Multiply Convergent Syntheses via Conjugate-Addition Reactions to Cycloalkenyl Sulfones

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I. Introduction

In executing the synthesis of a given target structure, the organic chemist is painfully aware of the inverse exponential relationship between the number of linear steps in a synthetic scheme and the overall yield for the process. There are only two conceptual ways to overcome this problem: (1) by optimization of each step along the synthetic route such that every reaction yield approaches 100%,[1a] and/or (2) by utilization of "multiply convergent" processes which rapidly assemble highly functionalized subunits of the target molecule, thus minimizing the absolute length of the linear sequence involved. Scheme 1 demonstrates the effect of convergency upon a hypothetical sequence of 22 steps.[1b]

In principle, one of the most powerful "triply convergent" strategies is that of the addition of an anionic nucleophile **26** to an olefin **27** to generate a new anion **28** which can be subsequently functionalized by an electrophile **29** to afford product **30**. Unfortunately, this specific reaction cannot be effectively utilized in organic synthesis. The activation energy necessary to effect anionic addition to isolated olefins is large, and

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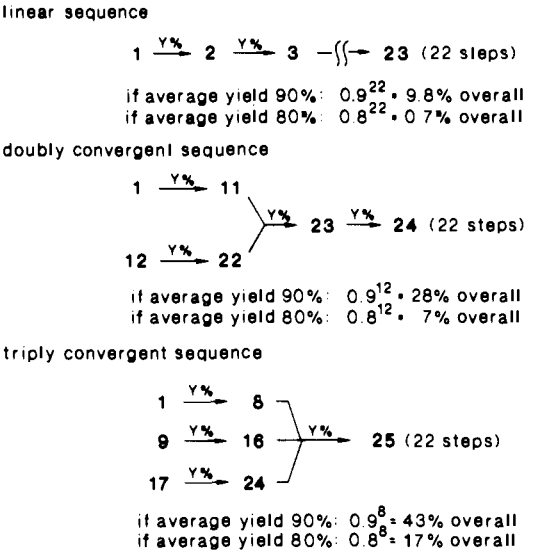

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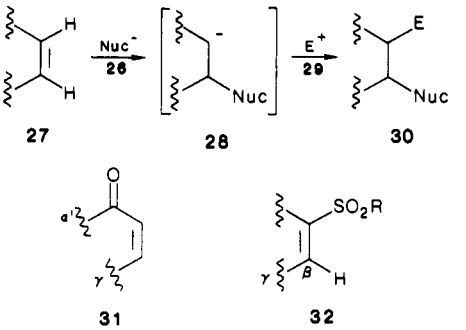

the reactivity of the initial nucleophile **26** and the olefin adduct **28** is similar; thus under those conditions where the first addition occurs, olefin adduct **28** possesses sufficient reactivity to undergo further reaction with the primary substrate **27**, and polymerization occurs.

A successful variant of this strategy utilizes olefins which are substituted with electron-withdrawing groups. This simple expedient lowers the activation energy for the initial conjugate-addition reaction and also provides stabilization for the intermediate adduct. Well-known examples of this approach include use of the carbonyl moiety **31** as the olefin activator, thereby fostering the development of triply convergent, Michael addition/enolate functionalization reactions.[2]

During the past eight years we have been exploring another variant of the strategy presented in Scheme 2, that of using the vinyl sulfone functional group **32** as a substrate for conjugate-addition/α-sulfonyl anion functionalization reactions. Several general observa-

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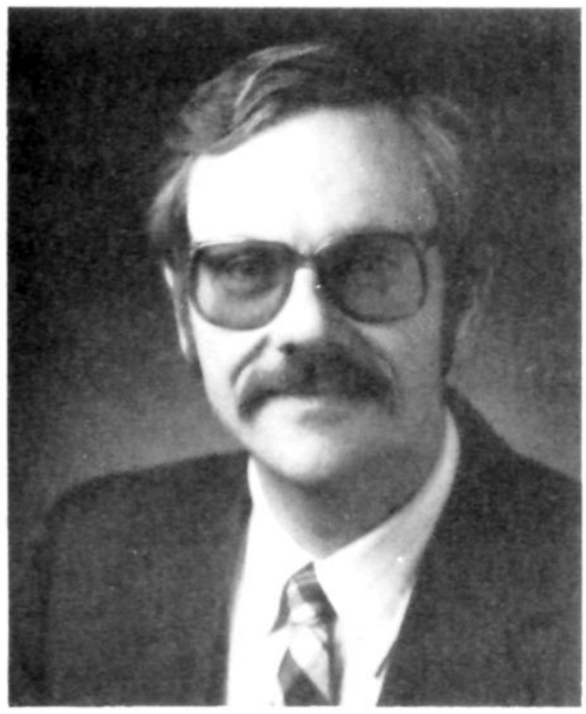
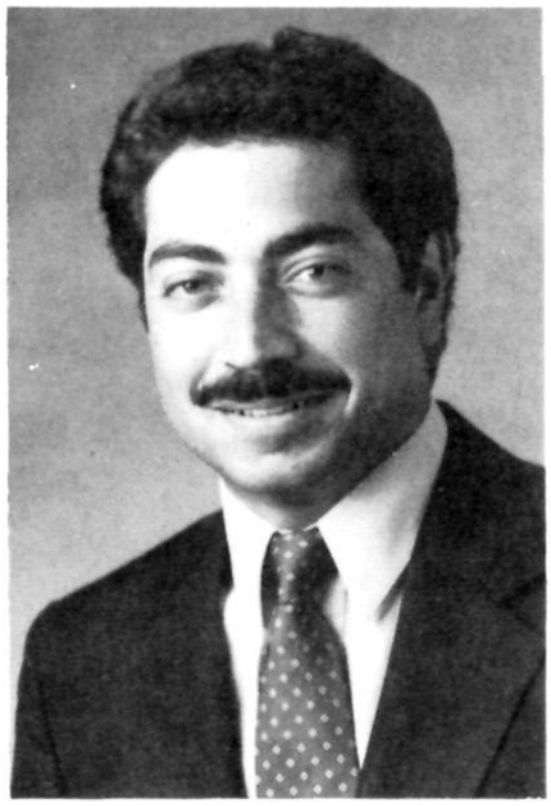


Fuchs received his B.S. in 1968 from the University of Wisconsin, Madison. He remained at that institution working with Edwin Vedejs and obtained the Ph.D. in 1971. After a 2-year postdoctoral stay in the laboratories of E. J. Corey at Harvard University, Fuchs joined the faculty of Purdue University in 1973 where he is now Professor of Chemistry. Fuchs has been awarded fellowships from Eli Lilly and the Alfred P. Sloan foundation. Fuchs's research interests include the efficient total synthesis of natural and unnatural products as well as laboratory automation utilizing robotics. Fuchs is a recipient of the 1985 Pioneer in Laboratory Robotics award.



