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Designer Discodermolide Segments via Ozonolysis of Vinyl Phosphonates[1]

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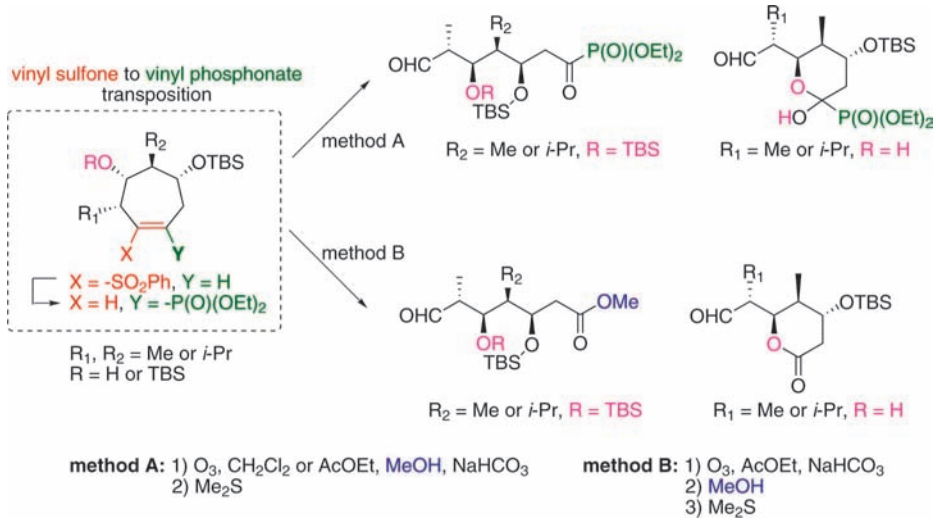
ABSTRACT



To apply our collection of enantiopure 7-ring vinyl sulfones to probe the anticancer SAR of a series of computer-designed (+)-discodermolide analogs, the ozonolytic reactivity of transposed cyclic vinyl phosphonates was explored. Successful preparation of the desired aldehyde-esters and lactones from vinyl phosphonates via an oxidative cleavage−phosphite/methanol exchange sequence is described.

Our laboratory's recent work on exploiting the intermediacy of vinyl sulfones for the synthesis of natural products has demonstrated the utility of five-, six- and seven-membered vinyl sulfones to elaborate contiguous chiral centers.[2] This strategy was expanded to provide acyclic arrays especially including *complete collections of dipropionate units* via oxidative cleavage of vinyl sulfones with OsO_4, RuO_4, and O_3.[2,3] Trapping the intermediate acyl sufone-aldehydes provided termini-differentiated acyclic products ready for sequential coupling.

Among the favored techniques for oxidative cleavage, ozone presents indubitable advantages including low cost, limited production of toxic byproduct, and simple reaction protocols. However, although ozonolysis of electron-rich olefins is widely used and fully documented, ozonolytic cleavage of electron-deficient alkenes is quite rare because of their diminished reactivity; electron-rich olefins are 10,000 times more reactive to ozone than are electron-deficient olefins.[4] Griesbaum and Fuchs reported the first ozonolysis of vinyl nitriles,[5] vinyl

(1) Synthesis via vinyl sulfones 96. Chiral Carbon Collection 18.

(2) El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.*, submitted for publication.

(3) El-Awa, A.; Mollat du Jourdin, X.; Fuchs, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 9086–9093.

(4) Pryor, W. A.; Giamalva, D.; Church, D. F. *J. Am. Chem. Soc.* **1983**, *105*, 6858–6861.

(5) Griesbaum, K.; Huh, T. S.; Gutsche, S. H. *Tetrahedron Lett.* **1990**, *31*, 3299–3300.

(6) (a) El-Awa, A; Fuchs, P. L. *Org. Lett.* **2006**, *8*, 2905–2908. (b) Kim, Y; Fuchs, P. L. *Org. Lett.* **2007**, *9*, 2445–2448.

(7) (a) Gao, J.; Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 9538–9540. (b) Chan, T-H.; Xin, Y-C. *Chem. Commun.* **1996**, 905–906.

