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Macrocyclic Phostones

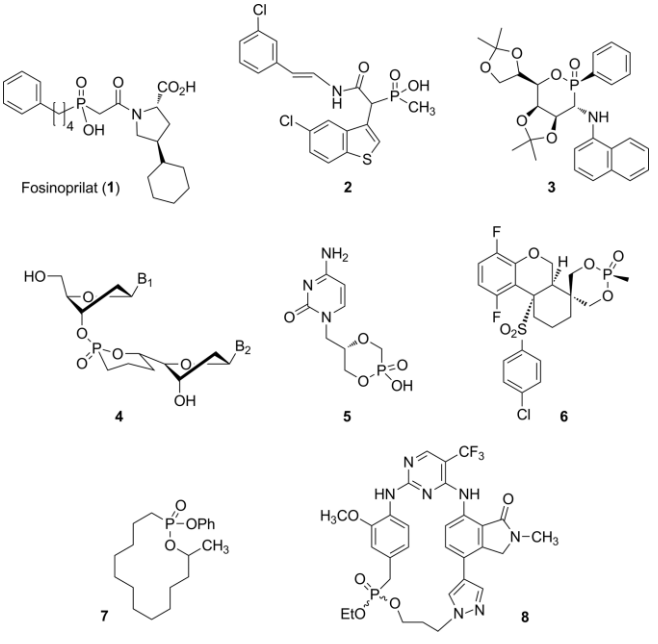
Synthesis of Benzothiophene-Containing 10- and 11-Membered Cyclic Phostones

Alexios N. Matralis[a] and Youla S. Tsantrizos*[a,b]

Abstract: Phosphinate and phosphonate derivatives can serve as useful transition-state analogues of proteases, as substrate mimics of DNA/RNA-processing enzymes, and as inhibitors of enzymes catalyzing the biosynthesis of isoprenoids. Synthetic methodologies for the preparation of medium-sized ring phosphonate-containing compounds (also known as phostones) are currently limited to a few examples. A synthetic protocol was developed that is amenable to the parallel synthesis of structurally diverse phostones containing a benzo[*b*]thiophene core, which enables the profiling of such novel compounds in biological screens of potential therapeutic targets.

Introduction

Phosphorus-containing ligands have been used as molecular probes for mechanistic investigations of enzymatic reactions and as key pharmacophores in the development of human therapeutics. In particular, phosphinate and phosphonate derivatives have been explored as transition-state analogues and inhibitors of therapeutically relevant protease enzymes. Examples include the antihypertension drug fosinoprilat (**1**, a potent inhibitor of the zinc-metallopeptidase angiotensin-converting enzyme; ACE)[1] and preclinical anti-inflammatory agent **2** (an inhibitor of the human mast cell chymase).[2] Six-membered ring phosphinates (known as oxaphosphinanes or phostines) and phosphonates (known as phostones) have also been previously explored in drug discovery as bioisosteres of the furanose or pyranose ring, in which the anomeric carbon atom is replaced by the phosphinate or phosphonate moiety. Examples of this type include C-glycoside mimics that block glioma stem cell proliferation (e.g., compound **3**)[3] and conformationally rigidified nucleotides that are potentially useful in antisense technologies (e.g., phostone-based dinucleotide **4**).[4] Six-membered ring phostones have also been explored as prodrugs of antiviral nucleosides, such as cidofovir (**5**),[5] and dioxaphosphinane 2-oxide **6** has been identified as an inhibitor of γ-secretase,[6] an important target associated with the progression of Alzheimer's disease.



However, far less attention has been devoted to the synthesis and biological evaluation of large ring systems of phostines, phostones, and phosphates. Recently, novel macrocyclic phosphates and phosphoramidates, with structural similarities to macrolide polyketides, were reported.[32] Macrocyclic compound **7** (a hapten for raising catalytic antibodies)[7] and antiproliferation and migration agent **8** (an inhibitor of focal adhesion kinase; FAK)[8] are two examples of reported macrocyclic phostones. As part of our program aimed at synthesizing bioactive phosphorus-containing heterocyclic compounds, herein we describe the synthesis of 10- and 11-membered macrocyclic phostones **9**–**11** having a benzo[*b*]thiophene core structure. The synthetic protocols developed are amenable to the parallel synthesis of structurally diverse analogues with general structure **I** or **II** that may be of interest in biological screening. These molecules are not flat (they possess a plane of asymmetry), a factor that has been proposed to play an important role in improving clinical success of exploratory therapeutics.[9]

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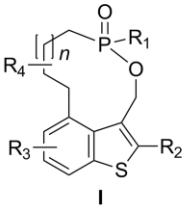
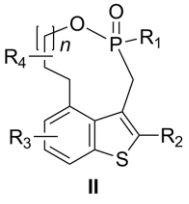
Results and Discussion

Previously, we reported on synthetic methodologies for the preparation of thieno[2,3-*d*]pyrimidine-based bisphosphonate[10] and monosphosphonate (ThP-MPs)[11] libraries of compounds with the ability to inhibit isoprenoid biosynthesis. In parallel, we also investigated the synthesis and biological properties of other phosphorus-containing heterocyclic compounds, including pyridopyrimidine-based bisphosphonates as inhibitors of HIV-1 reverse transcriptase.[12] In this repost, we focus on the synthesis of benzo[*b*]thiophene-containing macrocyclic phostones of general structures **I** and **II** (the latter will be referred to as the reversed analogues). As examples, the synthetic route leading to the preparation of 10-membered ring phostones **9** and **10** and 11-membered ring analogue **11** is described.



I

9, n = 1, R_1 = OH, R_2 = tolyl, R_3 = R_4 = H



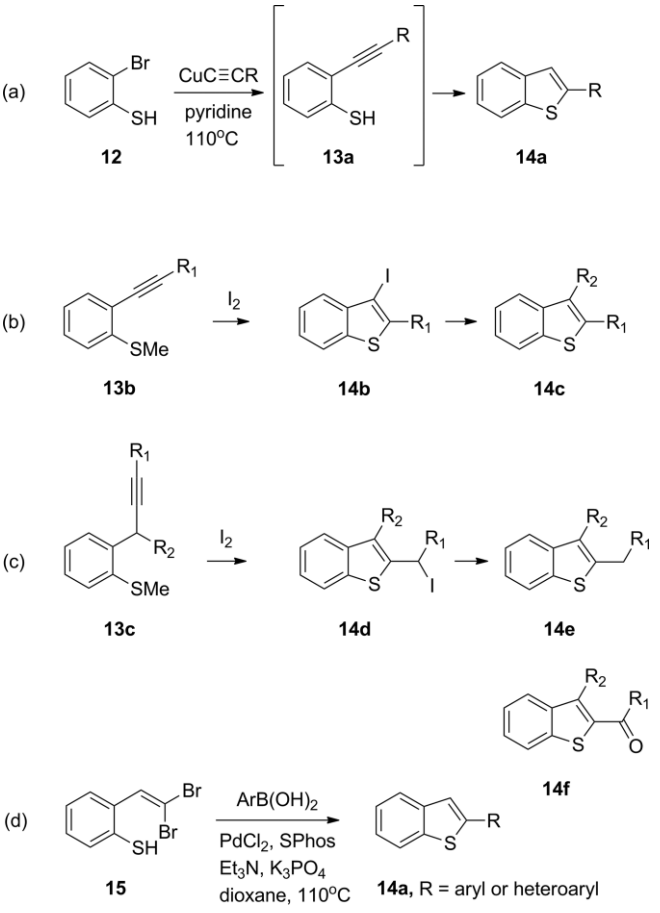
II

10, n = 1, R_1 = OH, R_2 = tolyl, R_3 = R_4 = H
11, n = 2, R_1 = OH, R_2 = tolyl, R_3 = R_4 = H

