) was added. The resulting toluene solution was washed with 1% hydrochloric acid (5 mL) and water (2 × 15 mL), dried over magnesium sulfate, and evaporated to afford ethylene ketal of the dione **19**: 0.46 g (92%); mp 145–147 °C (from Et_2O); ^{31}P NMR ($CHCl_3$) δ 30.3; ^{13}C NMR ($CDCl_3$) δ 7.48 (CH_3CH_2), 24.05 ($CH_3C(OCH_2)_2$), 36.34 and 36.60 ($CH_2C(OCH_2)_2$ and $CH_2C(O)$), 51.79 (d, CHP, $^1J_{PC}$ = 55.89 Hz), 64.55 and 64.68 (OCH_2CH_2O), 108.82 (d, $C(OCH_2)_2$, $^3J_{CP}$ = 14.71 Hz), 128.32–133.78 (aromatic C), 206.52 (d, C=O, $^3J_{CP}$ = 2.94 Hz); MS *m/z* (rel intensity) 373 (M^+ + 1, 0.9), 372 (M^+, 0.3), 87 (100).

Anal. Calcd for $C_{21}H_{25}PO_4$: C, 67.73; H, 6.77; P, 8.32. Found: C, 67.63; H, 6.81; P, 8.26.

The ethylene ketal (3.72 g, 10 mmol) prepared as above was dissolved in dioxane (30 mL) and water (3 mL), and 0.3 mL of concentrated hydrochloric acid was added. The reaction mixture was refluxed for 2 h. After removal of dioxane and water, the residue was dissolved in chloroform (25 mL). The organic solution was washed with saturated aqueous solution of $NaHCO_3$ (5 mL) and water (2 × 5 mL), dried, and evaporated. The crude dione **19** was purified by column chromatography on silica gel (Merck 70–230 mesh) using benzene–acetone (5:1) as eluent: yield 86% (2.82 g); mp 136–138 °C; ^{31}P NMR ($CHCl_3$) δ 27.7; ^{13}C NMR ($CDCl_3$) δ (CH_3CH_2), 29.32 ($CH_3C(O)$), 38.16 ($CH_3CH_2C(O)$), 41.02 ($CH_2C(O)$), 50.61 (d, CHP, $^1J_{CP}$ = 57.36 Hz), 128.51–132.35 (aromatic C); 204.63, 205.15, 205.87 (C=O); MS *m/z* (rel intensity) 329 (M^+ + 1, 2.0), 328 (M^+, 2.5), 229 (100).

5-(Diphenylphosphinyl)-2,3-dimethylcyclopent-2-en-1-one (20). Cyclization of the dione **19** (1.64 g, 5 mmol) to **20** was carried out according to the procedure described for the synthesis of **6**. The pure cyclopentenone **20** was obtained in 82% yield (1.27 g): mp 184–186 °C; ^{31}P NMR ($CHCl_3$) δ 31.1; ^{1}H NMR ($CDCl_3$) δ 1.57 (br s, 3 H, CH_3C=), 1.96 (br s, 3 H, CH_3C=), 2.69–3.01 (m, 2 H, CH_2CH), 3.47–3.78 (m, 1 H, $CHCH_2$), 7.27–8.04 (m, 10 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 8.06 (CH_3C=), 16.90 (CH_3CC=O), 33.76 (CH_2), 46.67 (d, CHP, $^1J_{CP}$ = 64.71 Hz), 127.93–135.01 (aromatic C), 137.03 (CH_3C=C), 168.75 (CH_3CC=O), 202.16 (C=O); MS *m/z* (rel intensity) 311 (M^+ + 1, 15), 310 (M^+, 62), 202 (100).

Anal. Calcd for $C_{19}H_{19}PO_2$: C, 73.54; H, 6.17; P, 9.98. Found: C. 73.31; H, 6.02; P, 10.12.

Methylenomycin B from 20. The Horner–Wittig reaction of the dione **20** (0.775 g, 2.5 mmol) with formaldehyde (36% aqueous solution) was carried out according to the procedure described for the synthesis of methylenomycin B from **6**. After 20 h and the usual workup methylenomycin B was obtained in 59% yield (0.18 g).