Dr. Braish received his B.S. degree with honor in 1981 at Indiana-Purdue University at Fort Wayne, IN. He obtained his Ph.D. degree in 1986 under the direction of Professor P. L. Fuchs at Purdue University. He is currently a Senior Research Associate with Professor Fuchs.

tions serve to compare and contrast the enone **31** and the vinyl sulfone functional groups with regard to substrates for triply convergent reactions: (1) The conjugate-addition reaction of anions to the enone may be complicated by competitive 1,2-addition to the carbonyl group, particularly with "hard" anions such as organolithium reagents. The vinyl sulfone functional group is immune to such difficulties; and conjugate-addition reactions are routinely observed with anions such as organolithium reagents, Grignard reagents, metalloimine anions, β-keto ester dianions, and α-thioacetal anions. (2) The enone functional group is susceptible to base-catalyzed enolization, either in the α'- or γ-position. Competitive metalation (in the β- or γ-position) is also a potential problem with the vinyl sulfone group, although in most cases metalation difficulties can be avoided by careful selection of the target sulfone. (3) The ketone enolate which results from conjugate addition to **31** is a substantially weaker nucleophile ($pK_a \approx 20$) than the α-sulfonyl anion which results from conjugate addition to vinyl sulfone **32** ($pK_a \approx 25$). This difference often has significant consequences with respect to the ease of performing the final electrophilic functionalization.

Inasmuch as the target molecules we are seeking to synthesize do not bear sulfone functionality, all synthetic routes must involve a reaction which removes this group. We have attempted to accommodate this requirement by utilizing the desulfonylation reaction in an *active* role, for further functionalization or as an aid in the establishment of stereochemistry, rather than simply performing reductive cleavage reactions.

This review will limit the scope of literature coverage to specifically include only chemistry pertinent to the synthesis and conjugate-addition reactions of cycloalkenyl sulfones.

II. Vinyl Sulfone Synthesis

A. Via 1,2-Functionalization of Olefins

Typical strategies for conversion of olefins to vinyl sulfones include chlorosulfenylation/oxidation/elimination reactions, direct sulfonylation/elimination reactions,[3] and epoxidation/mercaptide opening/oxidation/elimination reactions.[4]

This strategy affords considerable control with respect to the ultimate regiochemistry of the vinyl sulfone products. Chlorosulfenylation of a conformationally defined olefin yields products resulting from trans-diaxial opening of an episulfonium ion intermediate.[5] In the case of cholest-2-ene **40**, this reaction affords β-chloro sulfide **42**.[6,7] Heating **42** at 80 °C for 1.5 h yields the diequatorial β-chloro sulfide **43**.[7] Conversely, epoxidation of **40** followed by thiolate ring opening affords β-hydroxy sulfide **44**.[8] Finally, application of the Trost hydroxysulfenylation reaction on **40** generates the opposite β-hydroxy sulfide **45**.[8] Oxidation and elimination of **42** or **45** produces the 3-(phenylsulfonyl)cholest-2-ene,[6] whereas similar treatment of **43** or **44** generates the regioisomeric 2-substituted cholestene.

Application of these principles allows a smooth synthesis of vinyl sulfone *d*-**50**, a key chiral intermediate in our cytochalasin program (see section IVB). In this instance, reaction of phenylsulfenyl chloride[6] with olefin **46**[9] affords a single β-chloro sulfide **47**,[9] which upon oxidation/elimination produces the unwanted vinyl sulfone **48** in high yield.[9,10] However, treatment of the β-hydroxy sulfide **49** (prepared from olefin **46**)[9] with *m*-chloroperoxybenzoic acid followed by dehydration with phosphorus oxychloride produces the desired racemic vinyl sulfone *dl*-**50**.[11] Furthermore, reaction of racemic alcohol **49** with (*S*)-α-phenethyl isocyanate followed by sulfide oxidation provides an exceptionally convenient entry into the chiral series because the two diastereomeric urethane–sulfones are very easily separated on large scale by simple chromatography. Treatment of each of the two diastereomers with DBU

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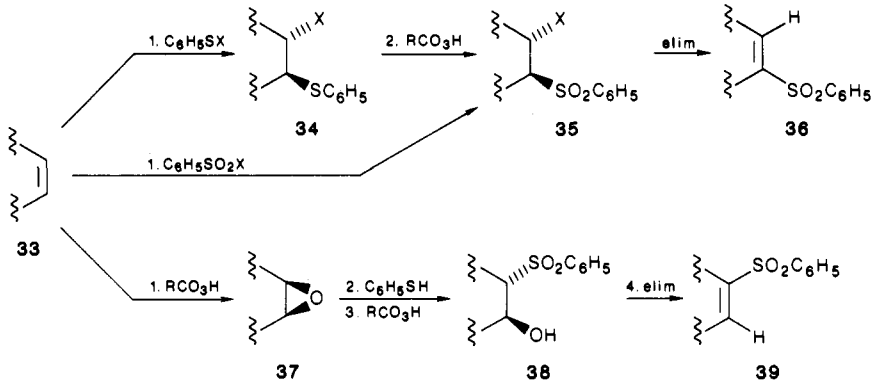