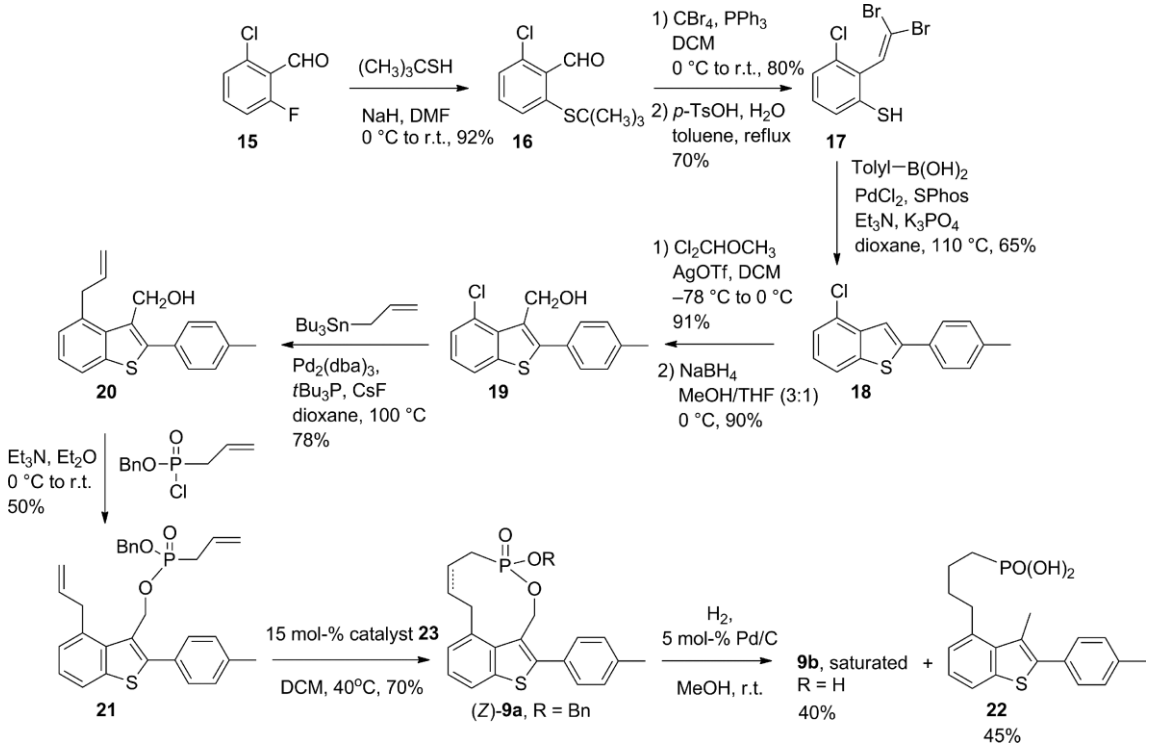
Testament to the value of the benzo[*b*]thiophene core in drug discovery, as well as materials chemistry, numerous synthetic protocols have been reported for the construction of this heterocycle in just the last decade.[13–17] Many of these methodologies stem from the initial [3+2] cycloaddition reported by Malte and Castro (Scheme 1, a).[14] The formation of the thiophene ring from benzenethiol **12** is presumed to proceed through intermediate acetylide **13a**. Various acetylides have been independently synthesized and cyclized in the presence of various catalysts, including elemental iodine; intermediates **13b** (Scheme 1, b)[15] and **13c** (Scheme 1, c)[16] represent a few key examples leading to structurally diverse 2,3-disubtituted benzo[*b*]thiophene cores.[17]

In our approach (Scheme 2), orthogonal functionalization at C3 and C4 of the benzo[*b*]thiophene core was required to allow construction of the desired P-containing macrocyclic ring. We employed the Pd-catalyzed tandem *S*-vinylation/Suzuki–Miyaura coupled reactions reported by Lautens and co-workers[18] to convert *gem*-dibromovinyl benzenethiol **17** into required 4-chlorobenzo[*b*]thiophene ring **18**. The synthesis of **17** was initiated from commercially available 2-chloro-6-fluorobenzaldehyde (**15**), which was first converted into *tert*-butyl thioether **16** through S_NAr displacement of the fluoride with the thiol under basic conditions (Scheme 2). The aldehyde moiety was then extended to the *gem*-dibromovinyl moiety under Ramirez olefination conditions,[19] and the thiol was deprotected with *p*-toluenesulfonic acid (TsOH)·H_2O under slightly modified conditions to those previously described[18,20] (Scheme 2). The *S*-vinylation/Suzuki–Miyaura coupled reactions (in the presence of tolylboronic acid)[18] proceeded smoothly to give **18** in 65 % yield. Intermediate **18** was selectively converted into the corresponding 3-carbaldehyde with dichloromethyl methyl ether in the presence of silver trifluoromethanesulfonate, and the 3-carbaldehyde was subsequently reduced with $NaBH_4$ to give intermediate alcohol **19** in excellent yield.[21] This intermediate was then treated with allyltributylstannane under Stille coupling conditions optimal for aryl chlorides[22] to form olefinic intermediate **20**. Reaction of the free hydroxy moiety of **20** with benzyl allylphosphonochloridate under basic conditions provided desired precursor diene **21** with nearly quantitative conversion (based on recovered compound **20**) but modest yield (50 %); the low yield is likely due to the chemical instability of the benzyl allylphosphonochloridate reagent, which needs to be prepared and used immediately without purification.

A number of previous reports have described the synthesis of six-membered ring phostines[23] and phostones[24] through

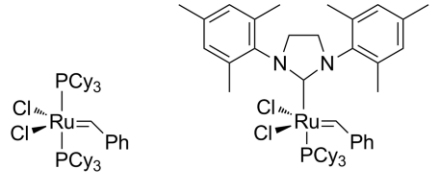


Scheme 1. Literature examples of benzo[*b*]thiophene synthesis (SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl).



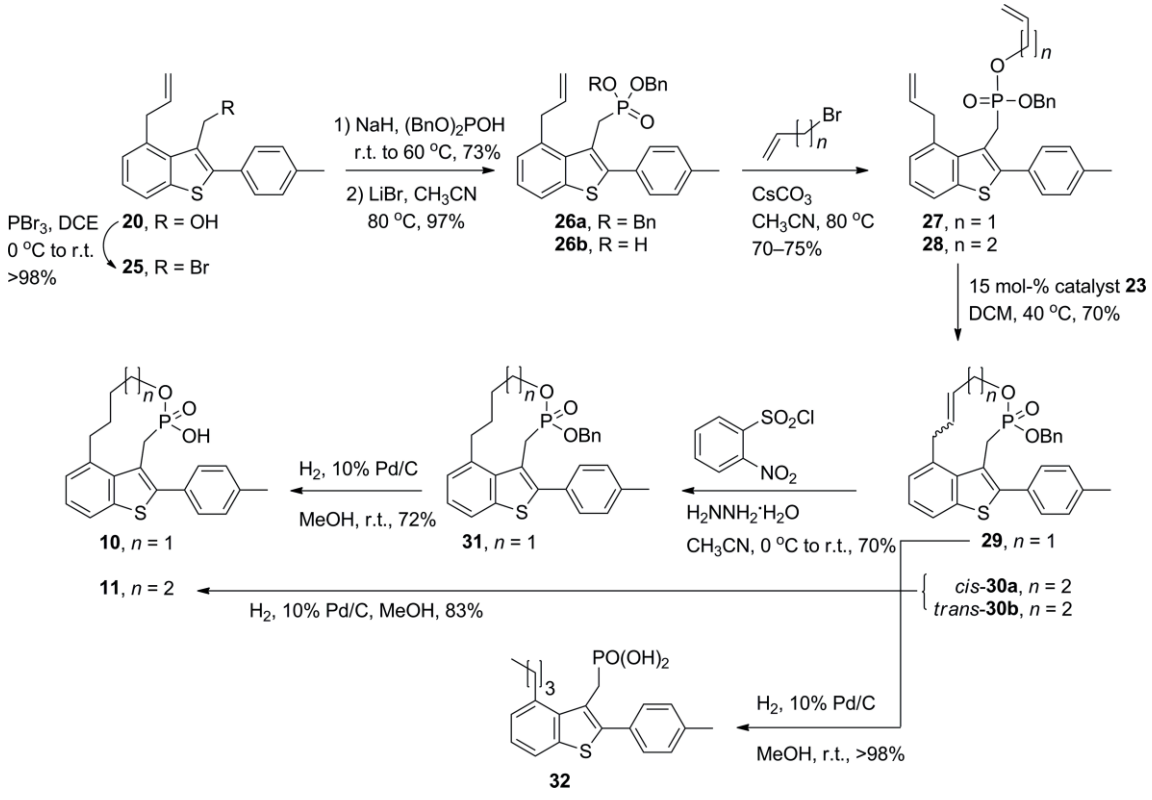
Scheme 2. Synthesis of 10-membered ring phostones **9** (DCM = dichloromethane, dba = dibenzylideneacetone).

