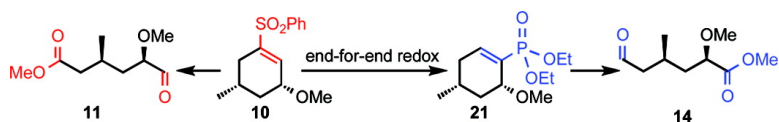


Conversion of Cyclic Vinyl Sulfones to Transposed Vinyl Phosphonates

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Conversion of Cyclic Vinyl Sulfones to Transposed Vinyl Phosphonates

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Abstract: Functionalized cyclic vinyl sulfones were directly converted to the “polarity reversed” vinyl phosphonates through an efficient one pot procedure. Ozonolysis of these vinyl sulfones and vinyl phosphonates furnish complementary sets of termini-differentiated ester-aldehydes. This strategy has been applied for preparation of segments needed for the synthesis of Aplyronine A. The scope and limitations of this transformation were defined.

Introduction

The synthesis of biologically significant compounds that incorporate polypropionate sequences has been the focal point for numerous research groups.¹ The challenge of preparing enantiopure polypropionates has prompted the Fuchs group to explore cross-conjugated six- and seven-membered cyclic dienyl sulfones as precursors of termini-differentiated acyclic arrays bearing multiple stereocenters (Figure 1).² This strategy exploits the binary nature of organic synthesis to evolve a collection of synthetic intermediates appropriate for the preparation of a large number of targets.

Pursuant to synthesis of aplyronine A **12**, vinyl sulfone **10** smoothly underwent ozonolysis to give the aldehyde ester **11** in excellent yield. Synthesis of **10** starts with known allylic alcohol **8**,³ which was selectively epoxidized to yield the *syn* epoxide **8a** in 85% yield and 19:1 diastereoselectivity.⁴ Nucleophilic opening of the epoxide **8a** using sodium thiophenoxide occurs through the chairlike transition state giving diol **9** as a single regioisomer in 92% yield.

Protection of the diol as the bismethyl ether was followed by oxidation of the sulfide to the sulfone **9b** and elimination of the OMe group to yield vinyl sulfone **10** in 78% overall yield (Scheme 1). However, difficulties encountered with the initial coupling strategy required preparation of the “reversed” aldehyde-ester fragment **14**. While one can conceive a multistep sequence that would accomplish the task from **11**, it appeared that reversing the polarity of the trisubstituted double bond in vinyl sulfone **10** would more efficiently effect the desired conversion. Initially the Taber reaction⁵ was employed to convert vinyl sulfone **10** to vinyl nitrile **13** (Scheme 2).

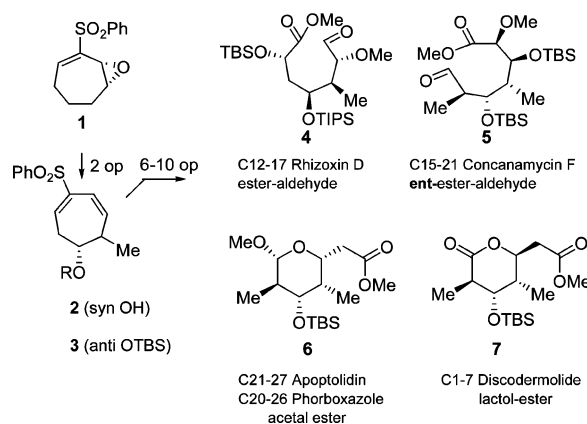


Figure 1. Termini differentiated acyclic arrays from dienyl sulfones.