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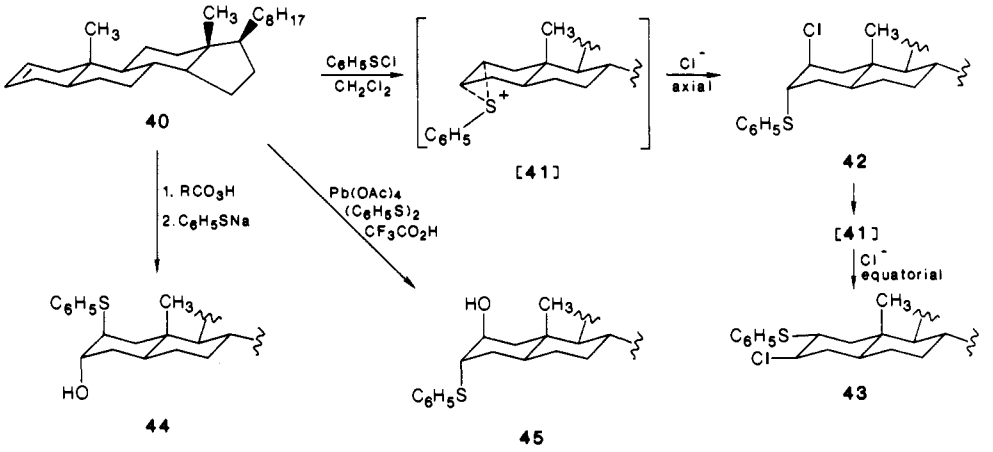

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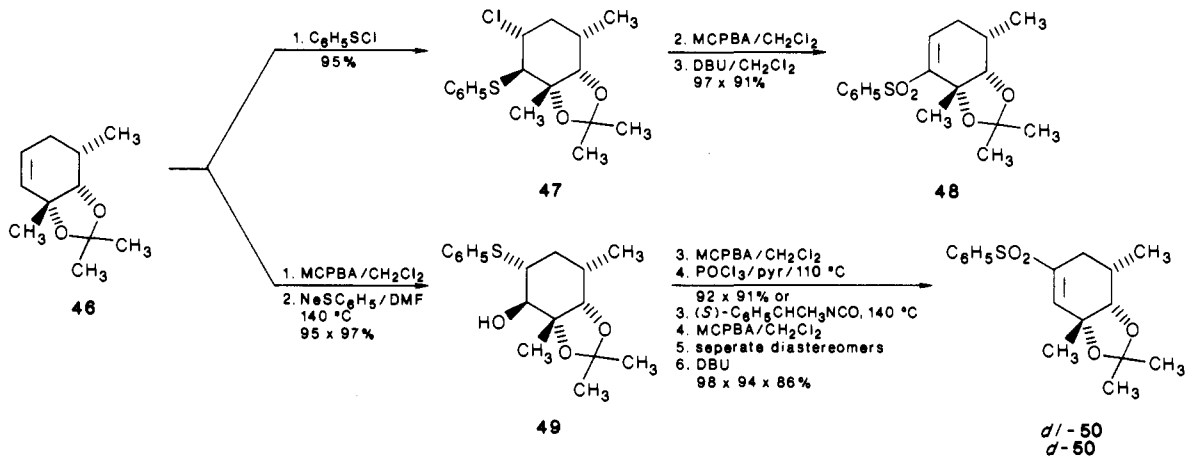

smoothly affords the individual enantiomers of vinyl sulfone **50**.[12]

B. Via 1,2-Functionalization of 1,3-Dienes[6,13-15]

Repetition of the above strategy with 1,3-dienes provides a convenient method for the synthesis of more highly functionalized vinyl sulfones. For example, chlorosulfenylation of cyclopentadiene **51** affords a 1,2-adduct which can be "frozen" by immediate oxidation to afford β-chloro sulfone **52** in 78% yield.[6,13,14] Oxidation of the olefin of **52** to diol **53**, followed by protection and elimination produces dioxygenated vinyl sulfone **54**. Alternatively, oxidation of cyclopentadiene **51** to the monoepoxide followed by addition of thiophenol and triethylamine affords the β-hydroxy sulfide *dl*-**55** (58% yield on a 5-mol scale[18]). Resolution by the method of Evans and Thomas[16] yields both enantiomers of sulfide–alcohol **55** (>65% of each).[17] Oxidation of *d*-**55** with 3 equiv of peracid smoothly provides the crystalline epoxy sulfone *d*-**56**.

Compound *d*-**56** serves as a precursor to two classes of vinyl sulfones. Activation of the hydroxyl moiety with methanesulfonyl chloride provides a monomesylate which is easily β-eliminated to epoxy vinyl sulfone *l*-**57** (80% overall). Alternatively, treatment of *d*-**56** with DBU and *tert*-butyldimethylsilyl chloride affords monosilyloxy vinyl sulfone *d*-**58** in 79% yield.

C. Via Refunctionalization Reactions

In the above synthesis, sulfide–alcohol *d*-**55** was resolved by a procedure which also produced a large quantity (1.6 mol) of the "unnatural" enantiomer *l*-**55**.

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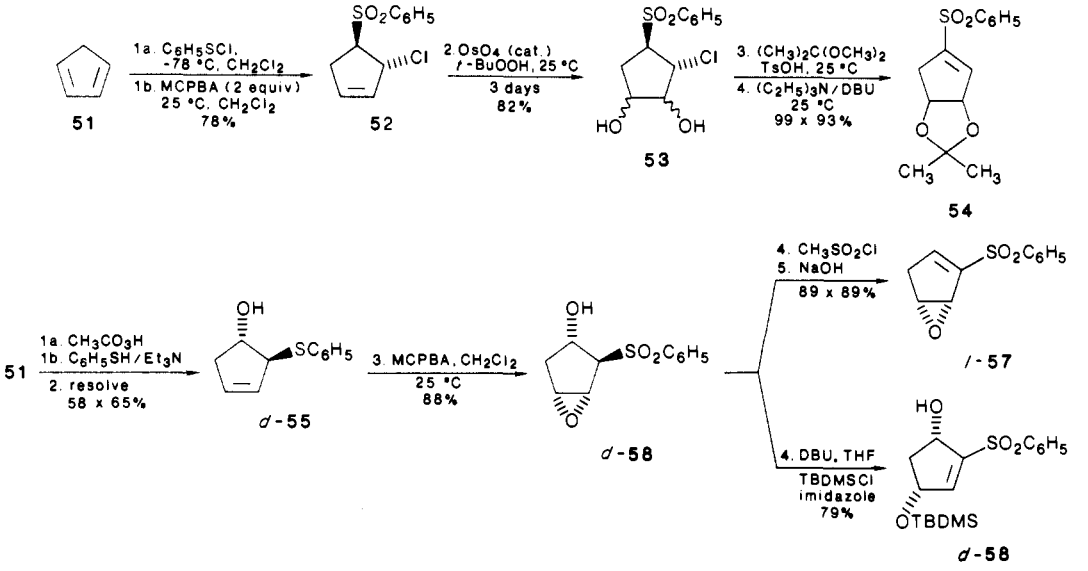

