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An Expeditious Synthesis of (±)-Desepoxy-4,5-didehydromethylenomycin A Methyl Ester

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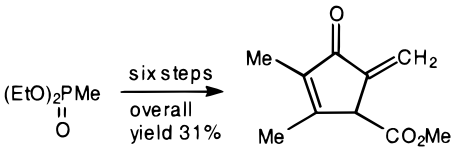
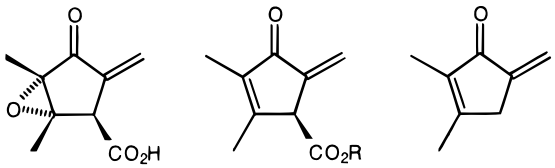
ABSTRACT



A total synthesis of the racemic methyl ester of desepoxy-4,5-didehydromethylenomycin A has been achieved in six steps with an overall yield of 31% starting from diethyl methanephosphonate. The key steps include the Nazarov cyclization of the dienone 7 leading to the α-phosphoryl cyclopentenone 8 and the Horner–Wittig reaction of the latter employed for the introduction of the exocyclic methylene moiety.

The cyclopentenone skeleton is a common structural motif in a variety of naturally occurring compounds. Among them, a family of cyclopentanoid antibiotics known as methylenomycins attracted considerable attention because of a wide spectrum of biological activity and structural diversity.[1] Methylenomycin A **1**, desepoxy-4,5-didehydromethylenomycin A **2a**, and methylenomycin B **3**, which have been isolated from the culture broth of *Streptomyces* species, show inhibitory activity against Gram-positive and Gram-negative bacteria.[2]



1 **2a**, R = H; **2b**, R = Me **3**

Although the structures of methylenomycins **1**−**3** are deceptively simple (they are simplest antibiotics), their syntheses are not trivial. This is because of the low chemical stability of these compounds and specific functionalization of the five-membered ring. Therefore, they became attractive synthetic targets in numerous laboratories. As part of our program aimed at development of efficient and versatile methods for the synthesis of functionalized cyclopentenones and cyclopentanones using organic phosphorus and sulfur compounds, we have also been engaged for the past few years in the synthesis of cyclopentanoid antibiotics and related compounds.[3] Our endeavors resulted in the elaboration of new and efficient synthetic approaches to methylenomycin B **3**,[4] sarkomycin,[5] isoterrein,[6] rosaprostol,[7] and

(1) See, for example: Mathew, J. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbiological Products*; Lucakcs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2, pp 435−474.

(2) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M. *J. Antibiot.* **1974**, *27*, 386−392. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *J. Antibiot.* **1974**, *27*, 393−399. Haneishi, T.; Terahara, A.; Hamano, K.; Arai, M. *J. Antibiot.* **1974**, *27*, 400−407.

(3) For a recent summary, see: Mikolajczyk, M.; Mikina, M.; Zurawinski, R. *Pure Appl. Chem.* **1999**, *71*, 473−480.

(4) Mikolajczyk, M.; Grzejszczak, S.; Lyzwa, P. *Tetrahedron Lett*. **1982**, *23*, 2237−2240. Mikolajczyk, M.; Balczewski, P. *Synthesis* **1984**, 691−694; **1987**, 659−661. Mikolajczyk, M.; Zatorski, A. *J. Org. Chem*. **1991**, 56, 1217−1223. Mikolajczyk, M.; Zurawinski, R. *Synlett* **1991**, 575−576. Balczewski, P. *Heteroatom. Chem.* **1997**, *8*, 67−69.

(5) Mikolajczyk, M.; Zurawinski, R.; Kielbasinski, P.; Wieczorek, M. W.; Blaszczyk, J. *Synthesis* **1997**, 356−365.

(6) Mikolajczyk, M.; Mikina, M.; Wieczorek, M. W.; Blaszczyk, *J. Angew. Chem*. **1996**, *108*, 1645−1647; *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1560−1562.