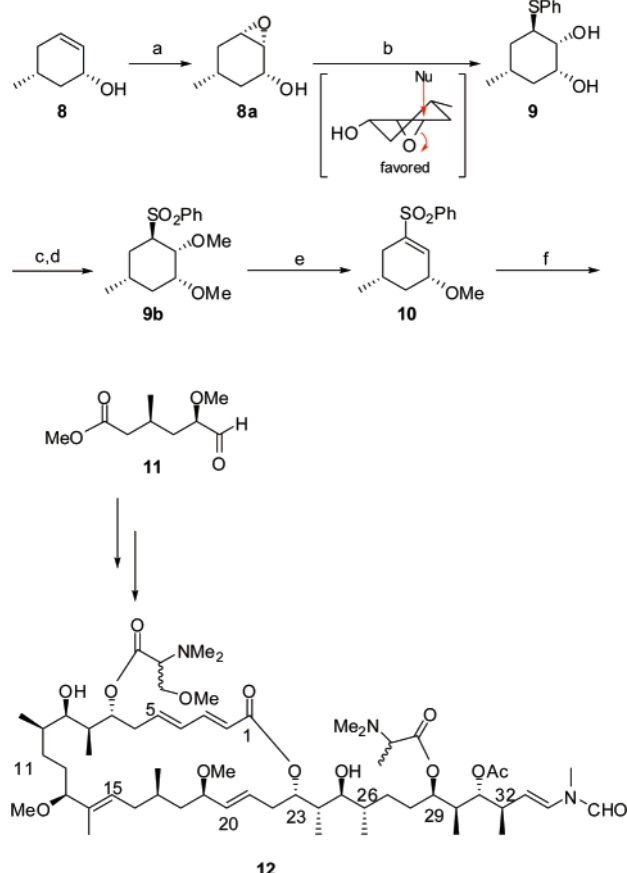
This conversion required treating vinyl sulfone **10** with 10 equiv of KCN, 10% 18-crown-6 in *t*-BuOH at reflux for 8 h to give vinyl nitrile **13** in a 60–70% yield. The conditions of this conversion and the toxicity of KCN/18-crown-6 prompted us to pursue a milder and safer procedure. Consequently, phosphorus nucleophiles were considered as an alternative to cyanide.

Initial trials involved mixing the substrate vinyl sulfone with 3.1 equiv of diethylphosphite and 3.2 equiv of LiHMDS at $-78\text{ }^{\circ}\text{C}$ for 28 h (Table 1).⁶

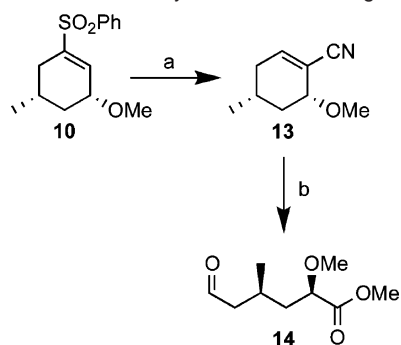
This procedure necessitated use of HMPA to enable any conversion to the target vinyl phosphonate. The requirement for carcinogenic HMPA combined with the protracted reaction times signaled the need for further optimization. Early attempts involved using KHMDS in the absence of HMPA. Preparation of the phosphite anion before mixing with the substrate was appealing based upon the known sensitivity of vinyl sulfones toward a strong base.⁷ Nevertheless, an *in situ* procedure is equally effective if excess base added is avoided. A typical procedure involves mixing 1.3 equiv of diethyl phosphite with

(1) (a) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; MuTou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443. (b) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037. (c) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041. (d) Paterson, I.; Blakey, S. B.; Cowden, C. J. *Tetrahedron Lett.* **2002**, *43*, 6005. (e) Calter, M. A.; Guo, X. *Tetrahedron* **2002**, *58*, 7093. (f) Calter, M. A.; Zhou, J. G. *Tetrahedron Lett.* **2004**, *45*, 4847.
(2) Synthesis via vinyl sulfones **93**; Chiral carbon catalog 15.
(3) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144.
(4) The minor isomer was easily separable by flash column chromatography.
(5) Taber, D. F.; Saleh, S. A. *J. Org. Chem.* **1981**, *46*, 4817.

(6) Torres, E. Ph.D. Thesis, Purdue University, 2003.
(7) Hirata, T.; Sasada, Y.; Ohtani, T.; Aasada, T.; Kinoshita, H.; Senda, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 75.

Scheme 1. Synthesis of Aplyronine A C16–C20 Segment^a

^a Conditions: (a) *m*-CPBA, DCM, rt, h, 85%, dr = 19:1; (b) PhSH, NaH, THF, rt, h, 92%; (c) NaH, MeI, THF, rt, 2 h; (d) *m*-CPBA, DCM, rt, 1 h; (e) NaH, THF, rt, h, 78% (three steps); (f) (i) O₃, CH₂Cl₂/MeOH (4:1), NaHCO₃, –78 °C; (ii) Ph₃P (1.2 equiv), rt, 2 h, 90% over two steps.