ring-closing metathesis (RCM) catalyzed by Grubbs first-generation catalyst **23**. However, a limited number of phosphorus-containing larger ring systems have been prepared successfully by RCM. The few reported examples include the conformationally restricted cyclic phosphates of dinucleotides;[25] in these examples, catalyst **23** did not work and more reactive second-generation Grubbs catalyst **24** was required for successful cyclization in modest yields (47–60 %).[25,26] Similarly, Snieckus and coworkers observed that RCM of a similar indole-based diene required 30 mol-% of catalyst **23** to produce the strained 10-membered ring macrocycle between C3 and C4 of the indole scaffold in reasonable yields.[27] We were pleased to see that RCM cyclization of diene **21**, using 15 mol-% of catalyst **23**, led to the formation of compound **9a** in 70 % yield (Scheme 2).



At the onset of this project, we examined the suitability of various commonly used protecting groups for phosphonates. The most commonly used protecting group is the ethyl ester, which is typically removed with TMSBr, followed by methanolysis of the intermediate trimethylsilyl esters. However, given the high strain of this particular 10-membered ring phostone and the likelihood that the bromide anion could attack the Cα atom of the endocyclic P–O–*CH*$_2$– bond (i.e., the benzylic position), we opted to make phosphonate benzyl ester **21**, fully aware that the deprotection could also be problematic. Not surprisingly, Pd-catalyzed (10 % Pd/C) hydrogenation of intermediate **9a** in methanol under atmospheric pressure at room temperature led to the formation of acyclic compound **22** in nearly quantitative yield. Decreasing the amount of the Pd catalyst to 5 % provided desired compound **9b** in modest yield, with an almost equivalent amount of **22** (40 and 45 % yields of **9b** and **22**, respectively). However, the use of the same catalyst loading in ethyl acetate or a solvent mixture of pyridine/methanol resulted in recovery of mainly the starting material or a mixture of **9a/b** and **22**, respectively. Optimization of this protocol and replacement of the benzylic ester will be investigated in the future and before the synthesis of a compound library (assuming our biological screening leads to hits for interesting biological targets).

The synthesis of reversed phostones **10** and **11** was initiated from common intermediate **20** (Schemes 2 and 3). Conversion of the hydroxy moiety into bromide **25** was easily achieved with PBr_3, and this compound was treated with dibenzyl phosphite in the presence of NaH to give dibenzyl ester **26a**, which was subsequently hydrolyzed to monoester **26b** by using LiBr (Scheme 3). Alkylation of the free hydroxy moiety with an alkenyl bromide under basic conditions provided acyclic dienes **27** and **28**, which were cyclized by RCM with the use of 15 mol-% of catalyst **23** in good yields. Interestingly, whereas diene **27** cyclized to *cis* 10-membered ring phostone **29**, diene **28** formed a mixture of *cis*/*trans* 11-membered ring macrocycles **30** in a 2:1 ratio. The structural identities of compounds **30a** and **30b** were confirmed by 1D and 2D ^{1}H NMR spectroscopy.



Scheme 3. Synthesis of reversed macrocyclic phostones **10** and **11**. DCE = 1,2-dichloroethane.

Although the olefinic H^3/H^4 protons appeared as multiplets (*J* coupling could not be easily assigned to a *cis* or *trans* double bond), the NOESY NMR spectrum of compound **30a** indicated characteristic strong NOEs between H^1–H^2 and H^1–H^5, as well as between H^3–H^4 and H^3–$H^{5'}$ (Figure 1). In contrast, the NOESY NMR spectrum of compound **30b** revealed strong NOEs only between H^1–H^3 and H^4–H^6, consistent with the *trans* geometry of the double bond (Figure 1).

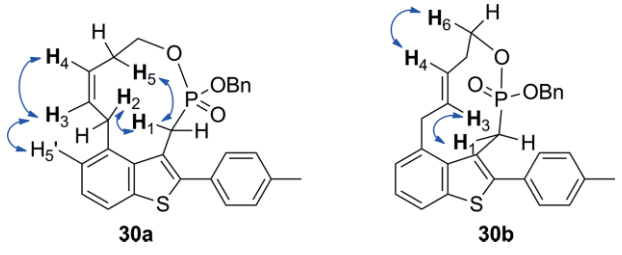


Figure 1. Characteristic NOE differences observed in the NOESY NMR spectra for 11-membered ring phostones **30a** versus **30b**.

On the basis of literature precedence of Pd-catalyzed deprotection of allyl ethers,[28] it was not totally surprising that attempts to remove the benzyl group of compound **29** by Pd-catalyzed hydrogenation led to acyclic side product **32** in nearly quantitative yield (Scheme 3). In contrast, deprotection of 11-membered ring analogues **30a** and **30b** under exactly the same conditions afforded the same product, which was desired phostone **11** in 83 % yield. We were able to overcome the Pd-mediated rind opening of **29** by reducing the allyl double bond in a two-step, one-pot reaction, as previously reported for the reduction of an allyl ether by Marsh and Carbery.[29] In situ formation of *o*-nitrobenzenesulfonylhydrizide (NBSH), followed by reduction of the alkene with diimine provided intermediate **31**, which was deprotected to give phostone **10** in good yield by using standard hydrogenation condition (Figure 1).

Conclusions

Phosphinate and phosphonate compounds are of significant interest to medicinal chemists as transition-state analogues of protease enzymes and as mimics of natural phosphate/pyrophosphate substrates. As part of our ongoing interest in bioactive heterocyclic compounds containing phosphorus, we developed a synthetic route for the preparation of benzo[*b*]thiophene-based, macrocyclic phosphonate ligands with general structures **I** and **II**. Our synthetic strategy is amenable to the parallel synthesis of analogues with significant structural diversity. For example, a variety of boronic acids or boronate esters can be introduced in the conversion of intermediate **17** into **18** (Scheme 2) to allow the preparation of a library of analogues with structural diversity at C2 of the benzo[*b*]thiophene core. Similarly, the allyltributylstannane reagent can be replaced with longer and/or branched alkene stannanes to provide structural diversity on the macrocyclic linker (i.e., vary both the sing size and the R^4 substituent of general structures **I** and **II**). Additionally, one can easily imagine replacing the 2-chloro-6-fluorobenzaldehyde starting material (i.e., compound **15**) with commercially available and synthetically equivalent building blocks (>300 analogues are commercially available or reported in the

literature) to achieve large structural diversity on the core. Therefore, a permutation library can lead to a very large number of final compounds of general structures **I** and **II**. It should be mentioned that as a result of the strained ring system, which prevents flipping of the phosphorus-containing linker from one side of the aromatic plane to the other, analogues **9**–**11** are expected to form as mixtures of atropisomers. Efforts towards the optimization of our synthetic scheme, crystallization of the final compounds, and synthesis of enantiomerically enriched analogues are currently in progress. To the best of our knowledge, such P-containing macrocyclic compounds have not been previously reported and, consequently, their potential value in drug discovery is currently unexplored.

