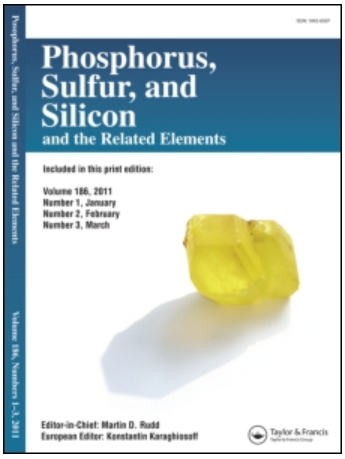


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

New Synthetic Methods Exploiting Vinyl Sulfones Discovered During the Synthesis of a Natural Product

Zhendong Jin[a]; P. C. Vandort[a]; P. L. Fuchs[a]
[a] Department of Chemistry, Purdue University, West Lafayette, IN

To cite this Article Jin, Zhendong , Vandort, P. C. and Fuchs, P. L.(1994) 'New Synthetic Methods Exploiting Vinyl Sulfones Discovered During the Synthesis of a Natural Product', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 1 — 19
To link to this Article: DOI: 10.1080/10426509408034198
URL: http://dx.doi.org/10.1080/10426509408034198

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95-96, pp. 1-19
Reprints available directly from the publisher
Photocopying permitted by license only

NEW SYNTHETIC METHODS EXPLOITING VINYL SULFONES DISCOVERED DURING THE SYNTHESIS OF A NATURAL PRODUCT[1]

ZHENDONG JIN, P. C. VANDORT, AND P. L. FUCHS*
Department of Chemistry Purdue University
West Lafayette, IN 47907

Abstract: Observations made during the synthesis of the anticancer agent homoharringtonine **37** have resulted in the development of several new synthetic methods based upon the alkylation and conjugate-addition chemistry of γ-methoxy allylsulfonyl anions. Enones, dienyl ketones, and trienyl ketones are readily constructed. Sultinium ion intermediates facilitate the sulfone to olefin transformation.

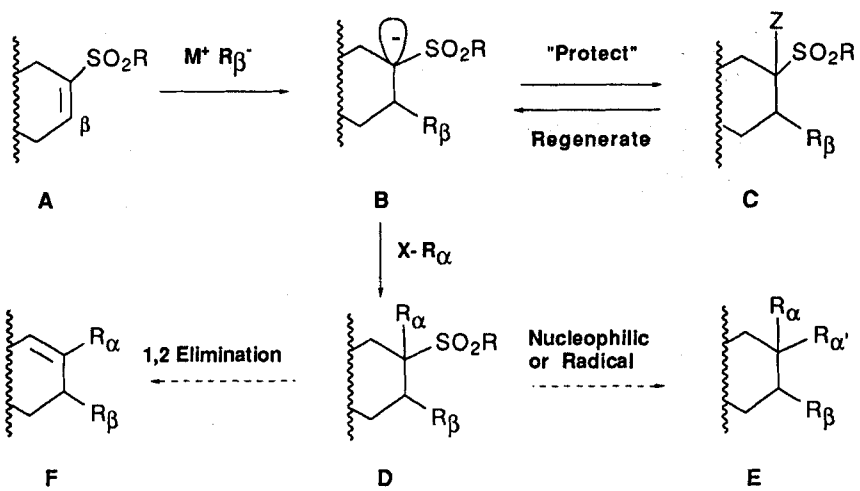
Key words: Intramolecular silylation of phenyl sulfone; sultinium ion; 1,2-elimination of tertiary sulfone to olefin, γ-methoxy vinyl sulfone; γ-methoxy allyl sulfonyl anion; alkylation; β–substituted enone; conjugate-addition; vinyl sulfone; dienyl ketone.

INTRODUCTION

We have been involved in an intense effort which has sought to establish the sulfone moiety as the "ideal functional group." The goal of this program was to develop the chemistry of sulfones to include the following highly desirable traits (Scheme 1):

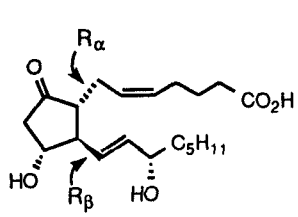
√	Activation of olefins for conjugate-addition at Cβ under kinetic conditions.
√	Facilitate subsequent functionalization at the Cα-site.
√	Support bidirectional interconversion between latent and reactive forms.
*	Serve as a leaving group in olefin-forming reactions.
*	Undergo replacement reactions to provide a second bond at the α-site.

Scheme 1

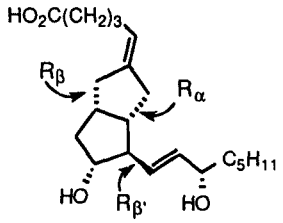


The first three goals have been largely achieved. Considerable success has been demonstrated at addressing the formation of bonds β and α to the sulfone moiety.[2] Scheme 2 indicates a collection of natural (**1**[3],**3**[4],**4**[5], & **5**[5]) and unnatural (**2**[6], **6-9**[7]) products which have been synthesized by the vinyl sulfone strategy. The use of α-silyl and α-bromosulfones as "protecting groups" for the α-sulfonyl anion and radical has also been shown to be practical.[8]