(8) Noshi, M. N.; El-Awa, A.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 11242–11247.

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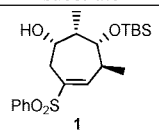
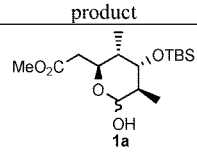
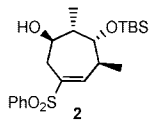
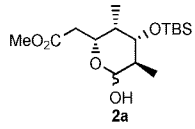
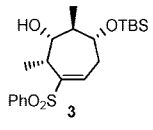
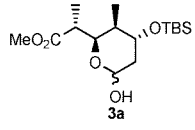
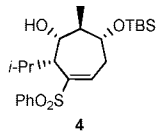
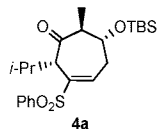
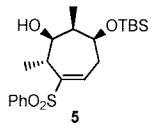
triflates, and vinyl sulfones, respectively, in the 1990s.[2,3] More recently, ozonolysis of seven-membered vinyl sulfones was more extensively studied for the synthesis of polypropionate fragments of apoptolidine and aplyronine A.[6] Ozonolysis of acyclic vinyl phosphonates was first reported in the late 1990s by Whitesides and Chan[7] and was then successfully applied to cyclic systems by Noshi and Fuchs for the synthesis of the C15−C20 fragment of aplyronine A.[8]

In the course of these studies, it was observed that conformation and substitution pattern greatly affected the reactivity of cyclic vinyl sulfones. Most importantly, it appeared that the β'-substituent dominated the reactivity of the olefin. As the size of the substituent increased, the reactivity of the olefin decreased (Table 1). Vinyl sulfones

Table 1. Ozonolysis of Vinyl Sulfones, β' Substituent Effect

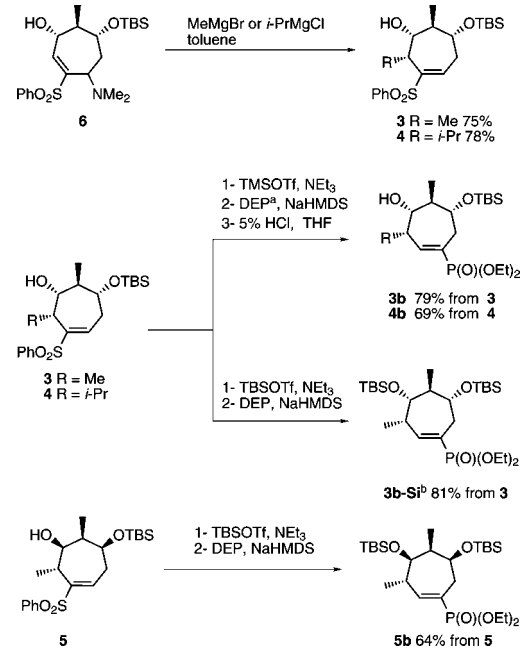
entry	substrate	product	yield
1[a]	 **1**	 **1a**	88% ($\alpha/\beta = 1$)
2[a]	 **2**	 **2a**	73% ($\alpha/\beta = 1$)
3	 **3**	 **3a**	65-77% (4:1 mixture)
4[b]	 **4**	 **4a**	65%
5[c]	 **5**	NR	NA

[a] See ref 9. [b] No oxidative cleavage is observed. [c] The reaction was run at 0.5 M in CH_2Cl_2/MeOH (2:1) with $NaHCO_3$ (3 equiv) at −78 to −30 °C for 1 h.

1 and **2** were ozonized in 15 min at −78 °C to provide good to excellent yields of the desired lactols as anomeric mixtures.[9] Increasing the size of the β'-substituent was detrimental to the rate of the reaction as vinyl sulfone **3** required 45−60 min at −30 °C to afford moderate to good yields of lactols. Substrates bearing an isopropyl group at the β'-position escaped oxidative cleavage of vinyl sulfone **4**, with oxidation of the alcohol moiety to ketone **4a** being the preferred pathway at −78 °C, to the exclusion of subsequent ozonolysis even with increase in time and/or temperature. However, β'-substitution is not the only parameter at play as vinyl sulfone **5** is unexpectedly unreactive to ozone even at −30 °C and at high concentration (0.5 M).

