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Synthesis and Stereochemical Elucidation of a 14-Membered Ring Phosphonate

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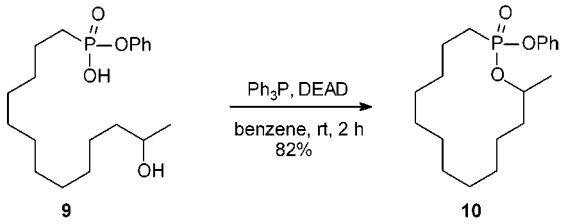
ABSTRACT



9 **10**

We report the synthesis and stereochemical elucidation of a 14-membered ring phosphonate. The key step in the synthesis of the macrolide phosphonate was the cyclization of the acyclic precursor using the Mitsunobu reaction, a mild reaction for the preparation of mixed phosphonates.

Phosphonate esters have been used extensively as haptens for the production of catalytic antibodies, and for this reason, we set out to synthesize the macrocyclic phosphonate **10**.

Macrocyclic phosphonates, like macrocyclic lactones, present a challenge to the synthetic chemist because of the difficulty in carrying out the ring-forming step. The use of the Mitsunobu protocol by Smith et al.[1] in the key lactone-forming step in the total synthesis of the latrunculins, a class of compounds containing a macrocyclic lactone ring, caught our attention. Over the past two decades, the Mitsunobu reaction has found extensive use in organic synthesis, particularly for the inversion of the stereochemistry of alcohols via an esterification/hydrolysis procedure.[2] The Mitsunobu reaction is a mild coupling reaction for the preparation of mixed phosphonates from phosphonic acid monoesters and primary or secondary alcohols.[3] It has been used with carboxylic acids, phenols, phosphates, and phosphonic acids as the nucleophilic component. Thus we designed the synthesis of phosphonate **10** such as to employ the Mitsunobu reaction in the key ring-forming transformation of the monophosphonic acid **9** into the cyclic phosphonate **10**.

The synthesis of macrocyclic phosphonate **10** (Scheme 1) began with the Grignard reaction of undecylenic aldehyde and methylmagnesium bromide to give the hydroxy alkene **1** in 90% yield. The hydroxyl group of **1** was subsequently protected as the THP ether **2** in 84% yield. The two diastereomers of **2** were not separated but were treated together in the following sequences. Hydroboration of **2** followed by oxidation gave **3** in 96% yield. The alcohol **3** was subsequently oxidized under Swern conditions to give the aldehyde **4** in 87% yield. Aldehyde **4** was then reacted with the stabilized Wittig reagent[4] **5** in refluxing toluene to give the vinyl phosphonate **6** in a moderate yield of 52% with a 4:1 ratio of *trans* to *cis* isomers. The alkene **6** was

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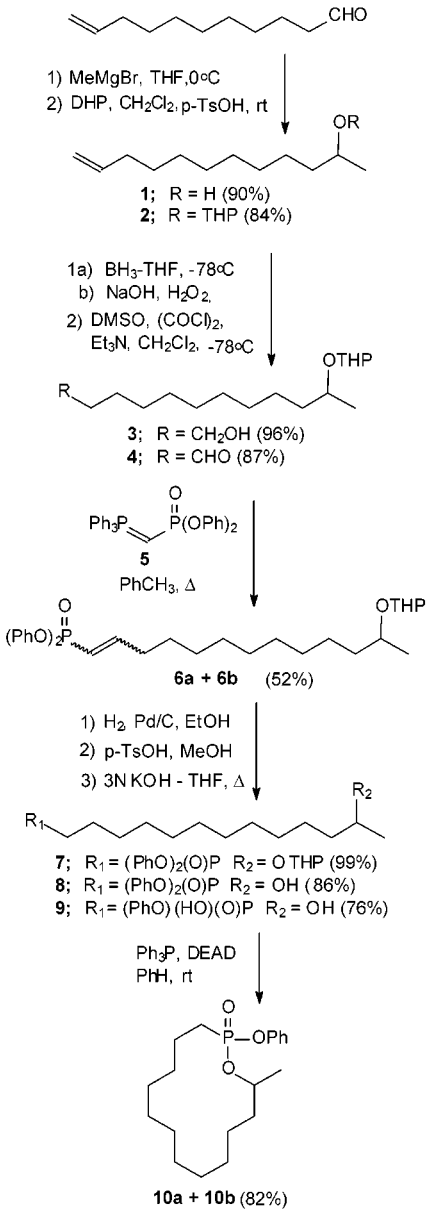
Scheme 1



then reduced using H_2 and 10% Pd/C in EtOAc to give the saturated diphenyl phosphonate **7** in 99% yield. Phosphonate **7** was subsequently reacted with *p*-toluenesulfonic acid to liberate the secondary hydroxyl of compound **8** in 86% yield. Phosphonic acid monoester **9** was produced in 76% yield by base hydrolysis of **8** in refluxing potassium hydroxide/THF.