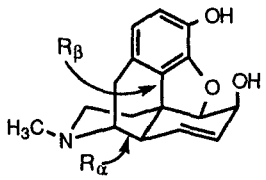
Scheme 2



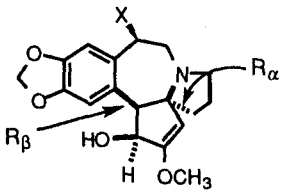
1 Prostaglandin E_2



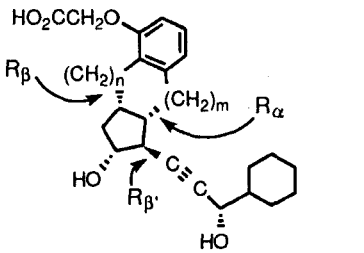
2 Carbacyclin



3 Morphine

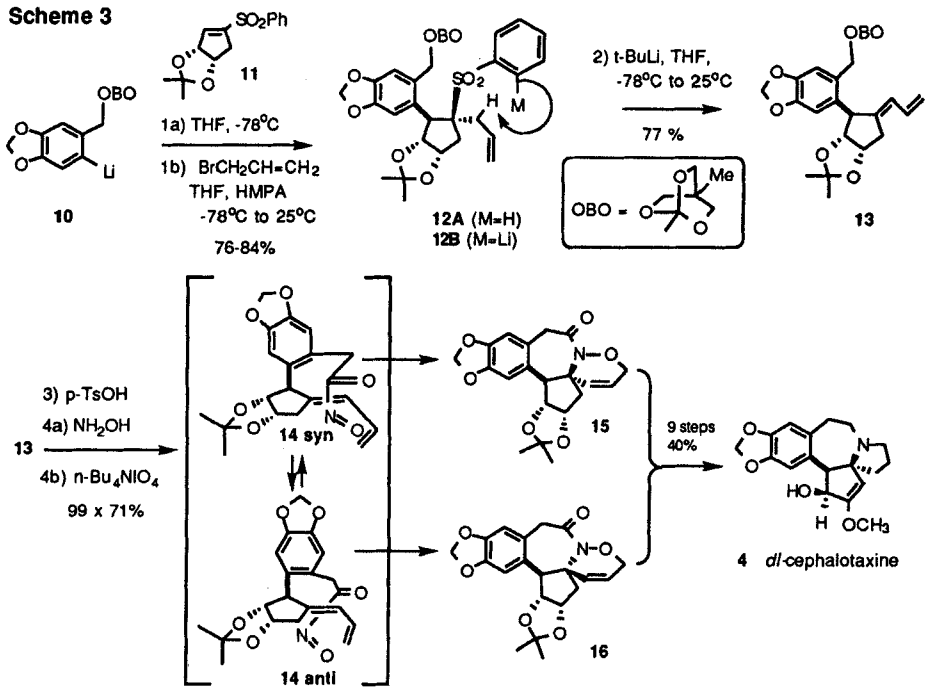


4 Cephalotaxine (X=H)
5 11-Hydroxycephalotaxine (X=OH)



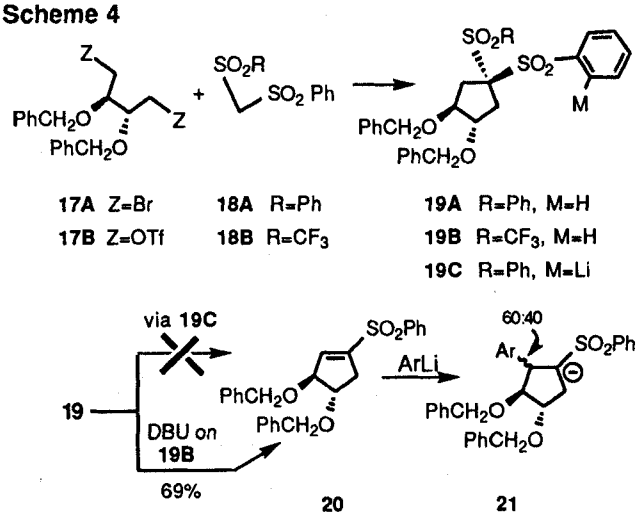
6-9 Four Prostacyclin Analogs
n=0,1 m=1,2

Our previous total synthesis[5e] of racemic cephalotaxine **4** featured conjugate-addition of aryllithium **10** to vinyl sulfone **11** followed by addition of allyl bromide to give homoallyl sulfone **12A**. Conversion of this material to exocyclic diene **13** involved a "self-immoliative" elimination sequence (via **12B**). Routine processing generated key acyl nitroso intermediate **14**. Hetero Diels-Alder cyclization of this species leads to a pair of adducts **15/16** (2:1) where the minor adduct was shown to have arisen via an unprecedented addition mode involving *delivery of the acyl nitroso moiety to the diene from the face* ***opposite*** *to the tethering aryl unit.* This mixture was inconsequential *in the racemic synthesis* since both adducts **15** and **16** were successfully converted to *dl*-cephalotaxine **4** (Scheme 3).



Parallel to the racemic synthesis shown above, we sought to employ optically active vinyl sulfone **20** in a similar way. C_2-symmetric sulfone **19A** was prepared from tartaric acid derivative **17A** and was metalated to **19C** in hopes of effecting a self-immoliative elimination. Unfortunately this strategy is apparently restricted to sulfones bearing allylically-activated hydrogen atoms, since anion **19C** failed to afford a trace of sulfone **20.** While the concept of using a better leaving group, namely triflone **19B**, was obvious from Hendrickson's important observations[9] (triflone is about a factor of 170 less reactive than chloride as a leaving group[10]), solution to this synthetic problem required close to a year's effort.[11] The electron-withdrawing properties of the triflone moiety, so desirable in the elimination reaction, caused great problems in the alkylation reaction. Only by alkylation of bis-triflate **17B** with the geminal dianion of **18B** in toluene-HMPA at -78° to 25°C was the synthesis of **19B** achieved in 95% yield (Scheme 4). Unfortunately addition of aryl anions to **20** proceeds with virtually no selectivity, precluding effective application to the synthesis of optically active cephalotaxine **4.**

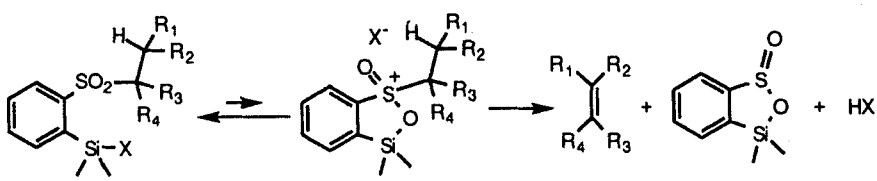
Scheme 4



Elimination of Sulfones to Olefins via Intramolecular Oxygen Silylation

The above problem vividly demonstrated the need for a **general method for elimination of unactivated aryl sulfones to olefins.** To our knowledge, there are no examples of aryl sulfones lacking activated β-protons which eliminate in high yield under reasonable conditions.[12] Trost and co-workers have demonstrated that Lewis acids can enhance the leaving group ability of certain phenyl sulfones and sulfoximines in intramolecular Friedel-Crafts reactions.[13] This led us to recently develop an efficient method for tertiary sulfone elimination employing intramolecular oxygen silylation of ortho-silyl sulfones **22B** to provide activated cyclic sultinium species **23** which undergo facile olefin formation.[14] Silyl triflates **22B** are easily generated from allylsilane precursors **22A** in the presence of catalytic triflic acid (Scheme 5).

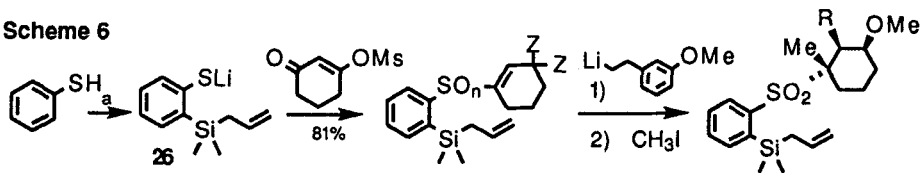
Scheme 5



Ortho-silylated mercaptide anion **26** is readily prepared from the dianion of thiophenol.[15] Conversion to γ-methoxyvinyl sulfone **28** is accomplished in 52% overall

yield. Reaction of m-methoxyphenethyl lithium with **28** followed by a methyl iodide quench provides tertiary sulfone **29** (Scheme 6).

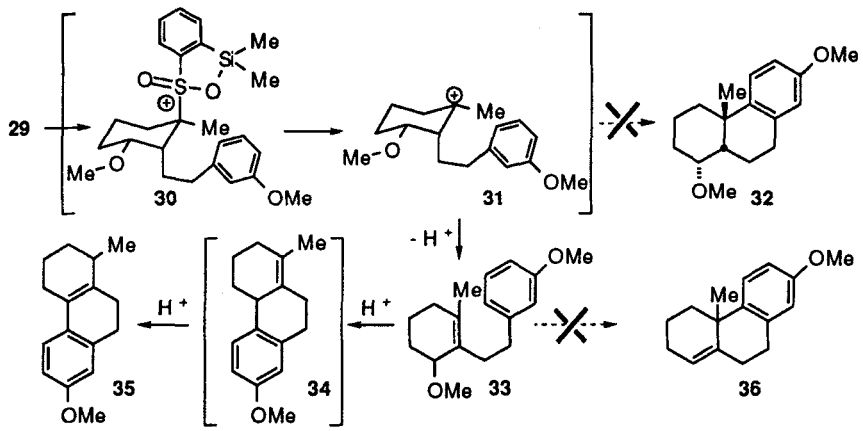
Scheme 6



(a) TMEDA (2.2 equiv), n-BuLi (2.2 equiv), cyclohexane, 0°C to 25°C, 24 h, then ClSi(Me)$_2$CH$_2$CH=CH$_2$, 50 / 50 cyclohexane / THF, -78°C to 25°C; (b) $CeCl_3$, $NaBH_4$ (1.0 equiv), 50/50 MeOH / CH_2Cl_2, 25°C, 1 h, MeI (10.0 equiv.), 25°C, 12 h (93%); (c) CH_3CN (10 equiv), K_2CO_3, H_2O_2 (6 equiv), MeOH, 25°C, 1 h (69%).