Scheme 2. Conversion of Vinyl Sulfone **10** to Fragment **14**^a

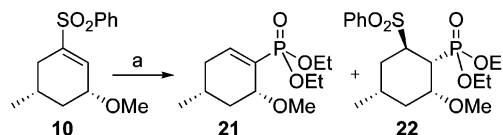
^a Conditions: (a) KCN (10 equiv), *t*BuOH, reflux, 8 h, 60–70%; (b) O₃, CH₂Cl₂/MeOH (4:1), NaHCO₃, –78 °C then Ph₃P, rt, 2 h.

1.2 equiv of KHMDS in THF at room temperature for 15 min followed by rapid addition of the solid vinyl sulfone. Within 30 s after addition the reaction color changes from a faint yellow solution to a deep canary yellow one. After an additional 30 s, a heavy white precipitate of potassium phenylsulfinate begins forming. This reaction generated two products in an essentially quantitative yield. The first product was the desired vinyl phosphonate **21** and the second was the addition product **22** in a 1.5:1 ratio, respectively (Scheme 3).

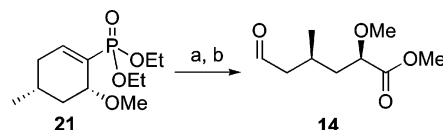
This result suggested that the presence of moisture was decreasing the yield of vinyl phosphonate **21**. Consequently, a series of reactions were executed with thoroughly dried sub-

Table 1. Substrates Used for Vinyl Phosphonate Formation

Vinyl Sulfone $\xrightarrow[3.2\text{eq LiHMDS}]{3.1\text{eq HP(O)OEt}_2}$ Vinyl Phosphonate THF/HMPA, –78 °C → rt 24h–36h		
Entry	Vinyl Sulfone	Vinyl Phosphonate
1		NR
2		 (67%)
3		 (82%)
4		 (87%)
5		NR
6		 (79%)

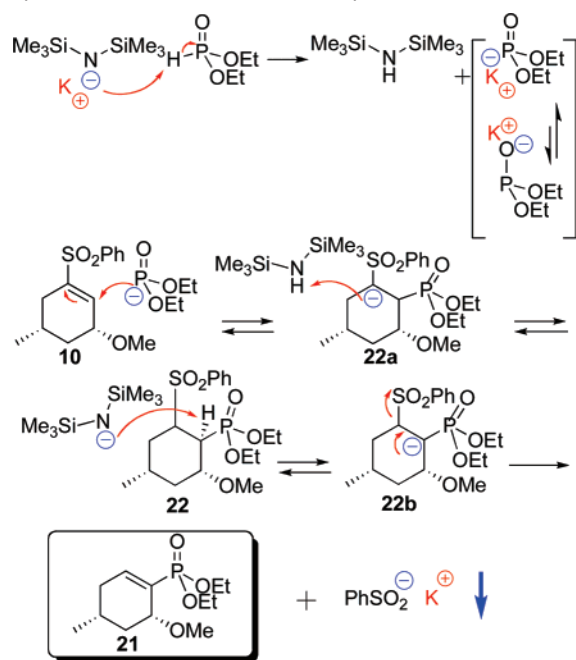
Scheme 3. Early Trials to Transpose Vinyl Sulfone **10** to Vinyl Phosphonate **21**^a

^a Conditions: (a) [KHMDS (1.2 equiv)/diethylphosphite (1.3 equiv)], THF, rt, 60 s, 98% (1.5:1 respectively).

Scheme 4. Ozonolysis of Vinyl Phosphonate **22**^a

^a Conditions: (a) O₃, CH₂Cl₂/MeOH (4:1), NaHCO₃, –78 °C; (b) Ph₃P (1.2 equiv), rt, 2 h, 78% over two steps.

strates, reagents, and solvents. Gratifyingly, the reaction gave vinyl phosphonate **21** in near quantitative yield with **22** observed in only trace amounts. The conversion was clean, fast, and higher yielding than that by the KCN procedure. Finally, ozonolysis of vinyl phosphonate **21** in CH₂Cl₂/MeOH (4:1) delivered aldehyde-ester fragment **14** in an 89% overall yield (Scheme 4). It is worth mentioning that this aldehyde was quite troublesome to handle. First, it was quite volatile, which resulted

Scheme 5. Proposed Mechanism for Vinyl Sulfone to Vinyl Phosphonate End-for-End Redox Transposition

in loss of mass upon vacuum drying. Second, it was very prone to air oxidation giving the acid.⁸