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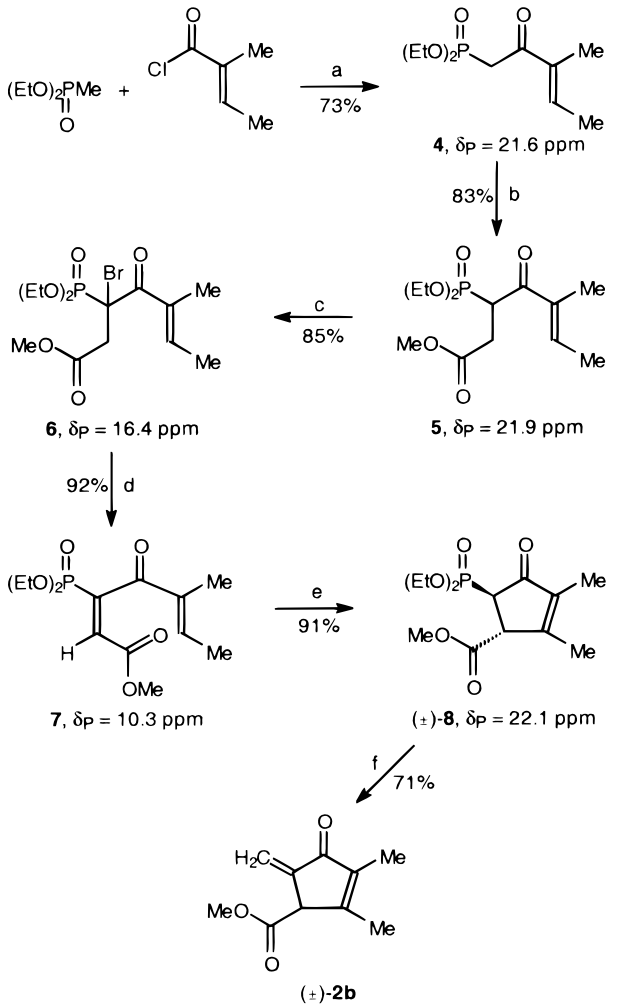
prostaglandin $B_{1\alpha}$ methyl ester.[8] Continuing our interest in this field, we wish to disclose herein a new total synthesis of the title compound (±)-**2b**[9,10] using diethyl methanephosphonate as a substrate. It is shown in Scheme 1 and briefly discussed below.

Scheme 1[a]



[a] (a) BuLi, −78 °C, Cu_2I_2, THF, −40 °C; (b) NaH, −10 °C → rt, $BrCH_2CO_2Me$, THF, −10 °C → reflux; (c) NaH, 25 °C → 60 °C, Br_2, THF, −10 °C; (d) DBU, CH_2Cl_2, rt; (e) $FeCl_3$, CH_2Cl_2, −30 °C → rt, 30 h; (f) NaH, CH_2O·gaseous, THF, rt.

In the first step, the lithium−copper salt of the starting phosphonate was acylated with tiglic acid chloride to give β-oxophosphonate **4** as a mixture of *E* and *Z* isomers in a 22:1 ratio.[11] Treatment of the sodium salt of the *E* isomer of **4** with methyl bromoacetate afforded the corresponding α-substituted β-oxophosphonate **5**. A simple bromination of the α-phosphonate carbanion of **5** with bromine and subsequent dehydrobromination[12] of the resulting bromophosphonate **6** using DBU allowed for the preparation of dienone **7**, which is a key intermediate because according to our synthetic strategy the construction of the cyclopentenone ring would be accomplished via the Nazarov reaction.

A newly formed olefinic bond in **7** has the *E*-geometry as indicated by the $^3J_{H,P}$ coupling constant value of 23.2 Hz.[13] Additional support for this assignment was provided by NOE experiments. Thus, irradiation of the olefinic methine proton at $\delta = 6.74$ ppm induced an enhancement in absorption intensity of the phosphorus signal of 4.6%. Interestingly, the observed NOE between two β olefinic protons in **7** of 16.9% points to their proximity and to a conformation suitable for the cyclopentenone ring formation via the Nazarov cyclization. The latter reaction, which has been found to occur with structurally related α-phosphoryl dienones in low to moderate yields,[14] was a priori the most uncertain step in the whole synthesis. To our satisfaction, however, the Nazarov cyclization of **7** carried out in the presence of iron(III) chloride in methylene chloride at −30 °C gave cyclopentenone **8** in 91% yield and with the *trans*-situated phosphoryl and methoxycarbonyl groups as the only product. In accord with the commonly accepted mechanism of the Nazarov reaction,[15] formation of the double bond exclusively at C(2) and C(3) of the cyclopentenone ring may be attributed to a better stabilization of an intermediate β-ketocarbocation by the two methyl groups. In the last step, the Horner−Wittig reaction of **8** with gaseous formaldehyde allowed for the introduction of the exocyclic α-methylene moiety under mild conditions and for completion of the synthesis of (±)-methyl ester of desepoxy-4,5-didehydromethylenomycin A **2b** in 31% overall yield. The spectral data of the product obtained were fully consistent with those reported in the literature.[10]