In an attempt to effect an intramolecular Friedel-Crafts alkylation via interception of the sultinium intermediate **30**, tertiary sulfone **29** was treated with 5 mol% triflic acid in $CDCl_3$ at 62°C. Tricyclic ether **32** was not detected, but at short reaction times intermediate olefin **33** could be isolated. Longer times (2 h) served to convert **33** to tricyclic olefin **35** (67%), with no apparent concomitant production of olefin **36** which would have occurred from arene alkylation at the more hindered site of the putative allylic cation (Scheme 7). Extensions of this strategy to secondary systems are underway.

Scheme 7

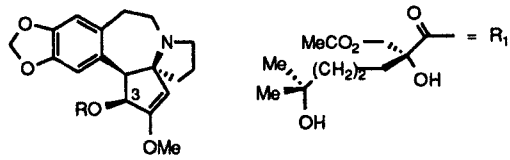


Plan for Synthesis of Cephalotaxus Alkaloids

The Cephalotaxus alkaloid cephalotaxine is the parent structure of a family of C-3 α-hydroxysuccinate esters designated the harringtonines which have recently been favorably evaluated in Phase II clinical trials as anticancer agents.[16] In order to

synthesize symchiral[17] homoharringtonine **37** (HHT),[18] an efficient total synthesis of symchiral cephalotaxine **4** is needed.

Scheme 8

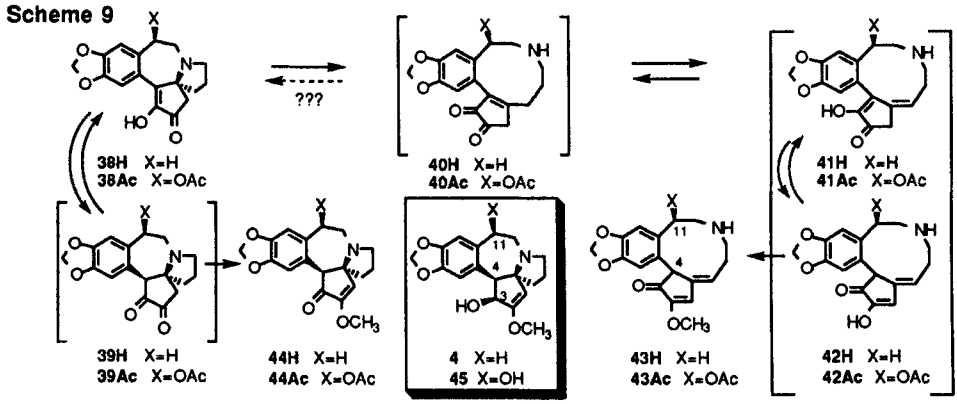


R = H Cephalotaxine **4**

R = R_1 Homoharringtonine **37**

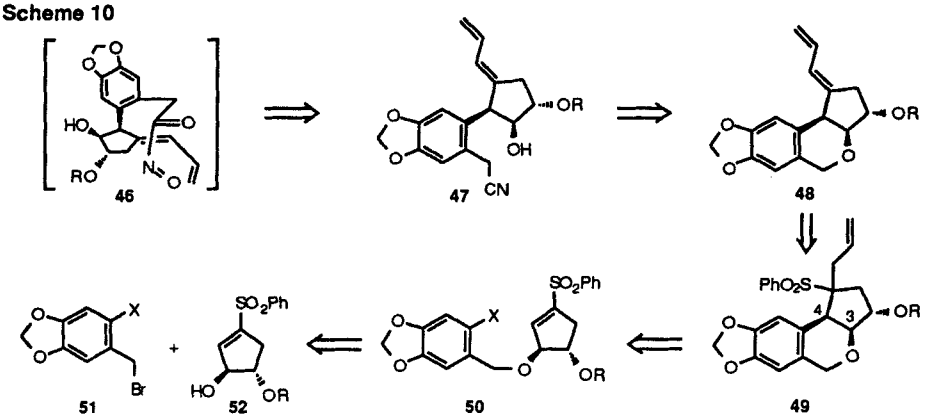
Returning to the chemistry described in scheme 3 reveals two flaws which prevent its being employed for synthesis of optically active cephalotaxine **4**. The facial specificity of the current IDA reaction **13** → **15/16** ultimately would translate to each symchiral diastereomer (**15**, **16**) resulting in the production of a different enantiomer of the cephalotaxine nucleus. While this problem might be solved by optimization, a much more deadly trap was discovered during our synthesis of 11-hydroxycephalotaxine **45**.[1] In the course of our synthesis of **racemic** cephalotaxine **4** we repeated the high-yielding Weinreb conversion of enol **38H** (dimethoxypropane, acid, heat) to cephalotaxinone **44H** (>90%).[19] When this procedure was employed with 11-acetoxy derivative **38Ac** we obtained a mixture of unreacted starting material **38Ac** (26%), 11-acetoxy-cephalotaxinone **44Ac** (43%) and ring-opened[20] secondary amine **43Ac** (a single C4,11 diastereomer, 17%). Since all previous syntheses of **4** were of racemic material, it is probable that any synthesis targeting the natural enantiomer and proceeding through **38H** will be subject to partial or total racemization via (previously undetected) equilibration of **38H** and **40H**.

Scheme 9



The above racemization trap required the formulation of a new plan (Scheme 10) for symchiral cephalotaxine synthesis which never involves a C-3 ketone, thereby avoiding potential β-eliminations of the amino moiety.

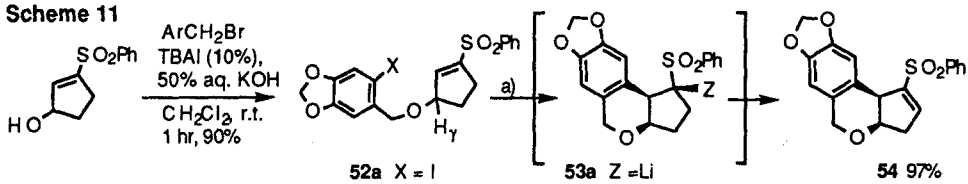
Scheme 10



Development of New Synthetic Methods Based On Gamma-methoxyallylsulfonyl anions

As shown above, intramolecular arylation was chosen to set the requisite cis $C_{3,4}$ stereochemistry. Our total synthesis of morphine[4c] suggested the sequence **52a→52b→53a→53b→54** (Scheme 11). Low temperature transmetalation of **52a** with t-butyl lithium followed by warming the solution generated a plethora of products. Fortunately, treatment of **52a** with a catalytic amount of $Pd(Ph_3P)_4$ and silver nitrate in acetonitrile at reflux provides compound **54** in nearly quantitative yield. This is the first instance of using vinyl sulfones as the acceptor for this well-known organopalladium reaction and its scope was briefly investigated.[21,22]