The key step[5] in the synthesis of the macrocyclic phosphonate **10** was the cyclization of **9** to give the 14-membered ring phosphonate **10**. The hydroxy phosphonic acid monoester **9** was reacted with DEAD and triphenylphosphine in benzene under high dilution conditions to produce the cyclic phosphonates **10a** and **10b** in 82% yield as a 5:1 mixture of diastereomers.[6]

In addition to the two 14-membered ring diastereomers **10a** and **10b**, a cyclic dimer side product **11** was isolated as rod-shaped crystals on purification of **10a** and **10b**. The structure of dimer **11** was determined by single-crystal X-ray diffraction (Figure 1).[7] Dimer **11**, a centrosymmetric 28-membered ring compound with two parallel chains bridged at both ends by the phosphonate group, contains four stereogenic centers with *R*R** stereochemistry on one bridge and the mirror image *S*S** stereochemistry at the opposite

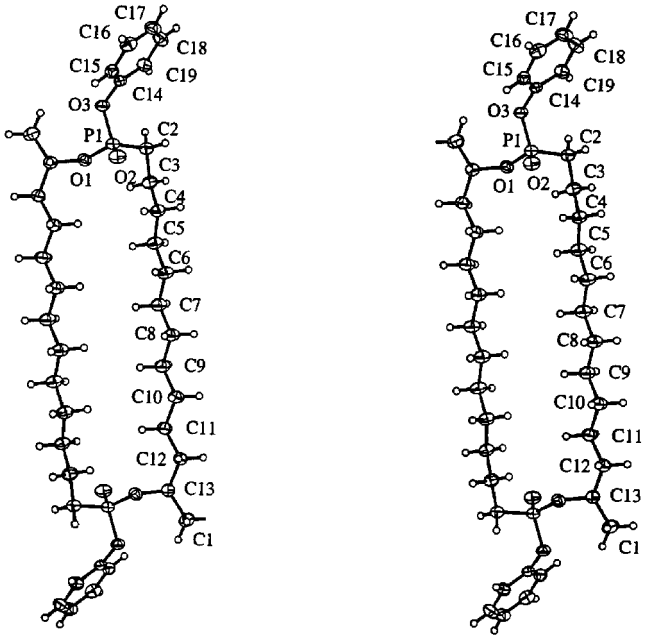


Figure 1. Stereoview of an ORTEP representation of dimer **11** showing 33% probability ellipsoids. Hydrogen atoms have been given arbitrary thermal parameters for clarity.

(5) To a stirred solution of compound **9** (125 mg, 0.351 mmol) in 150 mL of dry PhH at room temperature under N_2 was added Ph_3P (368 mg, 1.40 mmol), followed by DEAD (221 μL, 1.40 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by flash chromatography using 2:1 hexane and ethyl acetate to afford the separated diastereomers, **10a** and **10b**, in a 5:1 ratio based on recovered yields and a combined yield of 82%. In addition, 6 mg of dimer **11** was isolated as a colorless, crystalline solid.

(6) Selected data for compounds are as follows. **10a**: $R_f = 0.71$ (silica gel, petroleum ether/ethyl acetate 1:1); FTIR (neat) 2927, 2859, 1593, 1490, 1458, 1380, 1253, 1210, 1163, 1071, 991, 920, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05−7.38 (m, 5H), 4.75 (m, 1H), 1.24−1.88 (m, 22H), 1.22 (d, $J = 6.3$ Hz, 3H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 29.6; HRMS calcd for $C_{19}H_{31}O_3P$ 338.2011, found 338.2002. Anal. Calcd for $C_{19}H_{31}O_3P$: C, 67.42; H, 9.24. Found: C, 67.20; H, 9.20. **10b**: mp 97−99 °C.; $R_f = 0.57$ (silica gel, petroleum ether/ethyl acetate 1:1); FTIR ($CDCl_3$) 2932, 2860, 1593, 1492, 1456, 1223, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05−7.38 (m, 5H), 4.65 (m, 1H), 1.93 (m, 2H), 1.20−1.73 (m, 20H), 1.43 (d, $J = 6.2$ Hz, 3H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 27.8; HRMS calcd for $C_{19}H_{31}O_3P$ 338.2011, found 338.2009. Anal. Calcd for $C_{19}H_{31}O_3P$: C, 67.42; H, 9.24. Found: C, 67.15; H, 9.39. **11**: mp 103−105 °C; $R_f = 0.62$ (silica gel, petroleum ether/ethyl acetate 1:1); FTIR ($CDCl_3$) 2930, 2856, 1593, 1491, 1229, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.33 (m, 10H), 4.66 (m, 2H), 1.84 (m, 4H), 1.68 (m, 4H), 1.56 (m, 4H), 1.20−1.45 (m, 40H), 1.15 (d, $J = 6.2$ Hz, 6H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 29.0; HRMS calcd for $C_{38}H_{62}O_6P_2$ 676.4022, found 676.4002. Anal. Calcd for $C_{38}H_{62}O_6P_2$: C, 67.42; H, 9.24. Found: C, 67.51; H, 9.28.