To circumvent this lack of reactivity, vinyl sulfones **3**−**5** were transposed to vinyl phosphonates **3b**−**5b** using Noshi's method (Scheme 1).[8] This strategy, developed with relatively

Scheme 1. Vinyl Sulfone to Vinyl Phosphonate Transposition of Stereotetrads



[a] DEP = diethyl phosphite. [b] **3b-Si** refers to the fully TBS-protected intermediate **3b**.

nonhindered substrates, satisfactory extends to sterically more demanding stereotetrads and does not suffer from extensive β-elimination.

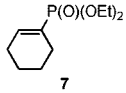
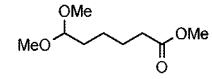
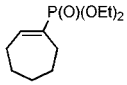
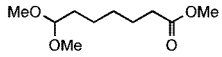
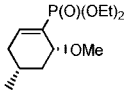
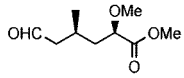
TMS protection followed by sulfone to phosphonate transposition and selective TMS deprotection gave 69−79% yield of the desired vinyl phosphonates **3b** and **4b** over 3 steps. TBS protection and transposition with vinyl sulfone **3** and **5** provided good to moderate yields of the desired vinyl phosphonates **3b-Si** and **5b**.

Early ozonolytic reactions with simple model cyclic vinyl phosphonates **7** and **8** under acidic conditions and vinyl phosphonate **9**[8] using methanol and $NaHCO_3$ for 15 min at −78 °C afforded the desired acetal-methyl esters **7a** and **8a** and aldehyde-methyl ester **9a** (Table 2), respectively. At this juncture, it was assumed that the reaction proceeded via the intermediacy of a simple α-keto phosphonate, as such species are known to be good acylating agents.[10]

Although oxidative cleavage of substrates **5b** and **11b** under Noshi's conditions (Table 3, entries 2 and 4) was successfully monitored by TLC, only traces of the desired aldehyde-methyl esters were observed after extended reaction times (10 h), suggesting a slow phosphite−methanol exchange. Although disappointing, these results shed light on

(9) Torres, E.; Chen, Y.; Kim, I. C.; Fuchs, P. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 3124–3131.

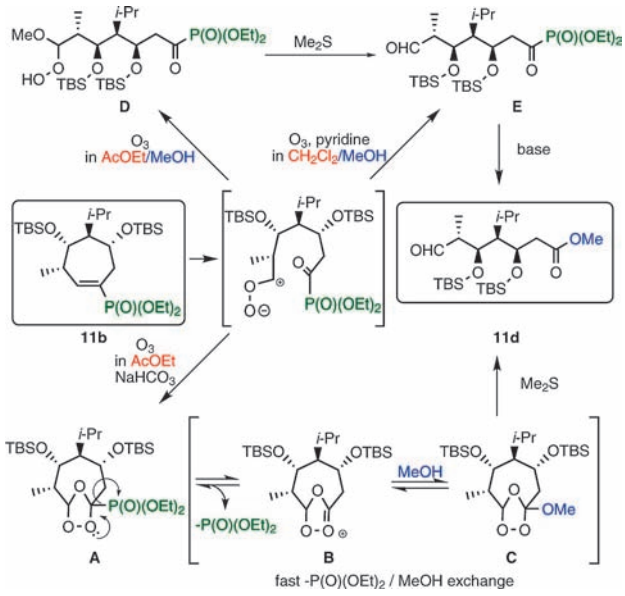
Table 2. Ozonolysis of Model Vinyl Phosphonates[a]

entry	substrate	product	yield
1	 **7**	 **7a**	68%
2	 **8**	 **8a**	92%
3	 **9**	 **9a**	89%

[a] Typical procedure: (i) O_3, $NaHCO_3$ (5 equiv), CH_2Cl_2/MeOH (4:1), −78 °C, 15 min; (ii) PPh_3 (1.1 equiv) or Me_2S (10 equiv), −78 °C to rt, 2−3 h; (iii) *p*-TSOH was added to obtain acetals **7a** and **8a**.