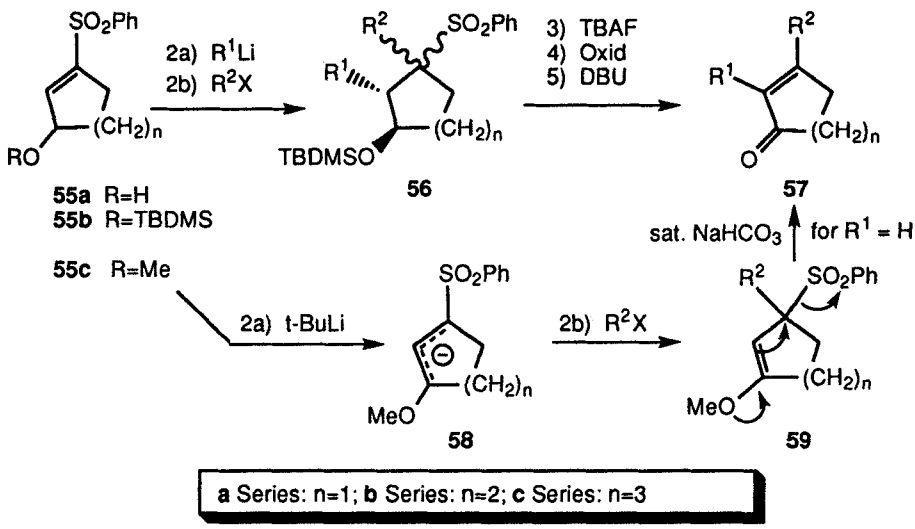
Scheme 11



Before returning to the cephalotaxine synthesis we defined the failure mode for the organolithium chemistry on **52a**.[23] The finding that deprotonation of the allylic hydrogen of γ-alkoxy vinyl sulfones is a facile process and that the resultant γ-alkoxy allyl sulfonyl anions are highly reactive has provided a number of useful synthetic procedures. The initial sulfone paper published from our group in 1978 detailed the use

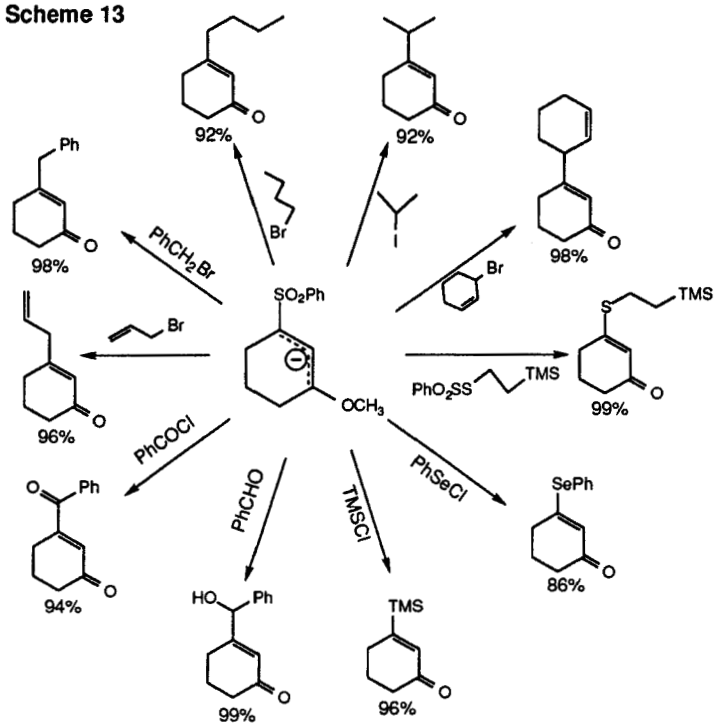
of γ-silyloxyvinyl sulfones **55b** as the focal point of a four-step synthesis of α,β-disubstituted enones **57** (Scheme 12).[24]

Scheme 12

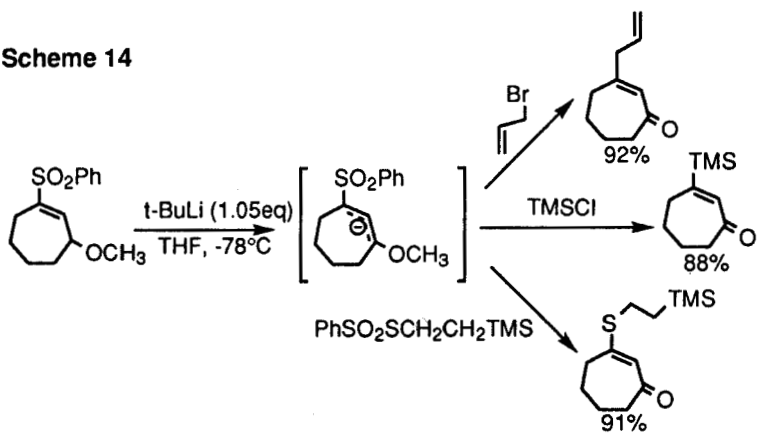


A serious deficiency of this strategy has been revealed by our recent need for β-substituted enones which bear a hydrogen in the α-position (**57**, R^1=H). This limitation has now been removed for six and seven-membered rings by implementation of an alternative one-pot metalation/ alkylation/hydrolysis sequence starting from γ-methoxy vinylsulfones **55c**.[23] These substrates are produced from γ-hydroxy vinyl sulfones **55a** which are readily available on the mole scale via a three-step procedure starting with the corresponding allylic halides. Reaction of γ-methoxy vinylsulfones **55c** with 1.05 equiv. of t-butyl lithium in THF at -78°C rapidly affords γ-methoxy allylsulfonyl anions **58** which undergo smooth alkylation with a variety of electrophiles to afford enones **57** in near-quantitative yield after treatment with aqueous sodium bicarbonate (Schemes 12-14).

Scheme 13



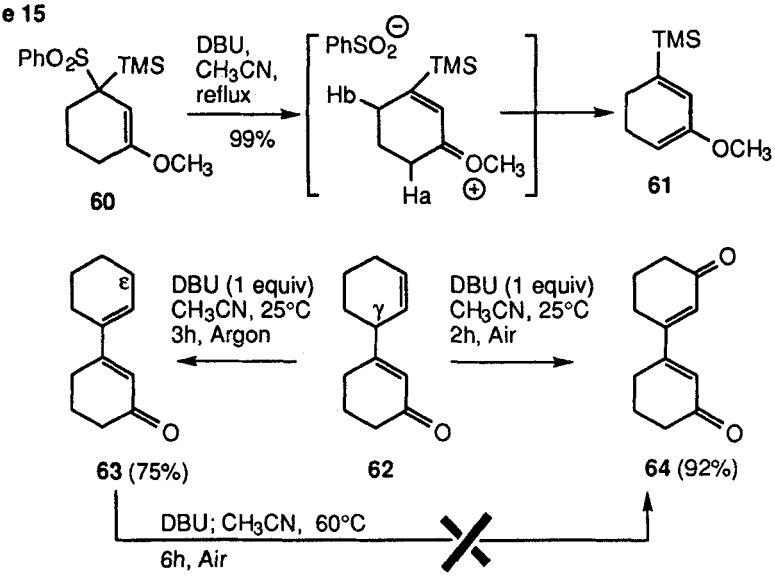
Scheme 14



Both the intermediates and products from these reactions can easily be further transformed into useful dienes by DBU mediated chemistry (Scheme 15). For example, silylated sulfone **60** affords dienyl ether **61** in near-quantitative yield after brief heating in acetonitrile. Allylated product **62** serves as a useful progenitor for dienyl ketone **63** simply by DBU mediated isomerization, providing that air is carefully excluded from the reaction medium. Initially we were surprised to obtain dione **64** with no trace of the