(7) Crystal data for **11**: $C_{38}H_{62}O_6P_2$; monoclinic; $P2_1/n$; $a = 7.841(1)$ Å; $b = 5.664(2)$ Å; $c = 43.378(1)$ Å; $\beta = 90.259(8)°$; V = 1926.4(5) Å^3; $Z = 2$; colorless; $T = 294$ K; $R = 0.030$; GOF = 2.27.

bridge. Dimer **11** has a center of symmetry as a result of the *R***R** and *S***S** stereochemistry at the bridge ends.

The ^{1}H and ^{31}P NMR spectra of the 28-membered macrocyclic phosphonate dimer **11**, together with the structural information from the X-ray structure of **11**, have allowed us to infer structural information about monomers **10a** and **10b**.

The stereoview of the ORTEP representation of the macrocyclic dimer **11** (Figure 1) reveals that the doubly bonded oxygen on the phosphorus atom is "*syn*" to the C-13 methine proton, and the C-1 methyl group is "*syn*" to the oxygen of the phenol moiety (Figure 2). Analysis of the

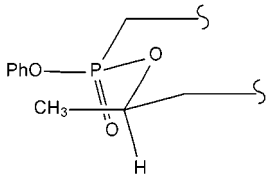


Figure 2. The relative stereochemistries of the OPh and C-1 methyl groups of compound **11**.

transition states for ring closure reveals that the pathway leading to *R***R** product has fewer steric interactions compared to cyclization to *S***R** product (Figure 3).

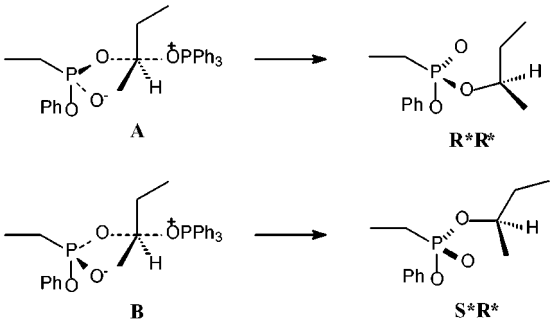
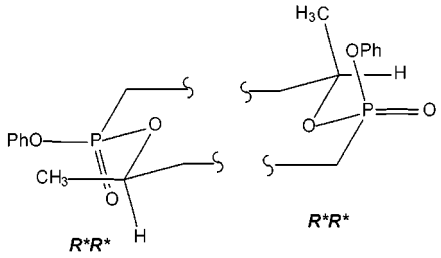


Figure 3. Suggested transition states A and B leading to the *R***R** and *S***R** products, respectively.

The condensation of two molecules of **9** via the Mitsunobu methodology resulted in the *R***R** stereochemistry. It follows that closure of the opposite end of the acyclic dimer would be governed by the same steric control, resulting in either the *SS* or *RR* stereochemistry for the second phosphonate bridge. Why is the *R***R***S***S** dimer **11** the only dimer molecule isolated on cyclization of **9**? Molecular models of the *R***R***S***S** and *R***R***R***R** diastereomers of dimer **11** were calculated using MACROMODEL. The *R***R***S***S** model was calculated according to the X-ray structure obtained for dimer **11**. The *R***R***R***R** model was calculated from the same conformation as **11**, where the second *R***R** bridge was created by inverting the stereochemistry at the *S***S** bridge.



This *R***R***R***R** model retained one *R***R** bridge common to **11**, where the aryloxy moiety attached to the phosphorus atom occupies a pseudoequatorial position, projecting away from the ring while the doubly bonded oxygen atom projects into the ring (as in Figure 1). However, the *R***R** stereochemistry at the opposite bridge of the *R***R***R***R** model forces the methyl and aryloxy moieties to project in toward the ring, as illustrated below. MACROMODEL calculations[8] on the *R***R***S***S** and *R***R***R***R** dimers using the MM2 force field[9] gave a lower energy conformation for the *R***R***S***S** dimer, 92.40 kJ/mol, compared to 109.23 kJ/mol for the *R***R***R***R** dimer.