Experimental Section

General Methods: All compounds were purified by normal-phase flash column chromatography on silica gel by using a CombiFlash instrument and the solvent gradient indicated. The homogeneity of all final compounds was confirmed to ≥95 % by reverse-phase HPLC. HPLC analysis was performed by using a Waters ALLIANCE instrument (e2695 with 2489 UV detector and 3100 mass spectrometer). Final compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy and HRMS. Chemical shifts (δ) are reported in ppm relative to the internal deuterated solvent (^{1}H, ^{13}C) or external H_3PO_4 (δ = 0.00 ppm, ^{31}P), unless indicated otherwise. High-resolution mass spectra of the final products were recorded by using electrospray ionization (ESI+/–) and a Fourier-transform ion cyclotron resonance mass analyzer (FTMS).

Method (homogeneity analysis using a Waters Atlantis T3 C18 5 µm column): Solvent A: H_2O, 0.1 % formic acid; solvent B: CH_3CN, 0.1 % formic acid; mobile phase: linear gradient from 95 % A and 5 % B to 0 % A and 100 % B in 13 min.

2-(*tert*-Butylthio)-6-chlorobenzaldehyde (16): To a flame-dried flask, NaH (60 % in mineral oil, 0.25 g, 10.4 mmol) was added in dry DMF (10 mL). The flask was purged with Ar, and a solution of *tert*-butylthiol (0.86 g, 9.5 mmol) in DMF (5 mL) was added dropwise at 0 °C. The mixture was allowed to stir at the same temperature for 2 h and then a solution of 2-chloro-6-fluoro-benzaldehyde (**15**; 1.51 g, 9.5 mmol) in DMF (5 mL) was added dropwise. The mixture was stirred at room temperature overnight. The mixture was diluted with diethyl ether (80 mL), and the organic phase was washed with 10 % aq. HCl (40 mL), water (40 mL), satd. $NaHCO_3$ (40 mL), water (40 mL), and brine (40 mL); dried with $MgSO_4$; filtered; and concentrated. The crude material was purified by column chromatography (silica gel, 100 % hexanes to 1 % Et_2O in hexanes) to afford the desired compound as a yellow oil, yield = 92 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9 H), 7.39–7.43 (m, 1 H), 7.48 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.53 (dd, *J* = 7.5, 1.3 Hz, 1 H), 10.66 (s, 1 H) ppm.

3-Chloro-2-(2,2-dibromovinyl)benzenethiol (17)

Step 1: Aldehyde **16** (1.76 g, 7.7 mmol) and carbon tetrabromide (3.81 g, 11.5 mmol) were dissolved in dichloromethane (50 mL) and cooled to 0 °C under an Ar atmosphere. A solution of triphenylphosphine (6.03 g, 23.0 mmol) in dichloromethane (25 mL) was added dropwise over 1 h. The mixture was warmed to room temperature and stirred for 1 h. The solvent was distilled, and the residue was purified by column chromatography (silica gel, 100 % hexanes to 1 % Et_2O in hexanes) to afford *tert*-butyl[3-chloro-2-(2,2-dibromovinyl)phenyl]sulfane as a colorless oil (2.34 g, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 7.26 (t, *J* = 8.3 Hz, 1 H), 7.42 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.48 (s, 1 H), 7.50 (dd, *J* = 7.7, 1.1 Hz, 1 H) ppm.

Step 2: The above dibromide (2.15 g, 5.6 mmol), $TsOH{\cdot}H_2O$ (1.10 g, 5.8 mmol), and toluene (10 mL) were added to a flask adopted with a Dean–Stark apparatus, and the air was removed from the system under high vacuum. Argon was added, and the mixture was heated at reflux (110 °C) under an atmosphere of Ar overnight. [*Note*: if the mixture was not degassed, a significant amount of disulfide was formed as a side product.] The mixture was cooled to room temperature, diluted with Et_2O (20 mL), and water (5 mL) was added. The biphasic mixture was stirred for 5 min (removal of $TsOH{\cdot}H_2O$), and the organic phase was separated. Then, a 5 % aqueous solution of NaOH (50 mL) was added to the organic phase and stirring was continued for another 10 min (extraction of the sodium salt of the desired product). The aqueous layer was acidified with 1 N HCl to pH 4–5, and the product was extracted with Et_2O (75 mL). The organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated to afford thiol **17** as a light yellow oil (1.29 g, 70 % yield). The product was kept under an atmosphere of Ar at –20 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (s, 1 H), 7.14 (t, *J* = 7.8 Hz, 1 H), 7.21 (d, *J* = 6.9 Hz, 1 H), 7.25 (d, *J* = 6.8 Hz, 1 H), 7.31 (s, 1 H) ppm.

4-Chloro-2-(*p*-tolyl)benzo[*b*]thiophene (18): *gem*-Dibromide intermediate **17** (0.69 g, 2.1 mmol), 4-methylboronic acid (0.49 g, 3.6 mmol), potassium phosphate (1.36 g, 6.4 mmol), and triethylamine (0.65 g, 6.4 mmol) were dissolved in dry dioxane (25 mL) in a pressure vessel, and the mixture was degassed with Ar for 15 min. Then, $PdCl_2$ (11 mg, 0.064 mmol) and SPhos (26 mg, 0.064 mmol) were added, and the mixture was degassed for another 30 min. The mixture was then stirred at room temperature for 15 min and at 110 °C for 18 h. The mixture was cooled to room temperature, and the solids were removed by filtration and washed with EtOAc (15 mL). The filtrate was concentrated and purified by column chromatography (silica gel, hexane) to give desired compound **18** as a white solid (0.35 g, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 7.20–7.28 (m, 3 H), 7.34 (dd, *J* = 7.7, 0.6 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 7.66 (s, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H) ppm.

[4-Chloro-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methanol (19)

Step 1: To an oven-dried flask containing intermediate **18** (0.70 g, 2.7 mmol) and AgOTf (2.1 g, 8.1 mmol) in dry CH_2Cl_2 (25 mL), a solution of dichloromethyl methyl ether (0.93 g, 8.1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at –78 °C under an atmosphere of Ar (color changed from deep yellow to deep green). The solution was stirred at –78 °C for 30 min and then at 0 °C for 1 h (color changed from deep green to black). The reaction was quenched with the addition of CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ solution (20 mL), and the biphasic mixture was stirred at room temperature for 30 min. The organic phase was separated, the aqueous phase was washed with EtOAc (2 × 30 mL), and the combined organic layer was washed with brine (30 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The mixture was purified by column chromatography (silica gel, 100 % hexane to 20 % EtOAc in hexane), and the desired aldehyde intermediate was isolated as a white solid (0.71 g, 91 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.36 (t, *J* = 7.9 Hz, 1 H), 7.50–7.54 (m, 3 H), 7.79 (dd, *J* = 8.0, 1.0 Hz, 1 H), 10.78 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 120.8, 125.6, 127.3, 128.5, 129.1, 129.4, 130.2, 130.8, 135.5, 140.0, 140.5, 154.3 ppm. HRMS (ESI+): calcd. for $C_{16}H_{11}ClOS$ 287.0297 $[M + H]^+$; found 287.0294.