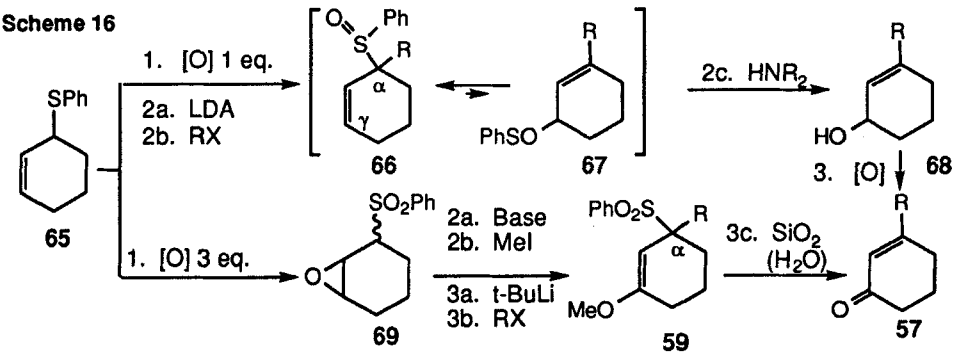
expected dienyl ketone **63**. Repeating the reaction with careful exclusion of oxygen affords the desired dienyl ketone in 75% yield (93% using CH_2Cl_2).

Scheme 15



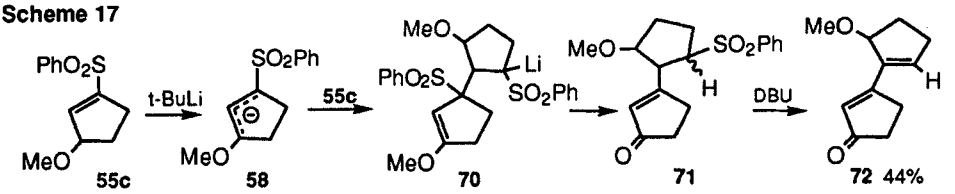
The β-substituted enone strategy can be seen to be complementary to a method developed in the Evans laboratories (Scheme 16).[25] In the Evans method, allyl sulfide **65** is oxidized to allylic sulfoxide **66a** (R=H) which is metalated and alkylated to provide **66b** (R=alkyl). Allyl sulfoxide **66b** (R=alkyl) is in equilibrium with allyl sulfenate **67** via 2,3 sigmatropic rearrangement. Treatment of the **66b/67** mixture with a thiophilic reagent like a secondary amine provides allyl alcohol **68**, which can be subsequently oxidized to enone **57**. The vinyl sulfone method also begins with allylic sulfide **65**, but proceeds via β-epoxysulfone **69** to the α-alkylated allylic sulfone **59** on the way to enone **57**. While both processes are of equivalent length, the Evans protocol provides lower overall yields as well as forming α/γ mixtures during addition of the allyl sulfoxide anion to carbonyl compounds,[26] while the alkylation of the allylic sulfone anion faithfully undergoes alkylation adjacent to the sulfone moiety in all cases examined.

Scheme 16



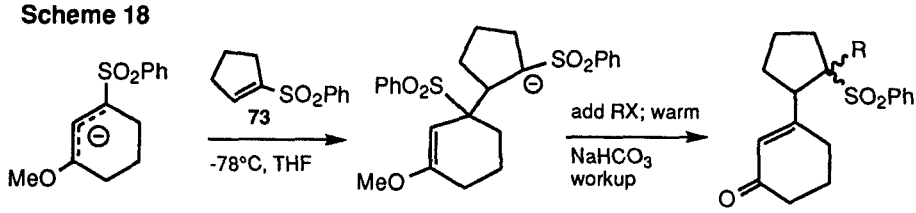
The specific "failure mode" for the five-membered ring γ-methoxy vinyl sulfone shown in scheme 11 was revealed by examining the details of the metalation chemistry of compound **55c**. As in the previous schemes with six and seven-membered ring substrates, metalation of **55c** generates heteroallyl anion **58**. At this stage the chemistry becomes dominated by the exceptional acceptor properties of five-ring vinyl sulfone **55c**, leading to adduct **71** after standard work-up. Treatment of **71** with DBU provides dienone **72** in 44% overall yield.

Scheme 17



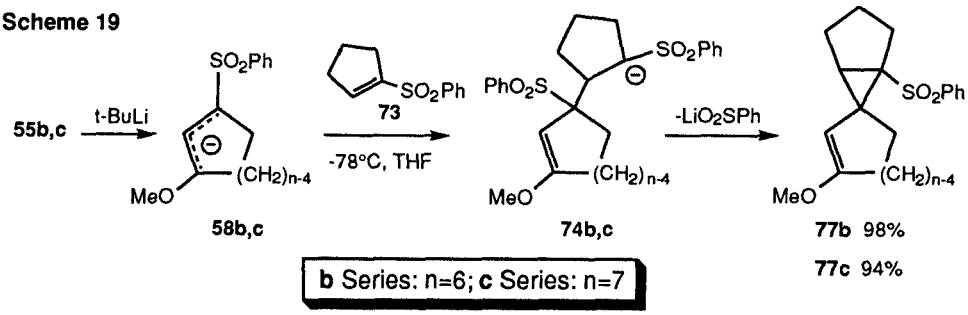
The ability of five-membered ring vinyl sulfones to serve as general Michael acceptors in unsymmetrical condensations was tested by adding a slight excess of cyclopentenyl phenyl sulfone **73** to a solution of γ-methoxy vinyl sulfonyl anion **58b** which was prepared in the normal fashion. Following the course of the reaction by thin layer chromatography (TLC) indicated that conjugate addition of anion **55b** was instantaneous at -78°C. The analytical profile of these reactions was complicated by the fact that several of the reaction products were unstable to silica gel as evidenced by two-dimensional TLC. Nevertheless, enone **75b** was obtained in excellent yield after an aqueous bicarbonate workup. Surprisingly, all attempts to trap the putative α-sulfonyl anion intermediate **74b** via alkylation with allyl bromide once again provided >90% yields of the "hydrogen quench product" **75b** with only traces of the expected allyl sulfone **76b** being detected in the crude reaction product (Scheme 18).[27]

Scheme 18



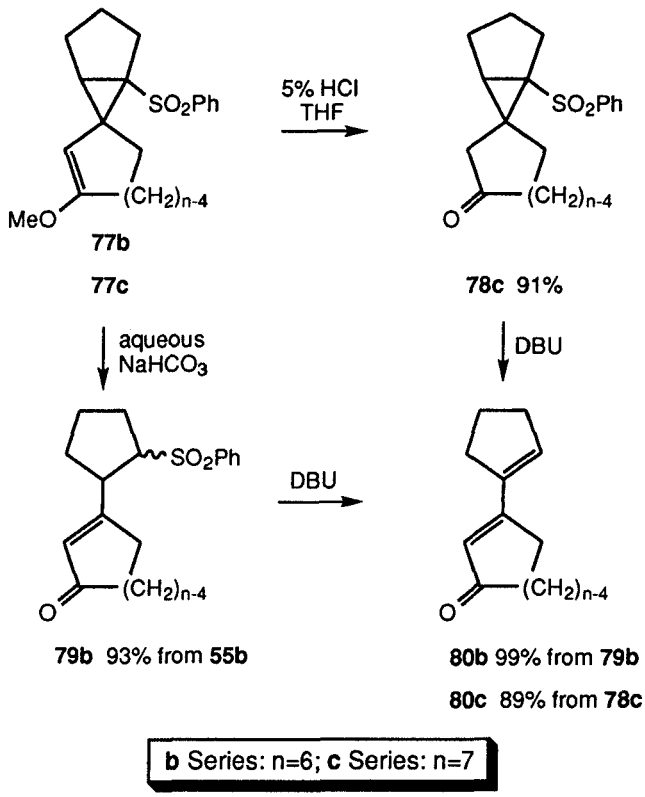
Reaction of vinyl sulfone **73** with cycloheptyl γ-methoxy allylsufonyl anion **58c** provided an intermediate which was far easier to handle. Careful workup and chromatography on deactivated silica gel afforded spirocyclopropyl sulfone **77c** in 94% yield. Repeating the reaction shown in scheme 18 followed by chromatography on fluoracil now permits isolation of the analogous six-membered spirocyclopropyl sulfone **77b** in 98% yield! Both compounds were isolated as single diastereomers of unknown syn/anti stereochemistry (Scheme 19).