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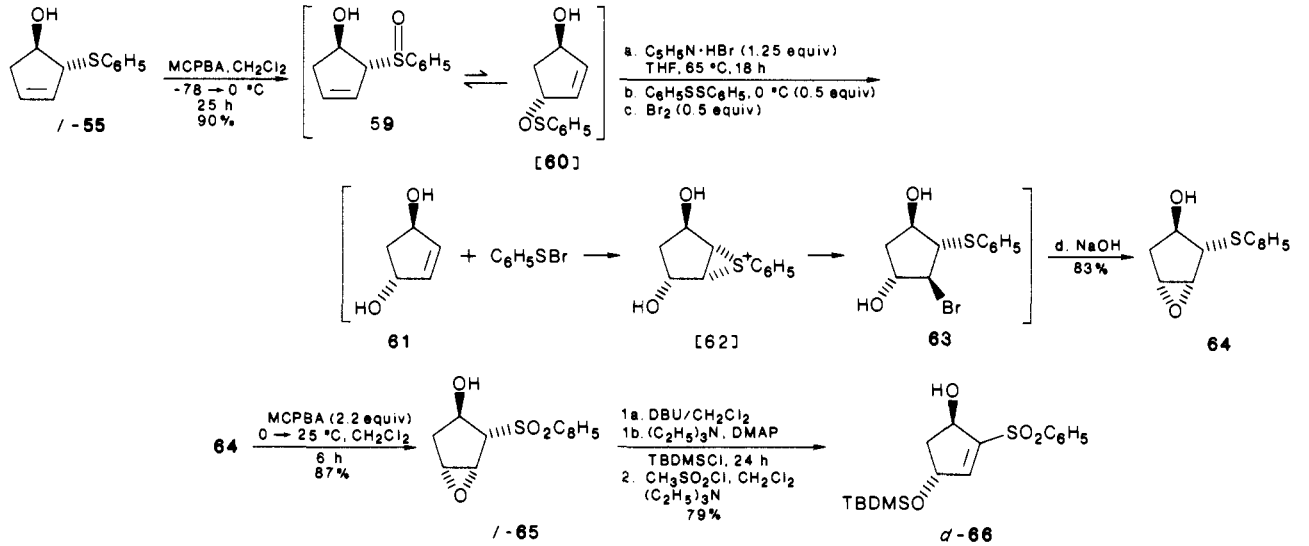

This material was converted to sulfoxide **59** which was known to be in equilibrium with sulfenate **60**.[19] Interception of sulfenate **60** with pyridine hydrobromide afforded diol **61** which was further bromosulfenylated in situ to produce unstable bromohydrin **63**. This bromohydrin was smoothly converted to epoxide **64** upon basic workup (74% yield from *l*-**55**).[20] The overall transformation is formally equivalent to a stereospecific sulfide-directed epoxidation in which the sulfur moiety has been retained in a potentially useful low oxidation state.

Oxidation of **64** produces sulfone *l*-**65** which can be converted to *d*-**66** (the trans isomer of *d*-**58**) by treatment with DBU and *tert*-butyldimethylsilyl chloride.

Sulfide–alcohol *l*-**55** can also serve as starting material for the synthesis of *either* of the enantiomers of epoxy vinyl sulfone **57**. For example, conversion of *l*-**55** via *l*-**65** to mesylate *l*-**67** followed by β-elimination affords *l*-**57**. Alternatively, alcohol-directed epoxidation followed by mesylation produces *l*-**68** which yields the enantiomeric epoxy vinyl sulfone *d*-**57** after elimination of the mesylate.[20] Thus, enantioconvergent methodology is available to provide either enantiomer of epoxy vinyl sulfone **57** from either enantiomer of sulfide–alcohol **55**.[20]

cis- and *trans*-hydroxy vinyl sulfones *d*-**58** and *d*-**66** comprise another pair of diastereomers which can be effectively converged to the same enantiomeric series. Reaction of these substrates with methanesulfonyl chloride provides mesylates **69** and **70**, respectively. Individual treatment of these two materials with dimethylamine affords the same amino vinyl sulfone *l*-**72**. Presumably this reaction proceeds via the intermediacy of **71**.[20]

Compound *l*-**72** serves as a progenitor for a pair of key substrates in our synthetic program. Quaternization of the amino moiety of *l*-**72** affords ammonium salt **73** (similarly, reaction of the *tert*-butyldiphenylsilyl analogue of *l*-**72** yields **74** which is best stored as its fluoroborate salt[21a]). Transformation of **73** to transposed vinyl sulfone *d*-**75** is smoothly accomplished by treatment with dimethylamine.[17]

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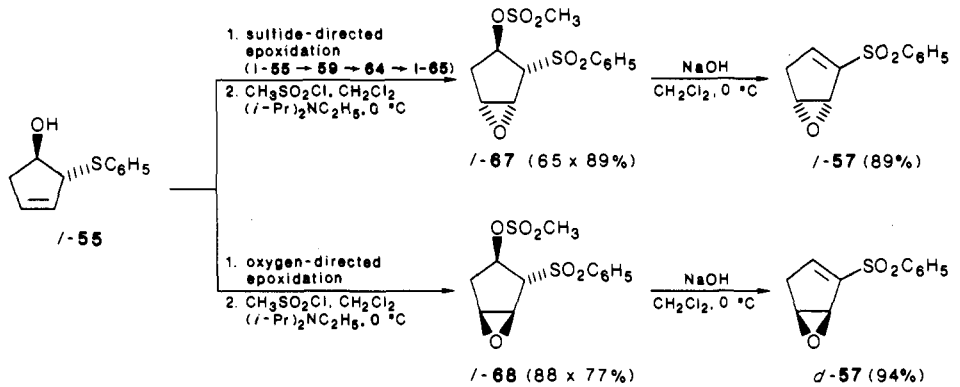