the difference of reactivity of acyl phosphonate-aldehyde **E** versus its acyl sulfone counterpart (Scheme 2). Extensive

Scheme 2. Hypothesis for Ozonolysis of Vinyl Phosphonates



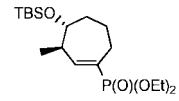
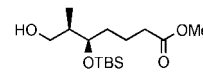
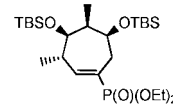
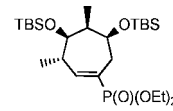
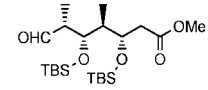
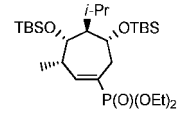
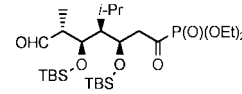
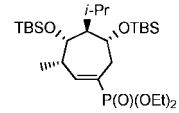
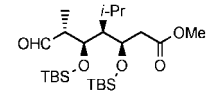
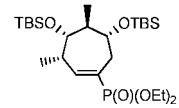
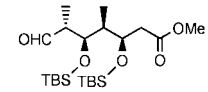
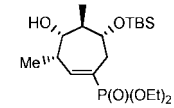
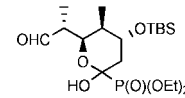
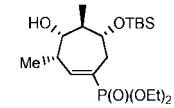
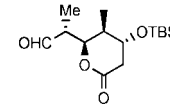
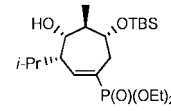
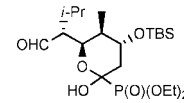
optimization performed on substrates **10**, **5b**, **11b**, **3b**, and **3b-Si** demonstrated that a rapid phosphite−methanol exchange could be achieved in two ways. First, ozonolysis could be performed in a mixture of MeOH/CH_2Cl_2/pyridine[11,12] or MeOH/AcOEt to provide, respectively, acyl phosphonate-aldehyde **E** directly or α-hydroxymethyl hydroperoxides **D**, which could be quenched with excess Me_2S

(10) Serine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 3617–3620.

(11) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Org. Lett.* **2006**, *8*, 3199–3201.

(12) Mohammad Noshi, PhD thesis, Purdue University.

Table 3. Ozonolysis of Cyclic Vinyl Phosphonates

entry	substrate	product	yield
1[a]	 **10**	 **10a**	82%
2[b]	 **5b**	Complex mixture	- - -
3[c]	 **5b**	 **5d**	81%
4[b]	 **11b**	 **11c**	90%[f]
5[c]	 **11b**	 **11d**	85%
6[d]	 **3b-Si**	 **3d-Si**	64%
7[e]	 **3b**	 **3c**	99%[g,h]
8[e]	 **3b**	 **3d**	74%
9[e]	 **4b**	 **4c**	99%[g,i]

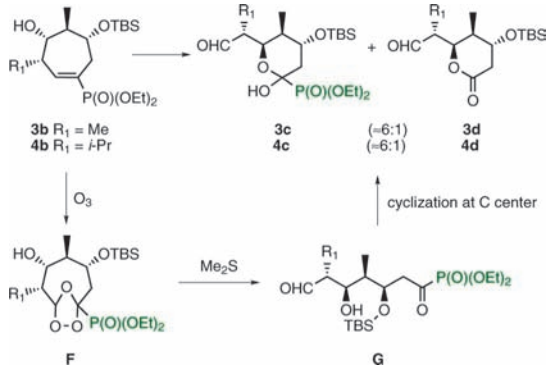
[a] (i) O_3, CH_2Cl_2/MeOH, pyridine; (ii) cat. DMAP; (iii) Bh_3, *t*-$BuNH_2$. [b] (i) O_3, DCM/MeOH, $NaHCO_3$; (ii) Me_2S. [c] (i) O_3, AcOEt, $NaHCO_3$; (ii) MeOH; (iii) Me_2S. [d] (i) O_3, AcOEt/MeOH; (ii) Me_2S; (iii) cat. DMAP. [e] (i) O_3, AcOEt, $NaHCO_3$; (ii) Me_2S, CH_2Cl_2/EA (9:1). [f] Acyl phosphonate could not be purified, yield was estimated by ^1H NMR. [g] **3c** and **4c** were converted to **3d** and **4d**, respectively, during purification and could not be isolated. [h] Estimated yield by ^1H NMR for mixture **3c** and **3d** (6:1). [i] Estimated yield by ^1H NMR for mixture **4c** and **4d** (6.2:1).