Scheme 19



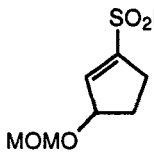
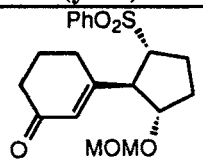
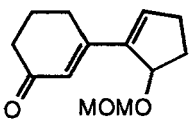
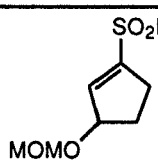
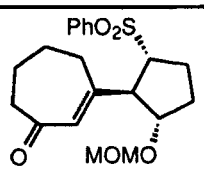
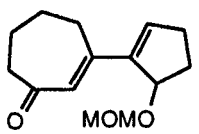
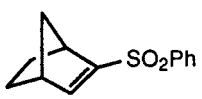
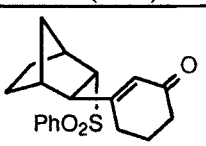
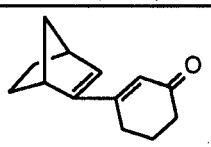
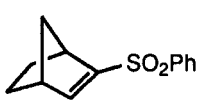
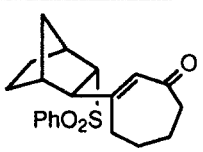
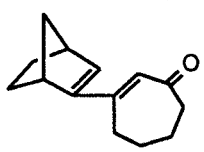
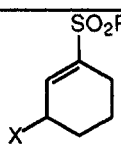
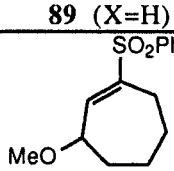
Mild acid hydrolysis of enol ether **77c** smoothly afforded tricyclic keto-sulfone **78c** without evidence of rupture of the activated cyclopropyl sulfone moiety. Treatment of **78c** with DBU effected cleavage of the cyclopropane, generating δ-sulfonyl enone intermediate **79c** which was further processed to dienones **80c** under the basic reaction conditions. In practice, for reactions utilizing cyclohexenyl sulfone donor **58b** there is no need to include the extra step of generation keto-sulfone **78b** (see also table 1) since simply adding aqueous bicarbonate to the one-pot reaction directly affords δ-sulfonyl enones **79b** in high overall yield. In comparison, the seven membered ring intermediate **77c** was slow to be converted to **79c** under the aqueous bicarbonate conditions and required processing via keto intermediate **78c**. Completion of the preparation of dienyl ketone **80b** is again accomplished by elimination of sulfinic acid using DBU in acetonitrile at reflux (Scheme 20).

Scheme 20



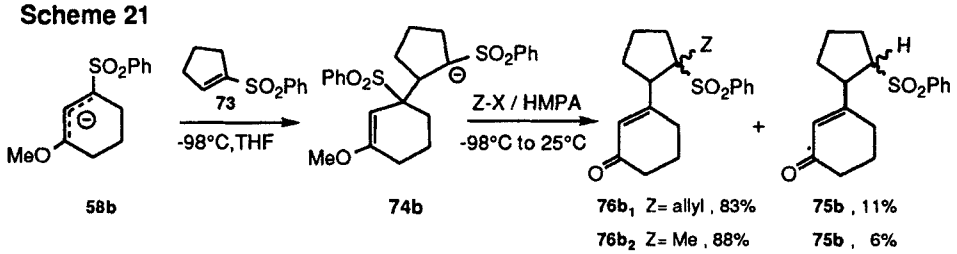
The chemistry described in scheme 20 appears to be general for other five-membered vinyl sulfone acceptors. Table 1 describes the synthesis of several additional dienyl ketones by this procedure. In these examples, no effort was made to isolate or characterize the probable cyclopropylsulfone intermediates. The δ-sulfonyl enones were subsequently subjected to the DBU-mediated elimination reaction (Table 1). As can be seen from the final five table entries, simple six and seven-membered ring phenyl vinyl sulfones do not serve as Michael acceptors in the conjugate-addition reaction.

Table 1. Synthesis of dienyl ketones.

Entry	Donor Anion	Acceptor sulfone	δ-sulfonyl enone (yield)	Dienylketone (yield)
1	**58b**	 **81**	 **82** (99%)	 **83** (96%)
2	**58c**	 **81**	 **84** (85%)	 **85** (92%)
3	**58b**	 **86**	 **87b** (94%)	 **88b** (80%)
4	**58c**	 **86**	 **87c** (84%)	 **88c** (30%)
5 6 7 8	**58b** or **58c**	 **55b** (X=OMe) **89** (X=H)	No Reaction	
9	**58c**	 **1c**	No Reaction	

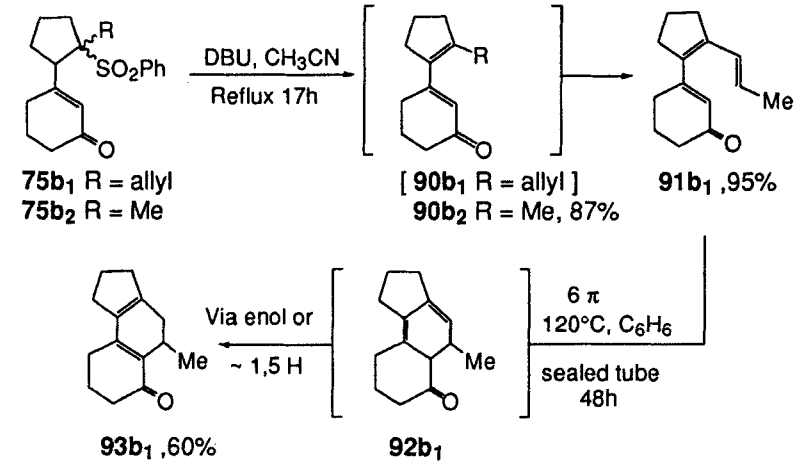
Having demonstrated that conversion of intermediates **74b,c** to cyclopropanes **77b,c** via intramolecular alkylation was responsible for our inability to effect intermolecular alkylation, we returned to reinvestigate the reaction of **58b** with cyclopentenyl sulfone **73** at lower temperatures. Conjugate-addition of γ-methoxyallyl sulfonyl anion **58b** to vinyl sulfone occurred rapidly at -98°C as judged by TLC assay. Immediate addition of HMPA and excess alkylating agent followed by a slow warming period and mild bicarbonate workup provided δ-functionalized enones **76b$_{1-2}$** in addition to variable amounts of "quenched" enone **75b**, probably by way of cyclopropyl sulfone **77b** (Scheme 21).