These calculations suggest that the *R***R***S***S** dimer is of lower energy and may provide a rationale for why only this dimer was isolated on cyclization of compound **9**.

If the transition state leading to the *R***R** stereochemistry is extended to the monomers **10a** and **10b**, it is reasonable to suggest that the major monomer **10a** might also exhibit the *R***R** relative stereochemistry. We are suggesting, therefore, that the major isomer **10a** has the *R***R** relative stereochemistry between the C-1 methyl and the phosphorus atom consistent with that of compound **11**. In addition, we believe that the C-1 methyl group and the OPh group on phosphorus are mainly in a conformation in which both are pseudoequatorial in isomer **10a** as found in the X-ray structure of **11** (Figure 2). The suggested relative stereochemical assignments, therefore, between the OPh and C-1 methyl groups of macrocyclic phosphonates **10a**, **10b**, and **11** are as shown in Figure 4.

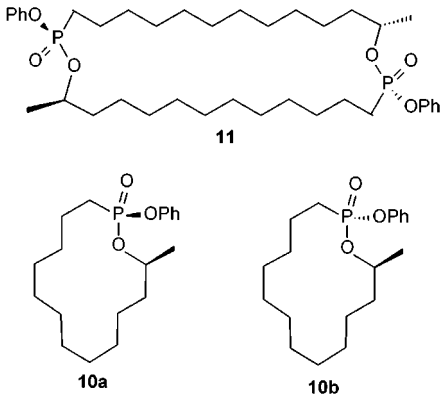


Figure 4. The relative stereochemistries of the macrocyclic phosphonates **10a**, **10b**, and **11**.

Support for the pseudoequatorial assignment of the OPh group on the phosphorus atom of the 14-membered ring phosphonate **10a** comes from correlations between the ^{1}H and ^{31}P NMR chemical shift data (see Table 1). It has been observed that the ^{31}P NMR signal for the equatorial P−OR isomer is approximately 2 ppm lower field than the corresponding axial isomer in the cyclic phosphonates of hexopyranoses[10] and in other six-membered ring phosphonates.[11] This trend supports our correlation between compounds **11** and **10a**, since the ^{31}P NMR shift for isomer **10a** is nearly 2 ppm downfield from that of isomer **10b**.

Table 1. Key ^{1}H, ^{13}C, and ^{31}P NMR Chemical Shifts (ppm) for the Cyclic Phosphonates

compound	δ ^{1}H for CH_3 protons	δ ^{1}H for methine proton	δ ^{13}C for CH_3 carbon	δ ^{13}C for C-13 methine carbon	δ ^{31}P
10a	1.22	4.75	22.4	74.5	29.6
10b	1.43	4.65	22.3	75.3	27.8
11	1.15	4.66	22.1	74.7	29.0

As further support for our relative stereochemical assignments for isomers **10a** and **10b**, ^{13}C NMR data was obtained for all three compounds, **11**, **10a**, and **10b**. It was anticipated that the ^{13}C NMR shifts of the C-1 methyl carbons and/or the C-13 carbon (bearing the methyl group; see Figure 1) might reveal a trend. Table 1 reveals that the ^{13}C NMR shifts for the C-1 methyl carbons of compounds **11**, **10a**, and **10b** are essentially the same. However, the ^{13}C NMR shifts for the C-13 carbons of compounds **11**, **10a**, and **10b** support our correlation between compounds **11** and **10a**, as the carbon chemical shifts for **11** and **10a** are consistent (see Table 1).

Finally, the relative stereochemical assignments for isomers **10a** and **10b** were confirmed through NOE difference experiments performed on macrocycles **11**, **10a**, and **10b**. These NOE experiments revealed the same positive NOE enhancements between the C-1 methyl protons and those associated with the OPh group for compounds **11** and **10a**; however, the NOE experiment for isomer **10b** did not reveal these enhancements. These NOE results further confirm our assignment for isomers **10a** and **10b**.

The macrocyclic phosphonate, **10**, was synthesized in nine steps with an overall yield of 17%. The key step in the synthesis of **10** was the use of the Mitsunobu reaction in the ring-closing step, which proceeded in an 82% yield with a 5:1 ratio of the two isomers **10a** and **10b**. The structural information from the X-ray structure of **11**, together with the ^{1}H, ^{13}C, and ^{31}P NMR spectra of compounds **11**, **10a**, and **10b**, allowed us to make structural assignments for diastereomers **10a** and **10b**. Finally, comparison of NOE difference experiments performed on the three compounds allowed us to confirm our relative stereochemical assignments for isomers **10a** and **10b**.

We shall report the use of **10** as a hapten for the generation of monoclonal antibodies for the purpose of catalyzing a macrolactonization reaction elsewhere.

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