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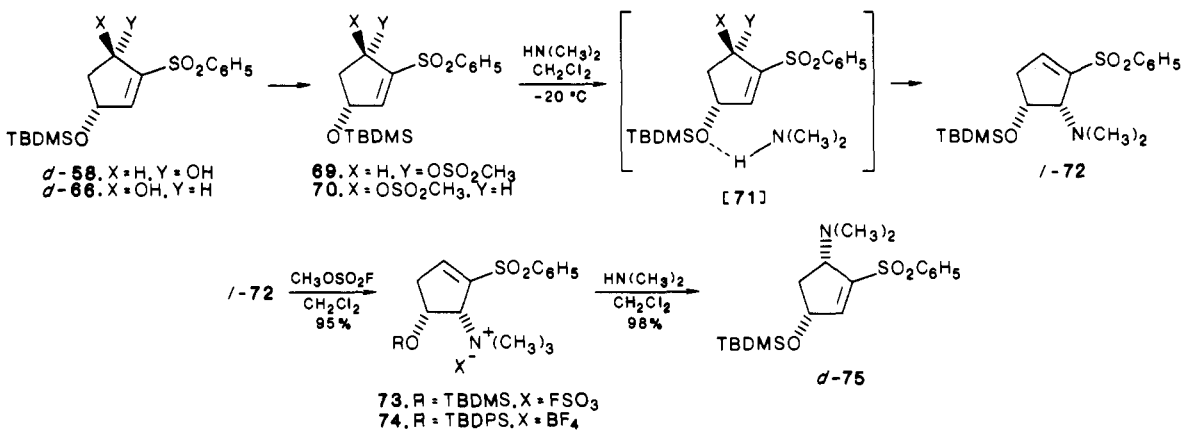

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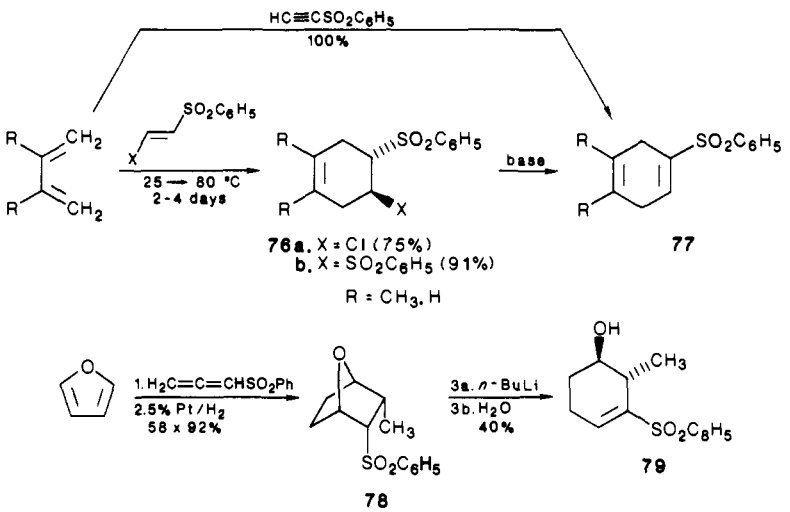

D. Via Diels–Alder Reactions

A useful strategy for synthesis of cyclohexenyl sulfones employes the Diels–Alder reaction. For example, acetylenic sulfones react with 1,3-dienes to afford the sulfone-substituted 1,4-diene **77**.[22a] Alternatively, access to the same system may be achieved in two steps by reaction of the diene with either β-chloro- or β-sulfonyl-substituted sulfonylethylenes to yield adducts **76a**[22b] or **76b**,[22c] respectively. Treatment with base converts these adducts into **77**.

A very creative application of the Diels–Alder strategy is seen in the preparation of cyclohexenyl sulfone **79**.[22d] Reaction of (phenylsulfonyl)propadiene[22d,e] with furan followed by exhaustive hydrogenation provides bridged bicyclic sulfone **78**. Exposure of this substrate to *n*-butyllithium provides vinyl sulfone **79** via β-elimination of the ether bridge.[22d]

E. Via Miscellaneous Methods

The synthesis of simple γ-oxygenated cycloalkenyl sulfones is accomplished by oxidation of the corresponding allyl sulfides **80–82** with peracid to produce β-epoxy sulfones **83–85** which may be converted to either γ-hydroxy vinyl sulfones **86–88** or γ-silyloxy vinyl sulfones **89–91**.[23–24] In practice, isolation of the γ-hydroxy vinyl sulfones is seldom undertaken, because

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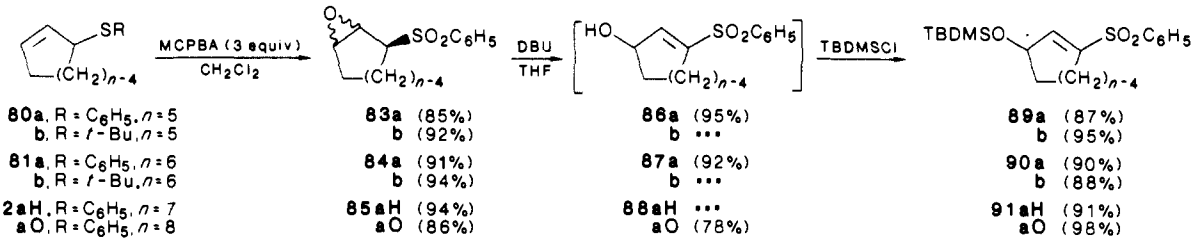