Step 2: To an oven-dried flask containing the above aldehyde (0.71 g, 2.5 mmol), MeOH/THF (3:1, 64 mL) was added, and the

solution was cooled to 0 °C. Then, $NaBH_4$ (0.19 g, 4.9 mmol) was added, and the mixture was stirred at 0 °C for 30 min. The mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (silica gel, 100 % hexane to 5 % EtOAc in hexane) to give desired alcohol intermediate **19** as a white solid (0.64 g, 90 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 4.99 (s, 2 H), 7.27–7.33 (m, 3 H), 7.44 (dd, *J* = 7.7, 0.9 Hz, 1 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.78 (dd, *J* = 8.0, 0.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 57.1, 121.3, 124.7, 126.4, 127.8, 129.5, 130.0, 130.3, 130.4, 135.9, 139.0, 141.4, 146.0 ppm. HRMS (ESI+): calcd. for $C_{16}H_{13}ClNaOS$ 311.0268 $[M + Na]^+$; found 311.0266.

[4-Allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methanol (20): To an oven-dried flask, intermediate **19**, $Pd_2(dba)_3$ (51 mg, 0.06 mmol), and CsF (1.02 g, 6.7 mmol, dried under high vacuum at 100 °C for 4 h) were added; air was removed under high vacuum, and the flask was purged with Ar. The ligand P(*t*Bu)$_3$ (0.13 g, 0.6 mmol), dry degassed dioxane (30 mL), and allyltributyltin (0.92 g, 2.8 mmol) were added under an atmosphere of Ar, and the mixture was then stirred at reflux for 48 h. The solvent was distilled off, and the residue was purified by chromatography (K_2CO_3/silica gel, 1:9 w/w; 100 % hexane to 5 % EtOAc in hexane). Desired compound **20** was isolated as a white solid (0.51 g, 78 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 (br. s, 1 H), 2.46 (s, 3 H), 4.08 (d, *J* = 5.5 Hz, 2 H), 4.84 (s, 2 H), 4.93 (dq, *J* = 17.2, 1.8 Hz, 1 H), 5.15 (dq, *J* = 10.2, 1.7 Hz, 1 H), 6.23 (m, 1 H), 7.26 (d, *J* = 6.7 Hz, 1 H), 7.30–7.34 (m, 3 H), 7.51 (d, *J* = 8.1 Hz, 2 H), 7.76 (dd, *J* = 7.9, 1.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 37.3, 57.7, 116.0, 120.6, 124.3, 127.3, 129.4, 129.9, 130.7, 131.1, 135.2, 137.7, 138.3, 138.6, 140.1, 144.8 ppm. HRMS (ESI+): calcd. for $C_{19}H_{18}NaOS$ 317.0971 $[M + Na]^+$; found 317.0970.

Synthesis of the Linker Benzyl Allylphosphonochloridate

Step 1:[30] To a stirred solution of dibenzyl phosphite (1.0 g, 3.8 mmol) in dry Et_2O (20 mL), a solution of *n*BuLi (2.5 M in hexanes, 4.2 mmol) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 1 h and allyl bromide (1.15 g, 9.5 mmol) was added dropwise. The mixture was stirred at room temperature for 5 h, then cooled to 0 °C and quenched with H_2O (40 mL). The organic layer was separated, washed with H_2O (20 mL) and brine (20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography (silica gel, 100 % hexane to 70 % EtOAc in hexane). The dibenzyl allylphosphonate was isolated as a slightly yellow liquid (0.86 g, 75 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.65 (dd, *J* = 22.1, 7.4 Hz, 2 H), 5.05 (ddd, *J* = 36.4, 11.9, 8.5 Hz, 4 H), 5.16–5.21 (m, 2 H), 5.74–5.84 (m, 1 H), 7.28–7.39 (m, 10 H) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 28.12 ppm.

Step 2:[31] LiBr (0.32 g, 3.6 mmol) was dissolved in dry acetonitrile (9 mL) and a solution of dibenzyl allylphosphonate (0.55 g, 1.8 mmol) in dry acetonitrile (3 mL) was added dropwise at room temperature. The mixture was heated at reflux for 18 h under an atmosphere of Ar. The white solid precipitate was filtered, washed with a small amount of cold acetonitrile, dried under high vacuum for 1 h, transferred into a flask, dissolved in 5 % aq. HCl solution (7 mL), and stirred for 10 min. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated under high vacuum to give benzyl hydrogen allylphosphonate as a slight yellow semisolid (0.32 g, 75 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.65 (dd, *J* = 22.5, 7.3 Hz, 2 H), 5.07 (d, *J* = 8.0 Hz, 2 H), 5.21–5.27 (m, 2 H), 5.76–5.86 (m, 1 H), 7.31–7.40 (m, 5 H), 8.90 (br. s, 1 H, OH) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.71 ppm.

Step 3: Benzyl hydrogen allylphosphonate (0.32 g, 1.5 mmol) was put into a well-dried flask and dissolved in anhydrous CH_2Cl_2 (15 mL). The solution was cooled to 0 °C under an atmosphere of Ar, and a small amount of dry DMF (ca. 2 drops) was added followed by the dropwise addition of oxalyl chloride (0.38 g, 3.0 mmol). The mixture was then stirred at 0 °C for 1 h and then at room temperature overnight. The progress of the reaction was monitored by ^{31}P NMR spectroscopy [^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.71 ppm for the acid and 40.0 ppm for the chloride]. The solvent and the excess amount of oxalyl chloride were distilled under vacuum, and the residue was dried for 1 h and then used in the subsequent reaction without purification (although the yield was assumed to be quantitative, this reagent is highly unstable). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 40.00 ppm.

[4-Allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methyl Benzyl Allylphosphonate (21): Intermediate **20** (0.15 g, 0.5 mmol) was dissolved in anhydrous Et_2O (15 mL) and dry triethylamine (0.15 g, 1.5 mmol) was added. The mixture was first cooled to 0 °C and then a solution of freshly prepared benzyl allylphosphonochloridate (0.35 g, 1.5 mmol) in anhydrous Et_2O (25 mL) was added dropwise. The mixture was subsequently stirred at room temperature for 48 h. The solvent was evaporated, and the residue was purified by flash column chromatography (100 % hexane to 33 % EtOAc in hexane). Desired product **21** was isolated as a colorless semisolid (0.12 g, 50 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 2.62 (dd, *J* = 21.9, 7.4 Hz, 2 H), 3.95 (d, *J* = 5.3 Hz, 2 H), 4.89 (dd, *J* = 17.2, 1.8 Hz, 1 H), 4.96 (dd, *J* = 11.8, 8.1 Hz, 1 H), 5.06–5.22 (m, 5 H), 5.31 (dd, *J* = 11.5, 4.7 Hz, 1 H), 5.71–5.81 (m, 1 H), 6.09–6.17 (m, 1 H), 7.24–7.28 (m, 4 H), 7.31–7.34 (m, 5 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 32.1 (d), 37.2, 60.4, 67.8, 116.1, 120.2, 120.6, 124.4, 126.0, 127.0, 127.4, 127.9 (2 C), 128.3, 128.5 (2 C), 129.4 (2 C), 130.0 (2 C), 130.4, 135.2, 136.4, 137.6, 138.0, 138.9, 139.8, 147.0 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.37 ppm. HRMS (ESI+): calcd. for $C_{29}H_{29}NaO_3PS$ $[M + Na^+]^+$ 511.1467; found 511.1472.