Scheme 21



Application of the DBU-mediated sulfinic acid elimination reaction to the above examples produced the useful δ-functionalized dienone **90b$_2$** as well as trienyl ketone **91b$_1$**, which was produced via further isomerization of **90b$_1$**. Heating **91b$_1$** for two days in benzene in a sealed tube at 120°C afforded the annulated dienyl ketone **93b$_1$** presumably by way of intermediate **92b$_1$** (Scheme 22).

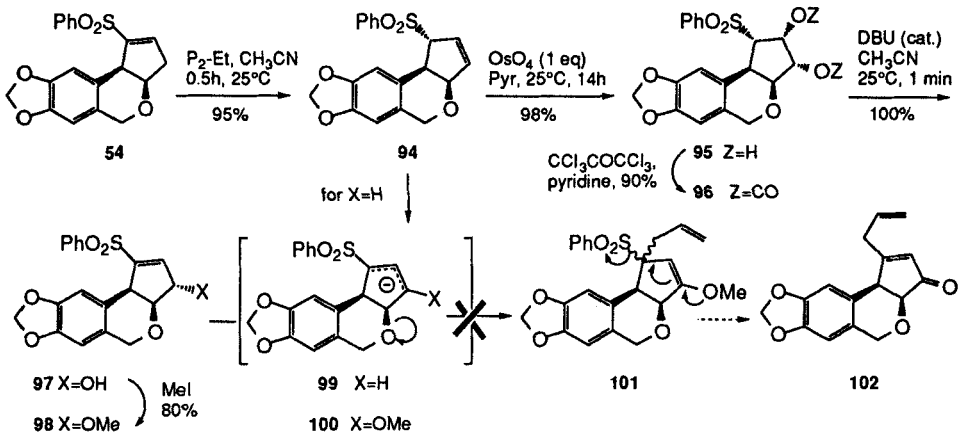
Scheme 22



Sulfone-Related Transformations Applicable to the Synthesis of Homoharringtonine

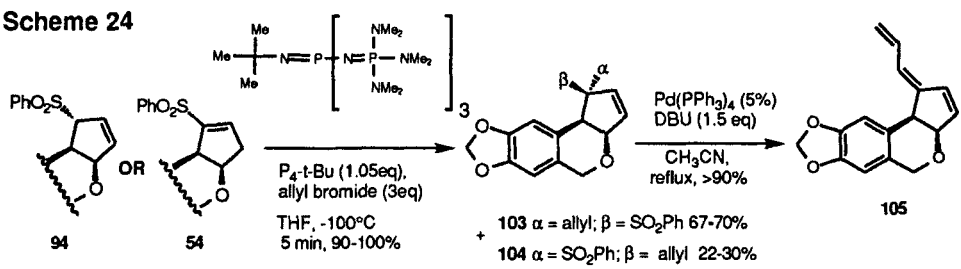
Returning to the cephalotaxine/homoharringtonine program, we wished to attempt the newly-developed enone synthesis in a more-highly functionalized substrate (**98**) which was to provide enone **102** via allylation of anion **100**. Unfortunately, metalation of **99** or **100** with alkyllithium reagents only serves to effect β-elimination of the benzylic ether bond (arrow, Scheme 23).

Scheme 23



Since no fragmentation was observed during the isomerization of **54** to **94** using the Schwesinger phosphazene base[28], we speculated that the nature of π-base extended "counterion" might be crucial in determining the lifetime of allylic anions like **99**. In the event, reaction of either allyl sulfone **94** or more conveniently, vinyl sulfone **54** with excess allyl bromide in the presence of 1.05 equivalents of P_4-t-Bu provides the same mixture of allylated sulfones **103/104** in extremely high yield.

Scheme 24

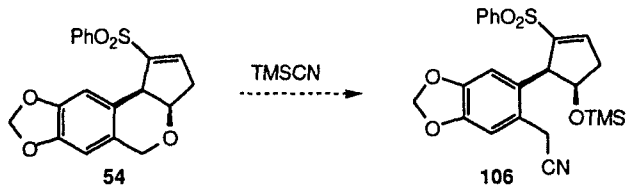


Palladium [0]-catalyzed elimination of **103** using the method of Trost[29] provided triene **105** in >90% yield, while the minor isomer **104** is recovered unchanged under

identical conditions, presumably for stereoelectronic reasons (Scheme 24). Attempts to convert **103** or **104** to **105** using KOt-Bu or the self-immoliative method were unsuccessful, underscoring the importance of the palladium chemistry.

Several additional sulfone-related facts have been uncovered in relation to the cephalotaxine/homoharringtonine project. At some stage of the synthesis the benzylic pyranyl ether moiety of sulfone **54** or other related substrates has to be regioselectively cleaved in order to be homologated by one carbon (Scheme 25). The original plan for this transformation was to react compound **54** with trimethylsilyl cyanide to hopefully provide nitrile **106**.

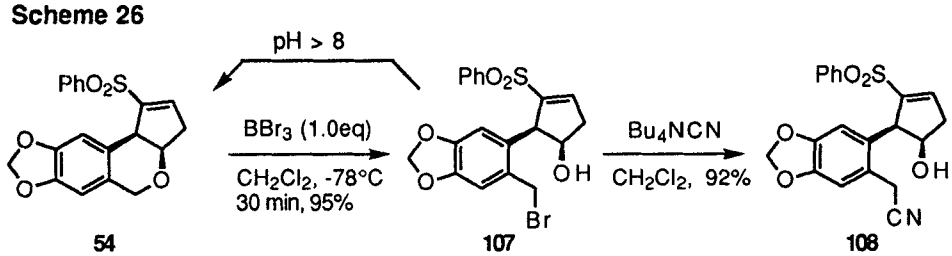
Scheme 25



54 106

This proved to be a surprisingly difficult prospect. It seems amazing that the p-alkoxybenzylic ether is recovered in quantitative yield after heating in neat TMSCN, even in the presence of $(n\text{-}Bu)_4NCN$ and/or TMS-triflate as a catalyst. More than ten different ether cleavage methods have been tried, with only BBr_3 proving capable of regiospecific cleavage of **54** to **107** in excellent yield. The activated benzyl bromide was easily converted to the benzyl nitrile **108** (Scheme 26).

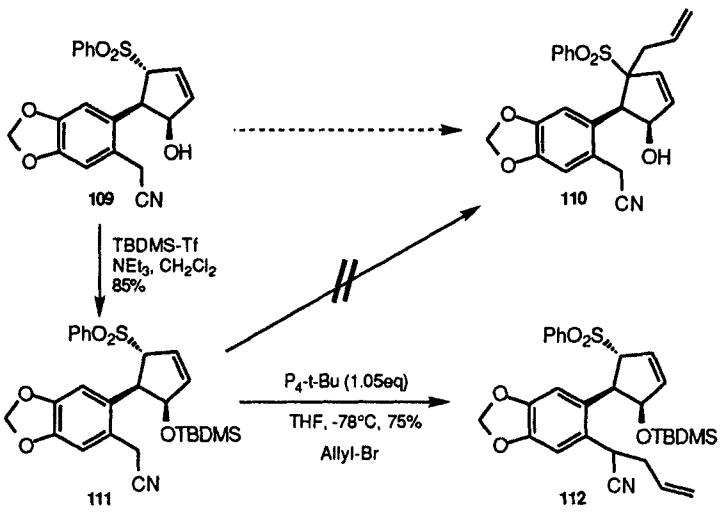
Scheme 26



54 107 108

Reaction of **108** or **109** with allyl halide in the presence of the phosphazene base failed to produce the desired allylated sulfone **110**. Similar reaction on silylated allyl sulfone **111** also was unrewarding, providing only **112** via allylation adjacent to the nitrile moiety. Clearly, refunctionalization of the nitrile must precede future attempts at allylation of the sulfone moiety.