80a, R = C_6H_5, n = 5	**83a** (85%)	**86a** (95%)	**89a** (87%)
b, R = *t*-Bu, n = 5	**b** (92%)	**b** •••	**b** (95%)
81a, R = C_6H_5, n = 6	**84a** (91%)	**87a** (92%)	**90a** (90%)
b, R = *t*-Bu, n = 6	**b** (94%)	**b** •••	**b** (88%)
82aH, R = C_6H_5, n = 7	**85aH** (94%)	**88aH** •••	**91aH** (91%)
aO, R = C_6H_5, n = 8	**aO** (86%)	**aO** (78%)	**aO** (98%)

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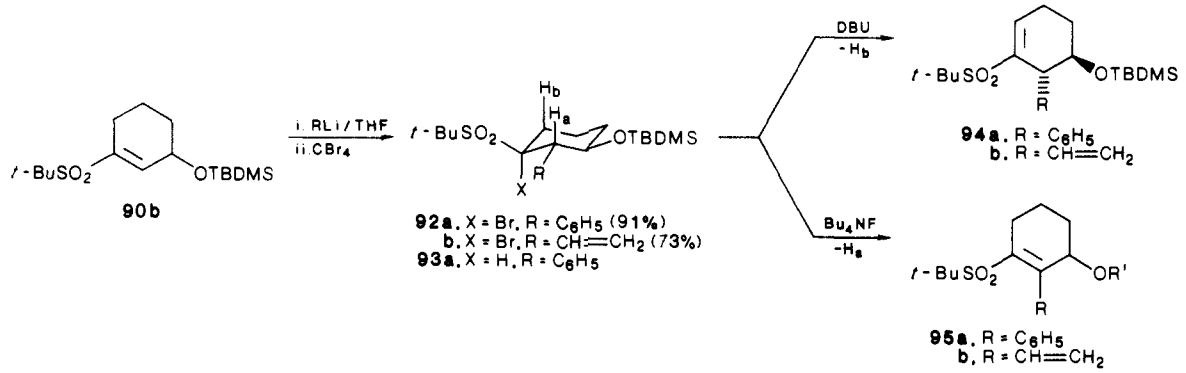

90b

92a, X = Br, R = C_6H_5 (91%)
b, X = Br, R = $CH{=}CH_2$ (73%)
93a, X = H, R = C_6H_5

94a, R = C_6H_5
b, R = $CH{=}CH_2$

95a, R = C_6H_5
b, R = $CH{=}CH_2$

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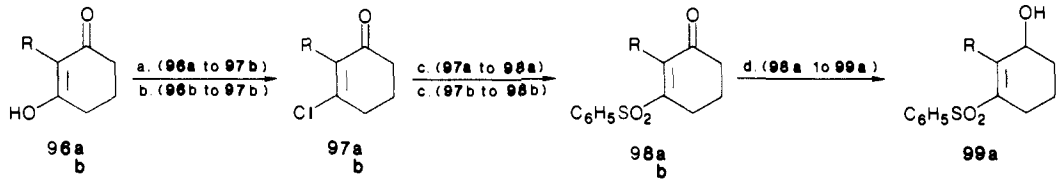

96a **b** **97a** **b** **98a** **b** **99a**

a, Ph_3P/CCl_4, 25 °C, CH_3CN (90%); b, $(COCl)_2$, $\ddagger CHCl_3$ (80%); c, $C_6H_6\ddagger$, $PhSO_2^-Na^+$, cat. $(n\text{-}Bu)_4N^+HSO_4^-$ (85-87%); d, $CeCl_3 \cdot 7H_2O$, $NaBH_4$, -20 °C, CH_3OH/CH_2Cl_2 (90%)

"a series" (R = $CH_2CH_2NCH_3SO_2C_7H_7$)
"b series" (R = $CH_2CH{=}CH_2$)

these substrates are often further utilized in situ.

The synthesis of γ-oxygenated cyclohexenyl sulfones which bear additional π-substituents in the β-position can be accomplished by a two-step halogenation/dehydrohalogenation procedure.[25] Thus, treatment of the α-sulfonyl anion (generated by conjugate addition of phenyl- or vinyllithium to vinyl sulfone **90b**) with "soft" brominating agents affords axial bromination products **92a,b**, respectively. Treatment of **92a** with a variety of bases was most revealing. Potassium *tert*-butoxide effects *reductive* debromination to afford sulfone **93a**. Reaction of **92a** with DBU produces the deconjugated vinyl sulfone **94a** with no trace of the desired product. Finally, reaction of **92a** with tetrabutylammonium fluoride yields the desired β-phenyl vinyl sulfone **95a** as a single regioisomer (99%); the same reaction with **92b** affords a 7:3 mixture of **95b**/**94b** in 65% yield.[25,26] Presumably the regiocontrol observed in the fluoride-catalyzed eliminations is a consequence of the smaller size and diminished basicity of fluoride ion relative to DBU.

A complimentary approach to β-substituted, γ-oxido vinyl sulfones is via functional group interconversion of β-diketones. For example, treatment of 2-alkylated 1,3-diones **96a**[25] and **96b**[28] with triphenylphosphine and carbon tetrachloride or oxalyl chloride affords vinylogous acid chlorides **97a,b** which undergo smooth addition–elimination reaction with sodium benzenesulfinate to produce enones **98a,b** in excellent yield. Borohydride reduction of **98a** provides the desired γ-oxido vinyl sulfone **99a**.[25,27]

III. Mechanistic and Stereochemical Aspects of Conjugate-Addition Reactions to Vinyl Sulfones

A. Additions to γ-Oxygenated Vinyl Sulfones

Addition of organolithium reagents (and several Grignard reagents) to γ-oxygenated vinyl sulfones is significantly affected by both the nature of the γ-substituent and the structure of the organometallic reagent. In general, it has been found that γ-silyloxy vinyl sulfones **89–91aH** undergo rapid conjugate addition at low temperatures to afford adducts **100** resulting from trans addition.[29] (The eight-ring substrate **91aO** is far less reactive than are the five-, six-, and seven-ring vinyl sulfones.[24]) Perhaps more striking are the conjugate additions to γ-oxido (X = Li) vinyl sulfones. Formation of product **102** apparently requires intramolecular-assisted delivery of the organometallic via the intermediacy of an alkoxide–organometallic complex **101**, thus resulting in cis stereochemistry.[24,29] In this instance the reaction temperature is typically between −20 and 0 °C. Isobe has shown that acyclic vinyl sulfones bearing a chelating γ-acetal group also afford products via a di-