(*Z*)-10-(Benzyloxy)-1-(*p*-tolyl)-6,9,10,12-tetrahydro-11-oxa-2-thia-10-phosphacyclodeca[*cd*]indene 10-Oxide (9a): Intermediate **21** (82 mg, 0.17 mmol) was placed in an oven-dried flask, a magnetic stirrer was added, and air was removed under high vacuum. Then, the flask was purged with Ar and catalyst **23** (21 mg, 0.025 mmol) was added to the flask under an atmosphere of Ar, followed by dry and degassed dichloromethane (67 mL, to bring the concentration of the solution to 2.5 mM). The mixture was stirred at 40 °C for 2 h under an atmosphere of Ar and then at room temperature for 1 h with the flask opened to air. The solvent was evaporated to dryness, and the residue was purified by flash column chromatography (silica gel, 100 % hexane to 33 % EtOAc in hexane). Desired macrocyclic phostone **9a** was isolated as a white solid (54 mg, 70 % yield). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3 H, CH_3), 2.64–2.71 (m, 1 H), 3.42–3.58 (m, 1 H), 4.48–4.58 (m, 1 H), 4.81 (dd, *J* = 25.3, 11.1 Hz, 1 H), 5.00 (dd, *J* = 11.7, 8.2 Hz, 1 H), 5.07–5.11 (m, 1 H), 5.36–5.44 (m, 1 H), 5.59–5.60 (m, 1 H), 5.73–5.81 (m, 2 H), 7.35–7.42 (m, 10 H), 7.48 (m, 1 H), 7.90 (d, *J* = 6.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 21.3, 24.1 (d), 32.5, 60.8, 66.3, 118.0, 118.9, 121.3, 125.3, 127.1, 128.0, 128.6, 128.8, 129.0, 129.2, 129.9, 130.1, 130.5, 134.7, 134.8, 136.1, 136.8, 139.3, 139.7, 145.5 ppm. ^{31}P NMR (202 MHz, [D$_6$]DMSO): δ = 25.80 ppm. MS (ESI): *m/z* = 461.2 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{27}H_{25}NaO_3PS$ $[M + Na]^+$ 483.1154; found 483.1157.

10-Hydroxy-1-(*p*-tolyl)-6,7,8,9,10,12-hexahydro-11-oxa-2-thia-10-phosphacyclodeca[*cd*]indene 10-Oxide (9b): Hydrogenation of intermediate **9a** (23 mg, 0.05 mmol) was performed by using H_2 at atmospheric pressure in dry MeOH (7 mL) and catalyzed by Pd/C (5 % w/w, 0.0042 mmol). The mixture was stirred at room temperature for 5 h, then filtered through Celite, washed with MeOH (10 mL), and concentrated to dryness. The crude product was purified by C18 reverse-phase HPLC by using a solvent gradient from 5 % CH_3CN in H_2O (containing 0.6 % formic acid) to 100 % 5 % CH_3CN (also containing 0.6 % formic acid). After lyophilization of the aqueous solvent, desired product **9b** was isolated as a white solid (7.5 mg, 40 % yield), along with side product **22** (8.4 mg, 45 % yield). Data for **9b**: ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): δ = 1.10–1.25 (m, 1 H), 1.65–1.73 (m, 3 H), 1.80–1.88 (m, 4 H), 2.38 (s, 3 H), 5.09 (s, 2 H), 7.20 (d, *J* = 7.1 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 7.7 Hz, 2 H), 7.44 (d, *J* = 7.9 Hz, 2 H), 7.75 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 20.7, 21.2, 21.7, 29.8, 30.5, 60.2, 120.7, 124.9, 127.5, 128.2, 130.0 (C1′ and 2 C2′ of the tolyl substituent are overlapping), 130.8, 136.8, 138.9, 139.6, 139.7, 144.2 ppm. ^{31}P NMR (202 MHz, [D$_6$]DMSO): δ = 19.00 ppm. HRMS (ESI–): calcd. for $C_{20}H_{20}O_3PS$ 371.0876 [M – H$^+$]$^-$; found 371.0878. Data for {4-[3-methyl-2-(*p*-tolyl)benzo[*b*]thiophen-4-yl]butyl}-phosphonic acid (**22**): ^{1}H NMR (500 MHz, MeOD): δ = 1.66–1.72 (m, 2 H), 1.78–1.79 (m, 4 H), 2.42 (s, 3 H), 2.60 (s, 3 H), 3.18 (t, *J* = 6.6 Hz, 2 H), 7.17–7.23 (m, 2 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 7.5 Hz, 1 H) ppm. ^{31}P NMR (202 MHz, MeOD): δ = 26.17 ppm. HRMS (ESI–): calcd. for $C_{20}H_{22}O_3PS$ [M – H$^+$]$^-$ 373.1033; found 373.1032.

4-Allyl-3-(bromomethyl)-2-(*p*-tolyl)benzo[*b*]thiophene (25): To a solution of [4-allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methanol (**20**; 0.29 g, 1 mmol) in dry dichloroethane (5 mL), a solution of PBr_3 (0.41 g, 1.5 mmol) in dichloroethane (2 mL) was added dropwise at 0 °C and under an atmosphere of Ar. When the addition was completed, the mixture was stirred at room temperature overnight. CH_2Cl_2 (10 mL) was added, the mixture was washed with water (5 mL), and the organic phase was dried ($MgSO_4$), filtered, and concentrated to afford the desired compound as a yellow oil, which was used directly in the next step because of its instability.

Dibenzyl {[4-Allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methyl}-phosphonate (26a): To a suspension of NaH (60 % mineral oil, 14 mg, 0.6 mmol) in dry THF (3 mL), a solution of dibenzyl phosphite (0.14 g, 0.5 mmol) in THF (1 mL) was added dropwise at room temperature. The mixture was then stirred at room temperature for 2.75 h and at 60 °C for 15 min. After cooling the mixture to room temperature, a solution of intermediate **25** (0.11 g, 0.3 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred overnight. THF was distilled off, EtOAc (25 mL) was added, and the organic phase was washed with brine (2 × 10 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 100 % hexane to 33 % EtOAc in hexane) to afford dibenzyl phosphonate **26a** as a yellow oil (0.11 g, 73 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 3.77 (d, *J* = 21.2 Hz, 2 H), 4.04 (d, *J* = 5.3 Hz, 2 H), 4.64 (dd, *J* = 11.8, 8.6 Hz, 2 H), 4.73–4.78 (m, 2 H), 4.81 (dd, *J* = 17.2, 1.7 Hz, 1 H), 5.04–5.10 (m, 1 H), 6.07 (ddd, *J* = 22.7, 10.6, 5.5 Hz, 1 H), 7.06–7.07 (m, 4 H), 7.16 (d, *J* = 7.2 Hz, 1 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 7.25–7.30 (m, 7 H), 7.40 (d, *J* = 7.9 Hz, 2 H), 7.73 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 27.5 (d), 38.1, 65.2, 67.3, 116.2, 120.7, 121.4, 121.5, 124.2, 127.0, 127.5, 127.6, 127.8, 128.2, 128.4, 128.5, 129.3, 130.2, 131.4, 135.5, 136.2, 137.7, 138.0, 138.1, 139.9, 141.2, 142.1, 142.2 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.45 ppm. HRMS (ESI+): calcd. $C_{33}H_{32}O_3PS$ [M + H]$^+$ 539.1804; found 539.1805.