1-(Diphenylphosphinyl)butan-3-one Dithioethylene Ketal (21). The phosphine oxide **13** (7.2 g, 25 mmol) in benzene (50 mL) was heated for 2 h under reflux in a Dean–Stark apparatus with an excess of ethanedithiol (3.6 g, 38 mmol) in the presence of $ZnCl_2$ (3.4 g, 25 mmol). The reaction mixture was cooled to room temperature, washed with a saturated aqueous solution of Na_2CO_3 (5 × 10 mL) and water (2 × 10 mL), dried ($MgSO_4$), and evaporated to give the crude **21**. Crystallization (benzene–ethyl acetate, 5:1) afforded the pure thioketal **21**: 7.66 g (88%); mp 127–129 °C; ^{31}P NMR ($CHCl_3$) δ 36.1; ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3 H, $CH_3C(SCH_2)_2$), 2.04–2.31 (m, 2 H, PCH_2), 2.44–2.76 (m, 2 H, $CH_2C(SCH_2)_2$), 3.28 (m, 4 H, SCH_2CH_2S), 7.43–7.89 (m, 10 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 27.46 (d, CH_2P, $^1J_{CP}$ = 72.07 Hz), 32.31 ($CH_3C(SCH_2)_2$, $^3J_{CP}$ = 16.18 Hz), 128.38–135.33 (aromatic C); MS *m/z* (rel intensity) 349 (M^+ + 1, 0.4), 348 (M^+, 0.4), 202 (100).

Anal. Calcd for $C_{18}H_{21}POS_2$: C, 62.04; H, 6.07; P, 8.89; S, 18.40. Found: C, 61.78; H, 6.13; P, 8.62; S, 18.71.

4-(Diphenylphosphinyl)-5-hydroxyheptan-2-one Dithioethylene Ketal (22). The reaction of **21** (5.22 g, 15 mmol) with *n*-propanal (0.87 g, 15 mmol) was carried out in the same manner as described for the synthesis of the adduct **18**. The crude product **22** was obtained as a 1:1.3 mixture of two diastereomers (δ ^{31}P = 38.6 and 40.3 ppm). Column chromatography afforded the pure adduct **22**, 5.24 g (86%).

Anal. Calcd for $C_{21}H_{27}PO_2S_2$: C, 62.04; H, 6.69; P, 7.62; S, 15.77. Found: C, 62.29; H, 6.82; P, 7.31; S, 15.49.

4-(Diphenylphosphinyl)-5-oxoheptan-2-one Dithioethylene Ketal (23). Oxidation of the adduct **22** (4.06 g, 10 mmol) by NCS (2 g, 15 mmol), Me_2S (20 mmol), and Et_3N (1.52 g, 15 mmol) was carried out according to the procedure described for oxidation of **18**. The crude product **23** was purified by crystallization from ether and ethyl acetate (10:1), 3.13 g (82%): mp 161–162 °C; ^{31}P NMR ($CHCl_3$) δ 31.1; ^{13}C NMR ($CDCl_3$) δ 7.74 (CH_3CH_2), 33.15 ($CH_3C(SCH_2)_2$), 39.91 and 40.43 (SCH_2CH_2S), 40.89 ($CH_2C(O)$, 55.25 (d, CHP, $^1J_{CP}$ = 52.94 Hz), 67.12 (d, $C(SCH_2)_2$, $^3J_{CP}$ = 13.24 Hz), 128.45–133.61 (aromatic C), 206.65 (d, C=O, $^3J_{PC}$ = 2.94 Hz); MS *m/z* (rel intensity) 405 (M^+ + 1, 2.3), 404 (M^+, 0.9).

Anal. Calcd for $C_{21}H_{25}PO_2S_2$: C, 62.35; H, 6.23; P, 7.66; S, 15.85. Found: C, 62.08; H, 6.33; P, 7.36; S, 16.14.

Hydrolysis of Thioketal 23 to Dione 19. To a mixture of **23** (2.02 g, 5 mmol), dioxane (20 mL), water (3 mL), and mercury chloride (1.49 g, 6 mmol) was added concentrated hydrochloric acid (0.3 mL). The reaction mixture was refluxed for 2 h. The insoluble material was filtered off. Evaporation of the solvents afforded the residue which was dissolved in chloroform. The resulting solution was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL) and water (5 mL), dried, and evaporated to give the crude dione **19**. The analytically pure product was obtained by column chromatography, 1.46 g (89%).

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