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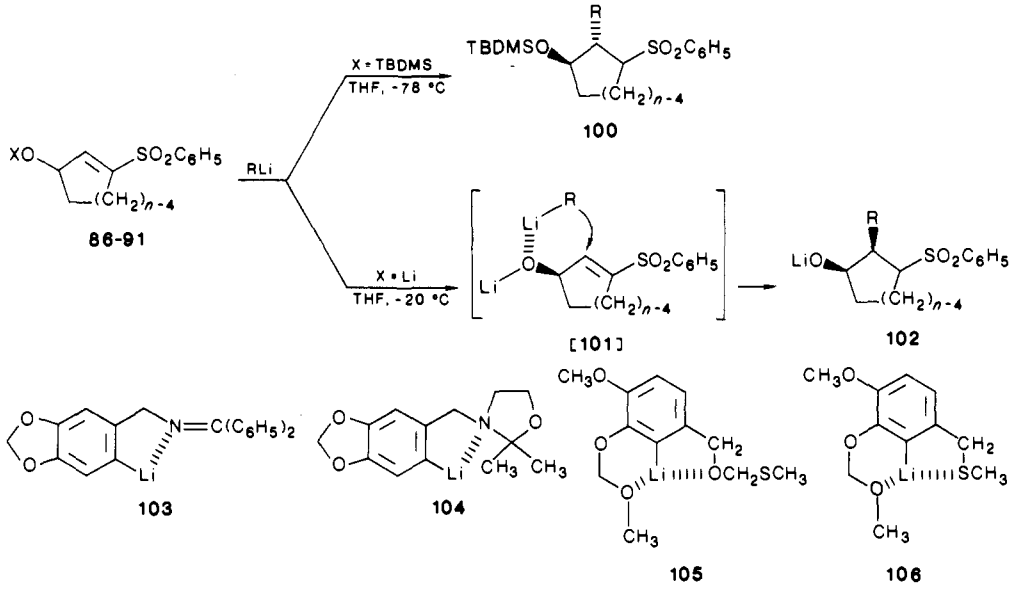

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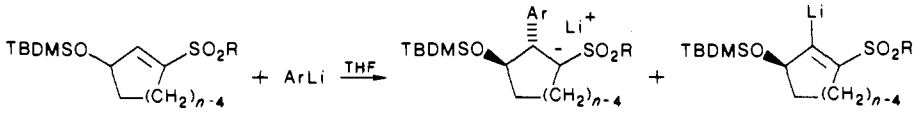


89a, $n = 5$, R = C_6H_5	103	65	35
b, $n = 5$, R = *t*-Bu	103	90	10
90a, $n = 6$, R = C_6H_5	105	25	75
b, $n = 6$, R = *t*-Bu	105	85	15

rected-addition mechanism.[30]

Consistent with the above rationale for cis addition via an alkoxide–organolithium complex is the finding that internally chelated organolithium reagents **103–106** will not undergo addition to the γ-oxido vinyl sulfones.[31,32] These reagents would not be expected to be appreciably stabilized by further complexation to the oxido moiety of the vinyl sulfone substrates. Without the intramolecular assistance provided by complex **101** the repulsion between the two species dominates in solution and the addition rate becomes impossibly slow.

B. Competition between Metalation and Conjugate Addition

Although we have examined hundreds of examples of the conjugate addition of "hard" anions to vinyl sulfones, we have only encountered serious problems with competitive deprotonation of the vinyl sulfone substrate in the case of hindered ortho- and bis-ortho-substituted aryllithium reagents.[32] For example, treatment of the cyclopentenyl phenyl sulfone **89a** with aryllithium reagent **103** affords a 2:1 mixture of addition to deprotonation (**107**/**108**). This problem is even more severe in the case of reaction of cyclohexenyl phenyl sulfone **90a** with the bis-ortho-substituted aryllithium reagent **105**, producing a 1:3 mixture of addition to deprotonation products. It should be noted that mesityllithium, another bis-ortho-substituted aryllithium reagent, is highly valued for its ability to function as a base rather than as a nucleophile.[33]

Because conjugate addition takes place perpendicular to the plane of the vinyl sulfone moiety and deprotonation occurs in the same plane, an increase in size of the sulfone group should retard deprotonation relative to conjugate addition. Consistent with this analysis, additions of aryllithium reagents **103** and **105** to cyclopentenyl and cyclohexenyl *tert*-butyl sulfones **89b** and **90b** proceed with 90% and 85% efficiency, respectively.[32]

As demonstrated above, the problem with intermolecular deprotonation being competitive with intermolecular conjugate addition is very rare. Although we have far fewer examples to compare, the problem of *intramolecular* deprotonation competing with *intramolecular* conjugate addition can be especially severe. While the reaction of aryl bromide **109a** with butyllithium affords an aryllithium intermediate (**110a**) which undergoes cyclization as the primary reaction pathway to produce intermediate (**111a**, 85%), the corresponding reaction on β-substituted vinyl sulfone **109b** undergoes intramolecular transmetalation (transfer of H_γ to the aryllithium moiety of **110b**) which produces allylic anion **112b**, thereby excluding the desired cyclization mode.[27] This balance between intramolecular addition and intramolecular deprotonation is strongly affected by conformational factors and can be successfully controlled[25,28] (see section IVf).