Benzyl Hydrogen {[4-Allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]-methyl}phosphonate (26b): LiBr (34 mg, 0.4 mmol) was dissolved in dry acetonitrile (3 mL) and a solution of dibenzyl phosphonate **26a** (0.11 g, 0.2 mmol) in dry acetonitrile (2 mL) was added dropwise at room temperature. Then, the mixture was heated at reflux overnight under an atmosphere of Ar. The mixture was concentrated under vacuum, and the residue was washed with cold hexane (5 mL), dried under high vacuum for 1 h, then dissolved in 5 % aq. HCl solution (10 mL), and stirred for 10 min. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated under high vacuum to give desired compound **26b** as a yellow oil (85 mg, 97 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 3.59 (d, *J* = 21.6 Hz, 2 H), 3.95 (s, 2 H), 4.55 (d, *J* = 7.0 Hz, 2 H), 4.79 (d, *J* = 17.2 Hz, 1 H), 5.05 (d, *J* = 10.2 Hz, 1 H), 6.02 (ddt, *J* = 15.9, 10.5, 5.5 Hz, 1 H), 7.07 (d, *J* = 6.1 Hz, 2 H), 7.11–7.13 (m, 3 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.28–7.31 (m, 5 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 9.98 (br. s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 27.2 (d), 38.0, 66.2, 116.1, 120.7, 121.2, 124.0, 127.5, 127.8, 128.1, 128.3, 129.1, 130.2, 131.3, 135.4, 136.0, 137.5, 138.0, 138.1, 139.9, 142.5 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 29.33 ppm. HRMS (ESI–): calcd. for $C_{26}H_{24}O_3PS$ [M – H$^+$]$^-$ 447.1189; found 447.1194.

Allyl Benzyl {[4-Allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methyl}-phosphonate (27): In a high-pressure vessel, intermediate **26b** (96 mg, 0.2 mmol), allyl bromide (51 mg, 0.4 mmol), and $CsCO_3$ (0.4 mmol) were dissolved in dry acetonitrile (5 mL), and the mixture was heated at 80–90 °C for 2.5–3 h. The solid was filtered, and the filtrate was purified by flash column chromatography (silica gel, 100 % hexane to 30 % EtOAc in hexanes) to obtain **27** as a yellow thick oil (78 mg, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 3.76 (d, *J* = 21.3 Hz, 2 H), 4.02–4.07 (m, 2 H), 4.10–4.15 (m, 1 H), 4.20–4.26 (m, 1 H), 4.67 (dd, *J* = 11.8, 8.3 Hz, 1 H), 4.82–4.85 (m, 2 H), 5.06–5.11 (m, 3 H), 5.66 (ddd, *J* = 15.7, 10.9, 5.6 Hz, 1 H), 6.10 (ddd, *J* = 22.7, 10.6, 5.5 Hz, 1 H), 7.11 (dd, *J* = 6.4, 2.8 Hz, 2 H), 7.18 (d, *J* = 7.2 Hz, 1 H), 7.24 (d, *J* = 7.9 Hz, 2 H), 7.27–7.29 (m, 4 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 27.4 (d), 38.1, 66.3, 67.2, 116.2, 117.7, 120.7, 121.4, 124.2, 127.6, 127.7, 128.1, 128.4, 129.3, 130.2, 131.4, 132.8, 135.4, 136.3, 137.7, 138.0, 138.1, 139.9, 142.1 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.32 ppm. HRMS (ESI+): calcd. for $C_{29}H_{30}O_3PS$ [M + H$^+$]$^+$ 489.1648; found 489.1641.

Benzyl But-3-en-1-yl {[4-Allyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methyl}phosphonate (28): Intermediate **28** was prepared by following the same protocol as that for the synthesis of **27** above, with the exception that 4-bromo-1-butene (85 mg, 0.6 mmol) was used to install the olefin moiety on the phosphonate. The compound was isolated as a yellow thick oil (75 mg, 70 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.11–2.20 (m, 2 H), 2.42 (s, 3 H), 3.61–3.67 (m, 1 H), 3.71–3.77 (m, 3 H), 4.05 (s, 2 H), 4.64 (dd, *J* = 11.8, 8.4 Hz, 1 H), 4.81–4.87 (m, 2 H), 4.93–4.98 (m, 2 H), 5.09–5.12 (m, 1 H), 5.54 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1 H), 6.10 (ddd, *J* = 22.7, 10.6, 5.5 Hz, 1 H), 7.11 (dd, *J* = 6.4, 3.1 Hz, 2 H), 7.18 (d, *J* = 7.0 Hz, 1 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 7.27–7.29 (m, 4 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.73 (dd, *J* = 7.9, 0.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 27.3 (d), 34.6, 38.1, 64.9, 67.3, 116.2, 117.3, 120.7, 121.5, 121.6, 124.1, 127.6, 128.1, 128.4, 129.3, 130.1, 131.5, 133.4, 135.4, 136.29, 136.34, 137.7, 138.0, 138.1, 139.9, 141.9 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.01 ppm. HRMS (ESI+): calcd. for $C_{30}H_{31}O_3NaPS$ 525.1624 [M + Na$^+$]$^+$; found 525.1621.

(*Z*)-11-(Benzyloxy)-1-(*p*-tolyl)-6,9,11,12-tetrahydro-10-oxa-2-thia-11-phosphacyclodeca[*cd*]indene 11-Oxide (29): Into an oven-dried flask, intermediate **27** (54 mg, 0.13 mmol) and a mag-

netic stirrer were added, and air was removed under high vacuum. The flask was purged with Ar and catalyst **23** (14 mg, 0.02 mmol) was added to the flask under an atmosphere of Ar followed by dry and degassed dichloromethane (53 mL) to bring the concentration of the solution to 2.5 mM with respect to the diene. The mixture was stirred at 40 °C for 3–4 h under an atmosphere of Ar. The flask was opened to the air, and the mixture was stirred for 2 h. The solvent was removed under vacuum, and the residue was purified by flash column chromatography (100 % hexanes to 33 % EtOAc in hexanes) to give **29** as a white solid (35 mg, 69 % yield). ^{1}H NMR (500 MHz, C_6D_6, 70 °C): δ = 2.06 (s, 3 H), 3.54 (dd, J = 20.4, 16.0 Hz, 1 H), 3.67 (dd, J = 21.8, 16.8 Hz, 2 H), 3.92–3.98 (m, 2 H), 4.70–4.79 (m, 2 H), 4.93–4.98 (m, 1 H), 5.11–5.15 (m, 1 H), 5.80–5.86 (m, 1 H), 6.89 (d, J = 7.8 Hz, 2 H), 6.98–7.04 (m, 5 H), 7.06–7.07 (m, 2 H), 7.38 (dd, J = 6.8, 2.2 Hz, 1 H), 7.50 (br. d, 2 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 21.2, 28.1 (d), 30.1, 63.1, 66.1, 120.8, 122.8, 123.9, 124.6, 128.1, 128.5, 128.8, 129.6, 130.4, 131.2, 135.3, 136.7, 138.5, 139.7 ppm. ^{31}P NMR (202 MHz, [D_6]DMSO): δ = 25.60 ppm. HRMS (ESI+): calcd. for $C_{27}H_{25}NaO_3PS$ [M + Na^+]$^+$ 483.1154; found 483.1151.