In summary, we have developed a short and efficient synthesis of the racemic methyl ester of desepoxy-4,5-

(7) Mikolajczyk, M.; Zurawinski, R. *J. Org. Chem.* **1998**, *63*, 8894−8897. Mikolajczyk, M.; Mikina, M.; Jankowiak, A.; Mphahlele, M. J. Submitted.

(8) Mikolajczyk, M.; Mikina, M.; Jankowiak, A. Submitted.

(9) The methyl ester **2b** is more stable than the corresponding free acid **2a**. It is also expected to be more biologically active than **2a** as was found in the case of methylenomycin A **1** methyl ester which showed stronger antibacterial and antifungal activity than methylenomycin A itself.

(10) For previous syntheses of (±)-**2b**, see: Sakai, K.; Amemiya, S.; Inoue, K.; Kojima, K. *Tetrahedron Lett.* **1979**, *25*, 2365−2368. Boschelli, D.; Scarborough, R. M. Jr.; Smith, A. B., III. *Tetrahedron Lett.* **1981**, *27*, 19−22. Mahidol, C.; Thebtaranonth, C.; Thebtaranonth, Y.; Yenjai, C. *Tetrahedron Lett.* **1989**, *30*, 3857−3860. Hong, F.-T.; Lee, K.-S.; Liao, Ch.-Ch. *Tetrahedron Lett.* **1992**, *33*, 2155−2158. Tius, M. A.; Kwok, Ch.-K.; Gu, X.; Zhao, Ch. *Synth. Commun.* **1994**, *24*, 871−885.

(11) Tiglic acid chloride was obtained from commercially available *trans*-2-methyl-2-butenoic acid (tiglic acid).

(12) Attempted phenylselenylation of the sodium salt of **4** with phenylselenenyl bromide as an alternative way for introduction of the olefinic bond failed.

(13) There is a clear-cut relationship between the *E* and *Z* geometry of β-monosubstituted vinyl phosphonates and the value of the $^3J_{H,P}$ coupling constant ($^3J_{H,P-trans} \sim 40$ Hz; $^3J_{H,P-cis} \sim 20$ Hz): Lehnert, W. *Tetrahedron* **1974**, *30*, 301−305. Reetz, M. T.; Peter, R.; von Itzstein, M.; *Chem. Ber.* **1987**, *120*, 121−122. Nickson, T. E. *J. Org. Chem.* **1988**, *53*, 3870. Midura, W. H.; Mikolajczyk, M.; *Tetrahedron Lett.* **1995**, *36*, 2871−2874.

(14) Minami, T.; Nakayama, M.; Fujimoto, K.; Matsuo, S. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1993**, *75*, 135−138. Motoyoshija, J.; Mizuno, K.; Tsuda, T.; Hayashi, S. *Synlett* **1993**, 237−238.

(15) Krohn, K. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H.-J., Braun, M., Krohn, K.; Reissig, H.-U. Eds.; VCH: Weinheim, New York, Basel, Cambridge, 1991; pp 137−144. Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1−158.

didehydromethylenomycin A. The key steps in this synthesis involve the highly efficient and regioselective Nazarov cyclization of α-phosphoryl dienone **7** and the use of the Horner−Wittig reaction for introduction of the exocyclic α-methylene moiety. Our synthesis compares favorably in terms of use of simple reagents and transformations with the majority of the previously reported syntheses. The synthesis of optically active **2b** is currently under study in our laboratory.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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