Mechanistic Insights

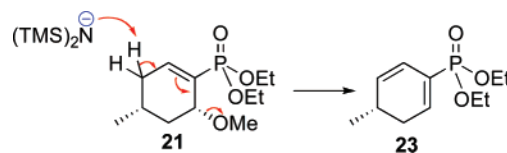
As shown in Scheme 5, KHMDS deprotonates diethyl phosphite in THF to give HMDS and a homogeneous yellow solution of potassium phosphite. The latter is known to undergo phosphite–phosphonate tautomerism favoring the nucleophilic phosphorus atom.⁹ The phosphite anion attacks vinyl sulfone **10** in a conjugate addition fashion to give the deep canary yellow anion **22a**. Having an estimated pK_a close to that of HMDS,¹⁰ **22a** deprotonates HMDS to produce **22** and KHMDS. The regenerated KHMDS deprotonates the phosphonate moiety to furnish anion **22b**. Anion **22b** is perfectly set for an E1cb elimination of potassium phenylsulfinate to afford the desired vinyl phosphonate **21**. This is the stage when the reaction starts forming a heavy yellowish white suspension.

Effect of Moisture

One can conclude from the proposed mechanism that any proton source in the reaction more acidic than HMDS will prematurely quench the anion **22a** and prevent regeneration of KHMDS. Old bottles of KHMDS contain unknown levels of KOH and HMDS due to adventitious hydrolysis. Using such aged reagents results in using less KHMDS than required, thereby increasing the relative stoichiometry of diethylphosphite.

Effect of Excess Diethylphosphite

Excess diethyl phosphite has the same effect of moisture. The anion **22a** is likely capable of deprotonating diethylphosphite to produce **22** and regenerate the phosphonate anion. To test this hypothesis, an experiment where only 1 equiv of KHMDS and 2 equiv of diethylphosphite was executed. The major

**Figure 2.** Effect of excess base on vinyl phosphonate **21**.

product was the addition product **22** with only a trace of the vinyl phosphonate **21**. The typically formed potassium phenylsulfinate precipitate was not observed. An experiment employing 40 mol % KHMDS with excess diethylphosphite probed whether the first step in the reaction is catalytic in the base. Again, the major isolated product was **22** (87%) proving that anion **22a** is quenched by diethylphosphite to regenerate the phosphite anion. In this experiment **21** was isolated in 10% yield.

Effect of Excess Base

Like vinyl sulfones, vinyl phosphonate **21** is also sensitive to strong bases. Reactions conducted at low concentration never went to completion, while adding excess KHMDS to convert residual **22** into **21** resulted in deprotonation of **21** at the allylic position with concomitant 1,4-elimination of the methoxy group, affording the dienyl phosphonate **23** in 79% yield (Figure 2).

Inadvertent use of excess base can result from impure diethylphosphite. The deleterious effect of excess base is not limited to vinyl phosphonate **21**. Vinyl phosphonates, like vinyl sulfones, undergo base-induced rearrangements to their allylic counterparts.¹¹

Counterion Effect

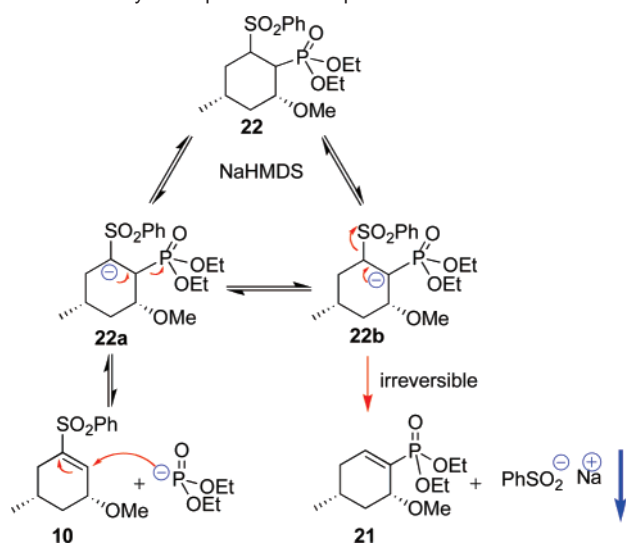
The effect of the counterion is especially interesting. As mentioned previously, 1.3 equiv of the anion are needed to effect complete conversion using KHMDS as a base. In comparison, following the same protocol with NaHMDS in THF resulted in a slower reaction rate with only about 50% conversion over the same time interval along with ~50% recovered starting material. The slow rate using NaHMDS suggested the use of an additional equivalent of NaOP(OEt)₂ anion to complete the reaction. Indeed, when 2.3 equiv of base was used with 2.4 equiv of diethylphosphite, the reaction was completed much more rapidly. While the 1 equiv KHMDS reaction takes approximately 60 s to complete, the 2 equiv NaHMDS reaction requires 10–20 min at equivalent molarity. This is presumably due to the stronger nucleophilicity of the K⁺ cation compared to the Na⁺ cation (during the initial step) combined with the better overlap of K⁺ empty 3s orbitals with the sulfone oxygens than that of Na⁺ 2s orbitals (during the final step). Also, it was assumed that potassium sulfinate is less soluble in THF than sodium sulfinate leading to a faster rate of precipitation due to a smaller K_{sp} . This is based on the fact that commercially available KHMDS in THF has a maximum strength of 0.91 M compared to 2.0 M in the case of NaHMDS in THF. Another difference is that the deep canary yellow color observable in the KHMDS reaction evident of the **22a** anion formation is not obvious in the case of NaHMDS. Despite these differences, the reaction yields were comparable in both cases. In stark contrast,