to provide **E** in a sequential fashion (Scheme 2). Acyl phosphonate-aldehyde **E** was then treated under basic conditions. After screening bases (pyridine, 2,6-lutidine, DABCO, DMAP, NEt_3, $NaHCO_3$), it was revealed that catalytic DMAP (20−50 mol %) was sufficiently basic and mild enough to

drive the reaction to completion and avoid detrimental β-eliminations/epimerizations (Table 3, entries 1 and 6).[12] Whereas the basicity of the reagent proved crucial for activity, its nucleophilicity is clearly also an important factor. A second successful protocol required addition of MeOH *after* ozonolysis in AcOEt in the presence of $NaHCO_3$[13] but *prior* to quenching with Me_2S (Table 3, entries 3, 5, and 8). These results and the presence of free diethyl phosphite in the reaction mixture[14] prior to quenching suggest that the phosphite was expelled from ozonide **A** to provide ozonide **C** after generation of oxonium intermediate **B** suggested by Griesbaum.[15] This equilibrium exchange is driven to **C** due to the large excess of MeOH (Scheme 2).

Oxidative cleavage of **3b** and **4b** provided aldehydes **3c** and **4c**[16] (Scheme 3) along with the desired lactones **3d** and **4d** as minor products in 6:1 ratio in AcOEt or CH_2Cl_2 (Table 3, entries 7 and 9). This result is in accord with the higher reactivity of acyl phosphonates at the C center than the P center[10,17,18] and with Whitesides' and Chan's results.[7]

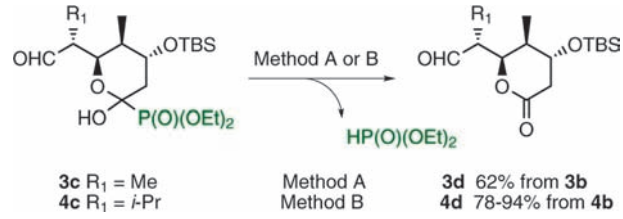
Scheme 3. Ozonolysis of Vinyl Phosphonates Bearing a Free -OH[a]



[a] Reactions were run in AcOEt/CH_2Cl_2 and quenched with Me_2S.

Initial attempts to drive lactonization to completion were unsuccessful due to the high base sensitivity of **3c** and **4c**. Problems included β-elimination, stereochemical erosion, and/or phosphite addition to the aldehyde. Fortunately, catalytic DBU (20 mol %) in CH_2Cl_2 could smoothly convert **4c** to **4d** without phosphite addition on the aldehyde (Scheme 4). Aldehyde **3c** was less tolerant to DBU and required dropwise addition of NaHMDS in the presence of *p*-nitrobenzaldehyde to provide **3d** while trapping the expelled diethyl phosphite.[19,20]

Scheme 4. Lactonization[a]



[a] Method A: NaHMDS (1 equiv), *p*-$NO_2C_6H_4CHO$ (4 equiv), THF, −10 °C. Method B: DBU (20 mol %), CH_2Cl_2, Room Temperature.

Ozonolysis of vinyl sulfones and vinyl phosphonates to acyl sulfones and acyl phosphonates reveals substantial reactivity differences as acylating agents.

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Supporting Information Available: Procedures, spectroscopic data, spectra, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Prior to quenching, the MeOH/$HP(O)(OEt)_2$ exchange takes place at 25 °C. $HP(O)(OEt)_2$ is usually visible by TLC with *p*-anisladehyde stain as a polar white spot.

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