Scheme 27



The synthesis of natural products is analogous to building a pyramid. One needs to forge a strong base before being in a position to complete the structure. The analogy extends to further to the merit of the exercise--those pyramids which have been carefully crafted will provide future benefit to all who follow.

Acknowledgment: Support of this work was provided by NIH: GM-32693.

REFERENCES AND NOTES

1 Synthesis Via Vinyl Sulfones 55. Abstract of a seminar presented at the 16th International Symposium on the Organic Chemistry of Sulfur, Merseburg Germany, July 1994. For a previous review see reference 2.

2 T. F. Braish and P. L. Fuchs, *Chem. Rev.*, **86**, 903 (1986).

3 a) R. E. Donaldson and P. L. Fuchs, *J. Am. Chem. Soc.*, **103**, 2108 (1981); b) J. C. Saddler, R. E. Donaldson, and P. L. Fuchs, *J. Am. Chem. Soc.*, **103**, 2110 (1981); c) J. C. Saddler and P. L. Fuchs, *J. Am. Chem. Soc.*, **103**, 2112 (1981).

4 a) J. E. Toth and P. L. Fuchs, *J. Org. Chem.*, **51**, 2594 (1986); b) J. E. Toth and P. L. Fuchs, *J. Org. Chem.*, **52**, 473 (1987); c) J. E. Toth, P. R. Hamann, and P. L. Fuchs, *J. Org. Chem.*, **53**, 4694 (1988).

5 a) P. C. Conrad, P. L. Kwiatkowski, and P. L. Fuchs, *J. Org. Chem.*, **57**, 586 (1987); b) X. Radisson, M. H. Nantz, and P. L. Fuchs, *Syn. Comm.*, **17**, 55 (1987); c) X. Radisson, P. L. Kwiatkowski, and P. L. Fuchs, *Syn. Comm.*, **17**, 39 (1987); d) T. P. Burkholder and P. L. Fuchs, *J. Am. Chem. Soc.*, **110**, 2341 (1988); e) T. P. Burkholder and P. L. Fuchs, *J. Am. Chem. Soc.*, **112**, 9601 (1990).

6 a) D. K. Hutchinson and P. L. Fuchs, *J. Am. Chem. Soc.*, **107**, 6137 (1985); b) D. K. Hutchinson and P. L. Fuchs, *J. Am. Chem. Soc.*, **109**, 4755 (1987).

7 a) S. A. Hardinger, J. A. Jakubowski, and P. L. Fuchs, *Biomed. Chem. Lett.*, **1**, 73 (1991); b) C. R. Nevill, Jr., T. F. Braish, J. A. Jakubowski, and P. L. Fuchs, *Biomed. Chem. Lett.*, **1**, 77 (1991); c) S. A. Hardinger, J. A. Jakubowski, and P. L. Fuchs, *Biomed. Chem. Lett.*, **1**, 79 (1991); d) C. R. Nevill, Jr., J. A. Jakubowski, and P. L. Fuchs, *Biomed. Chem. Lett.*, **1**, 83 (1991).

8 a) M. B. Anderson and P. L. Fuchs, *J. Org. Chem.*, **55**, 337 (1990); b) D. Scarpetti and P. L. Fuchs, *J. Am. Chem. Soc.*, **112**, 8084 (1990); c) M. Lamothe, M. B. Anderson, and P. L. Fuchs, *Syn. Comm.*, **21**, 1675 (1991).

9 a) J. B. Hendrickson, G. L. Boudreaux, and P. S. Palumbo, *J. Am. Chem. Soc.*, **108**, 2358 (1986); b) J. B. Hendrickson and P. S. Palumbo, *J. Org. Chem.*, **50**, 2110 (1985); c) J. B. Hendrickson and P. S. Palumbo, *Tetrahedron Lett.*, **26**, 2849 (1985); d) J. B. Hendrickson, A. Giga, and J. Wareing, *J. Am. Chem. Soc.*, **96**, 2275 (1974); e) J. B. Hendrickson, D. D. Sternbach, and K. W. Bair, *Acc. Chem. Res.*, **10**, 306 (1977).

10 X. Creary, *J. Org. Chem.*, **50**, 5080 (1985).

11 S. S. Magar and P. L. Fuchs, *Tetrahedron Lett.*, **33**, 745 (1992).

12 Typical conditions reported for elimination of simple phenyl sulfones require treatment with strong base at high temperatures; see: A. K. Colter and R. E. Miller, Jr., *J. Org. Chem.*, **36**, 1898 (1971).

13 a) B. M. Trost and M. R. Ghadiri, *J. Am. Chem. Soc.*, **106**, 7260 (1984); b) B. M. Trost and R. T. Matsuoka, *Synlett*, **92**, 27 (1992).

14 P. C. VanDort and P. L. Fuchs, *J. Am. Chem. Soc.*, **116**, 0000 (1994).

15 a) G. D. Figuly, C. K. Loop, and J. C. Martin, *J. Am. Chem. Soc.*, **111**, 654 (1989); b) E. Block, V. Eswarakrishnan, M. Gernon, G. Ofori-Okai, C. Saha, K. Tang, and J. Zubieta, *J. Am. Chem. Soc.*, **111**, 658 (1989).

16 a) J. A. Stewart, P. A. Cassileth, J. M. Bennett, and M. J. O'Connell, *Am. J. Clin. Oncol.*, **11**, 627 (1988); b) H. M. Kantarjian, M. J. Keating, R. S. Walters, C. A. Koller, K. B. McCredie,and E. J. Freireich, *Cancer*, **63**, 813 (1989); c) J. L. Welborn, J. P. Lewis, and F. J. Meyers, *Leukemia*, **2**, 711 (1988).

17 D. F. Taber, *Chem. and Eng. News*, August 19, pg. 5 (1991).

18 a) M. Suffness and G. A. Cordell, *Antitumor Alkaloids in the Alkaloids*; A. Brossi, Ed.; Academic Press: Orlando, Fl., **25**, 1 (1985); b) W. R. Cobb, A. E. Bogden, and S. D. Reich, *Cancer Treatment Rep.*, **67**, 173 (1983).

19 Improved procedure: Steve Weinreb, Personal Communication, 1982.

20 Similar ring-opening reactions have been previously observed: a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); b) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969); c) J. M. Schwab, R. J. Parry, and B. M. Foxman, *Chem. Comm.*, 906 (1975).

21 Z. Jin and P. L. Fuchs, *Tetrahedron Lett.*, **34**, 5205 (1993).

22 S. W. Lee and P. L. Fuchs, *Tetrahedron Lett.*, **34**, 5209 (1993).

23 Z. Jin and P. L. Fuchs, *J. Am. Chem. Soc.*, **116**, 0000 (1994).

24 P. C. Conrad and P. L. Fuchs, *J. Am. Chem. Soc.*, **100**, 346 (1978).

25 D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

26 a) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1385 (1973); b) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *ibid.*, 1389 (1973).

27 Z. Jin and P. L. Fuchs, submitted for publication.

28 R. Schwesinger, *Nachr. Chem. Tech. Lab.*, **38**, 1214 (1990).

29 B. M. Trost, N. R. Schmuff, and M. J. Miller, *J. Am. Chem. Soc.*, **102**, 5979 (1980).