(8) The half-life of **14** is roughly 30 min at ambient temperature while neat. However, it is very stable in an oxygen-free solution.

(9) Maffei, M.; Buono, G. *Tetrahedron* **2003**, *59*, 8821.

(10) Westerhausen, M. *Coord. Chem. Rev.* **1998**, *176*, 157.

(11) Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572.

Scheme 6. Proof of the Reversibility of the First Step in the Vinyl Sulfone to Vinyl Phosphonate Transposition

in the absence of HMPA, using even 3 equiv of LiHMDS resulted in the starting material being completely recovered after 24 h.

Effect of Reaction Concentration

Initial runs were performed at 0.1 M or 0.2 M concentrations. It was observed that 0.1 M reactions consistently have 10–20% of the starting material remaining. On the other hand, reactions at 0.2 M or higher result in almost complete consumption of the starting material.

This begged the question of whether the first step in the mechanism was reversible. To explore this possibility, purified adduct **22** was treated with 0.9 equiv of NaHMDS in THF at room temperature. Vinyl sulfone **10** was regenerated along with the formation of vinyl phosphonate **21** in almost a 1:1 ratio upon rapid quenching of the reaction (Scheme 6). This confirms that the first step is reversible and that both the sulfone and the phosphonate moieties are competent as leaving groups. However, the final sulfonate elimination is irreversible, consistent with the reported pK_a values for diethylphosphite and benzenesulfonic acid; 13¹² and 2.1¹³ respectively. Since the initial addition/elimination of phosphonate is reversible while the final elimination of sulfonate is irreversible, 0.2 M reactions perform better than 0.1 M ones due to increased local concentrations of starting materials. Also, this concentration effect explains why 2.3 equiv of the phosphite anion are needed in the case of NaHMDS since it is a weaker nucleophile than KHMDS (however, the NaOP(OEt)₂ nucleophilicity is somewhat compensated by the reaction concentration).

Reaction Scope and Limitation

Table 2 shows the data for using NaHMDS as a base. Vinyl sulfones **24**, **25**, and **18** underwent the transposition smoothly to the corresponding vinyl phosphonates in excellent yields while the addition products were detected only in trace amounts (Table 2, entries 1–3). While transposition of five- and seven-membered substrates was complete in 10–20 min, vinyl sulfone