(*Z*)- and (*E*)-12-(Benzyloxy)-1-(*p*-tolyl)-9,10,12,13-tetrahydro-6*H*-11-oxa-2-thia-12-phosphacycloundeca[cd]indene 12-Oxide (30a and 30b): Macrocyclization of diene **28** was achieved following the same protocol as that described above for the RCM reaction of diene **27**. The mixture was purified by flash column chromatography (silica gel, 100 % hexanes to 33 % EtOAc in hexanes) to give the pure *cis* and *trans* endocyclic double bond products, **30a** and **30b**, respectively, in a 2:1 ratio. Data for **30a**: white solid (22 mg, 40 % yield). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.60–1.67 (m, 1 H), 2.07 (s, 3 H), 2.29–2.35 (m, 1 H), 3.35 (dd, J = 22.1, 11.2 Hz, 1 H), 3.68 (dd, J = 20.5, 16.0 Hz, 1 H), 3.77–3.89 (m, 2 H), 4.01 (dd, J = 15.7, 8.7 Hz, 1 H), 4.28–4.34 (m, 1 H), 4.63 (dd, J = 11.7, 9.5 Hz, 1 H), 4.73 (dd, J = 11.9, 7.9 Hz, 1 H), 5.30–5.35 (m, 1 H), 5.89–5.93 (m, 1 H), 6.93 (d, J = 7.9 Hz, 2 H), 7.02–7.06 (m, 5 H), 7.15–7.17 (m, 2 H), 7.43 (d, J = 7.8 Hz, 1 H), 7.56 (d, J = 7.8 Hz, 2 H) ppm. ^{31}P NMR (202 MHz, C_6D_6): δ = 25.39 ppm. HRMS (ESI+): calcd. for $C_{28}H_{28}O_3PS$ 475.1491 [M + H^+]$^+$; found 475.1484. Data for **30b**: white solid (12 mg, 20 % yield). ^{1}H NMR (500 MHz, C_6D_6): δ = 1.28–1.35 (m, 1 H), 1.63–1.69 (m, 1 H), 2.06 (s, 3 H), 3.30 (br. m, 1 H), 3.48 (br. m, 1 H), 3.62 (br. m, 1 H), 3.76–3.91 (m, 2 H), 4.29 (br. m, 1 H), 4.48 (br. m, 1 H), 4.56 (dd, J = 12.0, 6.8 Hz, 1 H), 5.14–5.16 (m, 1 H), 5.76 (br. m, 1 H), 6.95 (d, J = 7.0 Hz, 2 H), 7.01–7.05 (m, 3 H), 7.07–7.11 (m, 2 H), 7.11–7.15 (m, 3 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 2 H) ppm. ^{31}P NMR (202 MHz, C_6D_6): δ = 29.77 ppm. HRMS (ESI+): calcd. for $C_{28}H_{28}O_3PS$ 475.1491 [M + H^+]$^+$; found 475.1487.

11-(Benzyloxy)-1-(*p*-tolyl)-6,7,8,9,11,12-hexahydro-10-oxa-2-thia-11-phosphacyclodeca[*cd*]indene 11-Oxide (10): To a cooled (0 °C) and vigorously stirring solution of 2-nitrobenzenesulfonyl chloride (65 mg, 0.3 mmol) and intermediate **27** (27 mg, 0.06 mmol) in dry CH_3CN (5 mL), hydrazine monohydrate (0.15 g, 2.9 mmol) was added dropwise over a period of 1 min. The resulting white suspension (hydrochloride salt of hydrazine hydrate) was allowed to slowly warm to room temperature, stirring vigorously for 4 d. The solvent was evaporated under high vacuum, EtOAc (15 mL) was added, and the organic phase was washed with aqueous saturated $NaHCO_3$ (3 × 5 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated to dryness under vacuum. The residue was purified by flash column chromatography (silica gel, 100 % hexanes to 25 % EtOAc in hexanes) to give desired compound **31** (18.6 mg) contaminated with approximately 10 % of unreacted starting material (9:1 ratio according to LC–MS and ^{31}P NMR spectroscopy). The mixture was used directly in the next step without further purification. ^{31}P NMR (202 MHz, [D_6]DMSO): δ = 25.36 ppm. Intermediate **31** (16 mg, ca. 0.034 mmol) and Pd/C (10 % w/w, 0.0034 mmol) were added to a flask, followed by dry MeOH (5 mL). The mixture was stirred at room temperature under H_2 for 2 h at atmospheric pressure. The mixture was filtered through Celite, washed with MeOH (10 mL), and concentrated to dryness under vacuum. The mixture was purified by C18 reverse-phase pre-HPLC to isolate desired compound **10** as a white solid (9 mg, 72 % yield). ^{1}H NMR (500 MHz, [D_6]DMSO, 90 °C): δ = 1.25–1.33 (m, 3 H), 1.97–2.07 (m, 2 H), 2.33 (s, 3 H), 3.19 (m overlapped by DMSO water peak, 3 H), 3.92 (m, 2 H), 7.19–7.24 (m, 4 H), 7.63 (d, J = 7.4 Hz, 1 H), 7.96 (m, 2 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 21.3, 26.0, 27.8, 29.8, 40.9, 64.0, 119.8, 123.8 (C5 and C6 of the thiophene core are overlapping), 125.4, 129.2, 129.9 (quaternary carbon of the thiophene core and C1′ of the tolyl substituent attached to the C2 of the thiophene core are overlapping), 131.2, 132.5, 137.3, 139.1, 139.3 ppm. ^{31}P NMR (202 MHz, C_6D_6): δ = 13.24 ppm. MS (ESI): m/z = 373.2 [M + $H]^+$, 371.2 [M – $H]^-$. HRMS (ESI–): calcd. for $C_{20}H_{20}O_3PS$ [M – H^+]$^-$ 371.0876; found 371.0888.

{[4-Butyl-2-(*p*-tolyl)benzo[*b*]thiophen-3-yl]methyl}phosphonic Acid (32): Intermediate **29** (16 mg, 0.035 mmol) and Pd/C (10 % w/w, 0.0034 mmol) were added to a flask, followed by dry MeOH (5 mL). The mixture was stirred at room temperature under H_2 for 1 h at atmospheric pressure. The mixture was filtered through Celite, washed with MeOH (10 mL), concentrated, and dried to afford ring-opening product **32** as a white solid (12.8 mg, 98 % yield). ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 0.92 (t, J = 7.3 Hz, 3 H), 1.35–1.42 (m, 2 H), 1.46–1.52 (m, 2 H), 3.28–3.32 (m, 4 H), 7.12 (d, J = 7.1 Hz, 1 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.26 (d, J = 7.9 Hz, 2 H), 7.57 (d, J = 7.8 Hz, 2 H), 7.72 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 14.4, 21.3, 22.39, 22.42, 33.8, 35.2, 120.01, 120.03, 123.8, 126.8, 129.2, 130.80, 130.83, 132.36, 132.38, 137.36, 137.37, 139.3 ppm. ^{31}P NMR (202 MHz, [D_6]DMSO): δ = 19.71 ppm. MS (ESI): m/z = 375.3 [M + $H]^+$, 373.2 [M – $H]^-$. HRMS (ESI–): calcd. for $C_{20}H_{22}O_3PS$ [M – H^+]$^-$ 373.1033; found 373.1034.

12-Hydroxy-1-(*p*-tolyl)-7,8,9,10,12,13-hexahydro-6*H*-11-oxa-2-thia-12-phosphacycloundeca[*cd*]indene 12-Oxide (11): In a flask containing a mixture of **30a** and **30b** (15.5 mg, 0.034 mmol), Pd/C (10 % w/w, 0.0034 mmol) was added followed by dry MeOH (5 mL). The mixture was stirred at room temperature under H_2 for 2 h at atmospheric pressure. The mixture was filtered through Celite, washed with MeOH (10 mL), concentrated, and dried. The mixture was purified by C18 reverse-phase pre-HPLC to isolate desired compound **11** as a white solid (9.3 mg, 72 % yield). ^{1}H NMR (500 MHz, [D_6]DMSO, 90 °C): δ = 1.50–1.55 (m, 2 H), 1.59–1.64 (m, 2 H), 1.93–1.98 (m, 2 H), 2.34 (s, 3 H), 3.14 (d, J = 19.7 Hz, 2 H), 3.23–3.37 (m, 2 H), 3.80 (dd, J = 8.5, 4.1 Hz, 2 H), 7.18–7.23 (m, 4 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.91 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 21.3, 24.8, 29.1, 29.9, 31.1, 31.8, 63.7, 119.9, 123.8, 125.1, 129.1, 129.3, 131.2, 132.6, 137.4, 138.2, 138.4, 139.4, 139.6 ppm. ^{31}P NMR (202 MHz, [D_6]DMSO): δ = 13.95 ppm. HRMS (ESI–): calcd. for $C_{21}H_{22}O_3PS$ 385.1033 [M – H^+]$^-$; found 385.1029.

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