26 required 2 h. Substituted vinyl sulfone **10** underwent smooth conversion to the vinyl phosphonate. However, unwanted elimination of the methoxy group leads to dienyl phosphonate **23** if excess base is present. Vinyl sulfone **26** proved to be quite resistant to the transformation due to hindrance of both faces of the substrate. The reaction showed no conversion for 12 h after which the starting material underwent slow decomposition. The phosphonate anion adds regioselectively to epoxide **31** in a 1,4-addition fashion to afford the addition product in 85% yield. It is worth mentioning that the regio- and stereoselective phosphite addition to **31** could also be catalytic in the base. Employing 8 mol % KHMDS in THF resulted in roughly the same yield of the sole product. Vinyl sulfones **32–35** test protecting group compatibility with this conversion. These substrates have two substituents trans to each other and close to the sulfone moiety presumably reflecting the somewhat longer reaction times (~30–50 min). Nevertheless, the conversion was clean with no side products being observed. Substrates **32**¹⁴ and **33**, bearing acyl functionality, undergo the reaction without difficulty to give the corresponding vinyl phosphonates in 63–82% and 83% yield, respectively. Hydroxy vinyl sulfones **27** and **28** (entries 10 and 11, respectively) bearing unprotected alcohol groups proved to be quite challenging substrates. Nevertheless, the desired vinyl phosphonates were detected via NMR as minor products while the major products were the elimination products/caged phosphonates (depending on the position of –OH on the substrate). This is presumably because the initially formed alpha-sulfonyl anion is immediately quenched by the free hydroxyl group (Table 2, entry **28**), thus preventing advancement to the vinyl phosphonate. The thus formed O-anion¹⁵ then attacks the phosphonate moiety to afford the caged product **28a**¹⁶ (see Supporting Information). In contrast, vinyl sulfone **27** gave the transposed product **27b** after elimination of the –OH group. This is presumably because the initially formed alpha-sulfonyl anion suffers immediate E1cb elimination of the –OH group and gives a new vinyl sulfone. In the basic medium, this vinyl sulfone is rearranged to an allyl sulfone that is transposed to **27b** (see Supporting Information). To overcome the free hydroxyl limitation, it was appealing to transiently protect the –OH with a labile protecting group which would be cleaved during the postreaction workup. The first strategy attempted protecting the alcohol function as the monoanions **27a** and **28b** using a sodium, potassium, or lithium base at –78 °C. This was followed by the cannulation of the phosphite anion at –78 °C and then warming to room temperature. Initial trials utilized NaHMDS and KHMDS as bases. To our surprise, even using 1 equiv of either base resulted in complete and immediate decomposition of the vinyl sulfones. Next, LiHMDS was employed with hopes that the oxidolithium intermediate might be more stable. Indeed, treating the free hydroxyl vinyl sulfone **28** with 1 equiv of LiHMDS resulted in a stable LiO moiety and no decomposition was observed. Unfortunately, however, cannulation of the potassium salt of diethylphosphite anion to the reaction again yielded the elimination product **28c** as the sole product.

(14) ¹H NMR of vinyl sulfone **32** shows the acetate methyl at δ 1.57 ppm, an interesting deviation from the expected value around δ 2.5 ppm.

(15) X-ray structure of caged product **28a** suggests that the O-anion is formed through an intermolecular proton transfer rather than an anticipated intramolecular proton transfer (see Supporting Information for suggested mechanism).

(16) Structure confirmed by X-ray crystallography (see Supporting Information).

(12) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 236.

(13) Burkhard, R. K.; Sellers, D. E.; DeCou, F.; Lambert, J. L. *J. Org. Chem.* **1959**, *24*, 767.

Table 2. Substrates Used for Vinyl Phosphonate Formation Using NaHMDS^a or KO^tBu^b as a Base

Entry	Vinyl Sulfone	Product	Entry	Vinyl sulfone	Product
1 ^a			9 ^a		
2 ^a			10 ^a		complex mixture
3 ^a			11 ^a		complex mixture
4 ^a			12 ^a		
5 ^a		NR	13 ^a		
6 ^a			14 ^{a,b}		
7 ^a			15 ^{a,b}		
8 ^a			16 ^a		
			17 ^{a,b}		

The next option involved transient protection of the alcohol as an –OTMS group to be deprotected during the workup stage. Therefore, the protection method requires the medium to be “proton-free” by literally “evaporating” the –OH problematic protons. The only applicable method was using HMDS as a

silylating agent in the presence of an ammonium salt catalyst.¹⁷ This was accomplished by heating the vinyl sulfone at THF reflux with 0.5 equiv of HMDS and catalytic ammonium sulfate

(17) Montero, J. L.; Toiron, C.; Clave, J. L.; Imbach, J. L. *Recl. Trav. Chim. Pays-Bas* 1988, 107, 570.

for 12 h resulting in clean and complete protection of the free $-OH$ as $-OTMS$ (vinyl sulfones **29** and **30**). After checking the reaction pH to make sure the medium is neutral, the diethylphosphite anion was cannulated into the reaction flask at 25 °C. To our disappointment, we retrieved a mixture of products among which were free hydroxyl vinyl sulfone, free hydroxyl addition product, and free hydroxyl vinyl phosphonate. This suggested that the phosphonate anion attacks the $-OTMS$ resulting in its deprotection. Fortunately, protection of the free OH as OTES or OTBS (Table 2, entries **34** and **35**) enables smooth conversion to the desired vinyl phosphonate.¹⁸ It is worth mentioning that a successful conversion of **34** and **35** to their vinyl phosphonates could be achieved successfully using KO^tBu in THF utilizing an *in situ* procedure. Finally, stereotriad vinyl sulfone **36** was successfully converted to the desired vinyl phosphonate using either KO^tBu or KHMDS to afford **36a** in 60% and 78% yield, respectively.

Conclusion

This paper reports a new one-pot vinyl sulfone to vinyl phosphonate transposition. Since ozonolysis of vinyl sulfones afford termini-differentiated fragments ready for coupling, ozonolysis of the corresponding vinyl phosphonates beautifully elaborates the complementary “reversed” aldehyde-ester fragments. This methodology is fast, run at ambient temperature, high yielding, and tolerant of many functional groups. Many substrates smoothly underwent this conversion, and this methodology has been successfully applied to the synthesis of Aplyronine A, which will be published separately.

General Experimental Procedure Using NaHMDS

Solvents, starting materials, and reagents must be thoroughly dried for a successful reaction. A flame-dried three-neck 100 mL flask is charged with diethylphosphite (2.3 mL, 17.25 mmol) and then with freshly distilled dry THF (27 mL) at ambient temperature. The mixture is stirred for 1 min, then 2 M NaHMDS in THF (8.25 mL, 16.5 mmol) is added dropwise via syringe, and stirring is continued for 30 min. Stirring is stopped, and dry solid¹⁹ vinyl sulfone **10** (2 g, 7.5 mmol) is

added in one portion under positive dry N_2 pressure. Stirring is resumed for 1–30 min or until a heavy yellowish white precipitate is observed. The reaction is monitored by TLC (60% ethyl acetate/hexanes, PAA stain) for completion. Ether (10 mL) and brine solution (35 mL) are added followed by a few drops of $DI-H_2O$, and the mixture is stirred for 10 min. The organic layer is separated and dried over anhydrous Na_2SO_4 for 30 min and then filtered. Evaporation under reduced pressure affords crude vinyl phosphonate **21**. Purification by column chromatography (60% ethyl acetate/hexanes) yields pure vinyl phosphonate **21** as a light yellow oil (1.8 g, 93%).

Alternative *in Situ* Procedure Using KHMDS

Solvents, starting materials, and reagents must be thoroughly dried for a successful reaction. A flame-dried three-neck 25 mL flask is charged with solid vinyl sulfone **10** (266 mg, 1 mmol), diethylphosphite (0.17 mL, 1.3 mmol), and then with freshly distilled dry THF (4.5 mL) at ambient temperature. The mixture is stirred for 1 min, then 0.91 M KHMDS in THF (1.3 mL, 1.2 mmol) is added dropwise via syringe, and stirring is continued for 30 min or until a heavy yellowish white precipitate is observed. The reaction is monitored, worked up, and isolated as before to afford pure vinyl phosphonate **21** as a light yellow oil (228 mg, 87%).

Alternative *in Situ* Procedure Using KO^tBu

A flame-dried three-neck 50 mL flask is charged with solid vinyl sulfone **34** (50 mg, 0.2 mmol), diethylphosphite (40 μL , 0.3 mmol), and then with freshly distilled dry THF (1 mL) at ambient temperature. The mixture is stirred for 1 min at 0 °C, then 2 M KO^tBu in THF (0.14 mL, 0.28 mmol) is added dropwise via syringe, and stirring is continued for 30 min or until a heavy yellowish white precipitate is observed. The reaction is monitored, worked up, and isolated as before to yield pure vinyl phosphonate **21** as a light yellow oil (38 mg, 78%).

Acknowledgment. We thank Dr. Douglas Lantrip for intellectual and technical support. We acknowledge Arlene Rothwell and Karl Wood for providing the MS data. Xavier Mollat du Jourdin graciously provided the sample of substrate **36** used in this study.

Supporting Information Available: Experimental procedures, spectroscopic and analytical data for new compounds, 1H and ^{13}C NMR spectra of key compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA072890P

(18) The Taber reaction⁵ is known to successfully convert substrates with free hydroxyl functionalities to their corresponding vinyl nitriles.

(19) Cannulation of the dissolved vinyl sulfone in dry THF was equally effective and more appealing for large-scale reactions.