C. S_N2' Functionalization of β′-Substituted Cyclopentenyl Sulfones

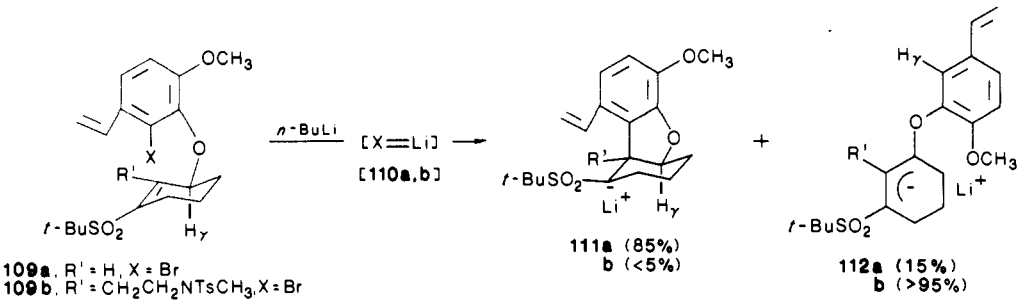
Chiral epoxy vinyl sulfone *l*-**57** can be further functionalized by treatment with nucleophilic methylating agents.[34] Reaction of *l*-**57** under conditions favoring association of the methylating agent with the epoxide

TABLE I

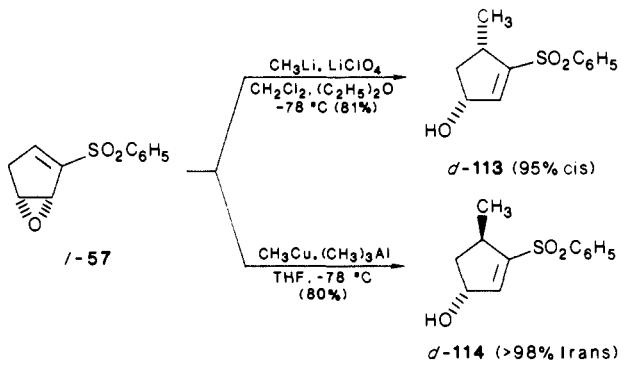
substrate	RM	conditions	product	yield	stereoselectivity[e]
115	CH_3Li	Et_2O, -10 °C, 10 min	*trans*-118a	87% × 99%[c]	1:>99
115	C_6H_5Li[a]	Et_2O, -10 °C, 10 min	*trans*-118b	77% × 91%[c]	<5:>95[d]
115	$H_2C{=}CHCH_2Li$[a]	Et_2O, -10 °C, 10 min	*trans*-118c	81% × 63%[c]	4.9:95.1
115	$H_2C{=}CHLi$[b]	Et_2O, -10 °C, 10 min	*trans*-118d	86% × 88%[c]	1:>99
115	*t*-BuLi	Et_2O, -10 °C, 10 min	*trans*-118e	46% × 85%[c]	3.6:96.4
115	$(CH_3)_3SiC{\equiv}CLi$	THF, 0 °C, 30 min	*trans*-118f	67% × 65%[c]	1:>99
74	$(CH_3)_2CuLi$	Et_2O or THF, -78 °C, 20 min	*cis*-118a	99%	98.7:1.3
74	CH_3Li	THF, -78 °C, 10 min	*cis*-118a	33%	72.8:27.2
74	CH_3CeCl_2	THF, -78 °C, 25 min	*cis*-118a	95%	97.4:2.6
74	$(C_6H_5)_2CuLi$	THF, -78 °C, 20 min	*cis*-118b	91%	>95:5[d]
74	$(CH_2{=}CHCH_2)_2CuLi$[a]	THF, -78 °C, 20 min	*cis*-118c	91%	>99:1
74	$(CH_2{=}CH)_2CuLi$[b]	THF, -78 °C, 20 min	*cis*-118d	78%	>99:1
74	$(t\text{-Bu})_2CuLi$	THF, -78 °C, 30 min	*cis*-118e	25%	96.1:3.9
74	$(CH_3)_3SiC{\equiv}CLi$	THF, -78 °C, 10 min	*cis*-118f	85%	>99:1

[a] Via transmetalation from tetraallyltin. [b] Via transmetalation from vinyltributyltin. [c] The first yield reported corresponds to the conjugate-addition reaction with 115; the second yield represents the overall yield for the alkylation/elimination reaction. [d] *trans*-118b and *cis*-118b could not be separated by HPLC; the figures given represent a minimum ratio derived from 470-MHz ^1H NMR.

SCHEME 16



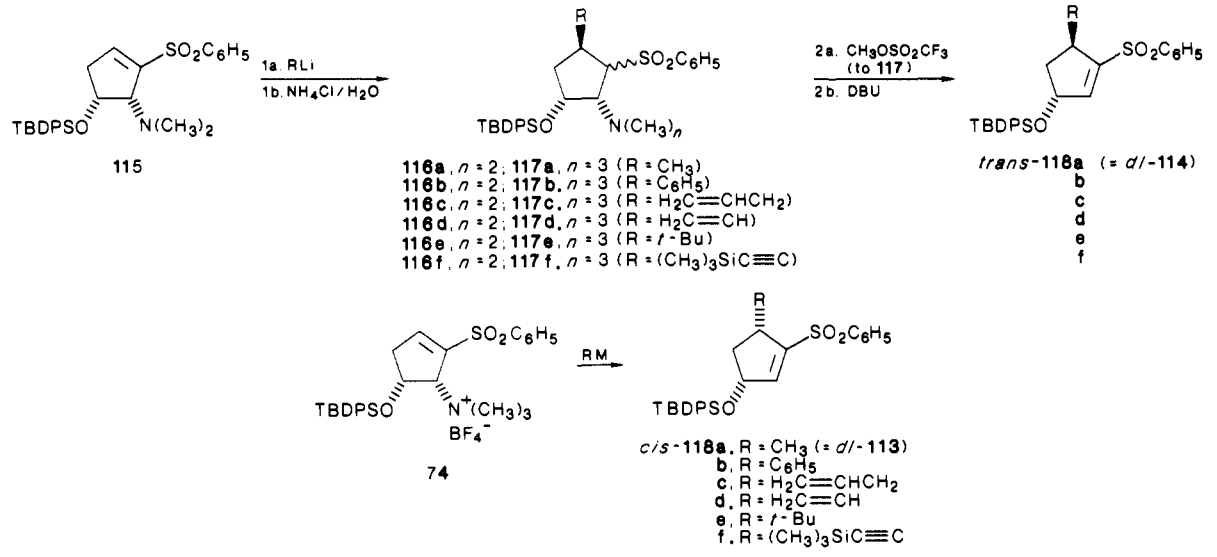
SCHEME 17



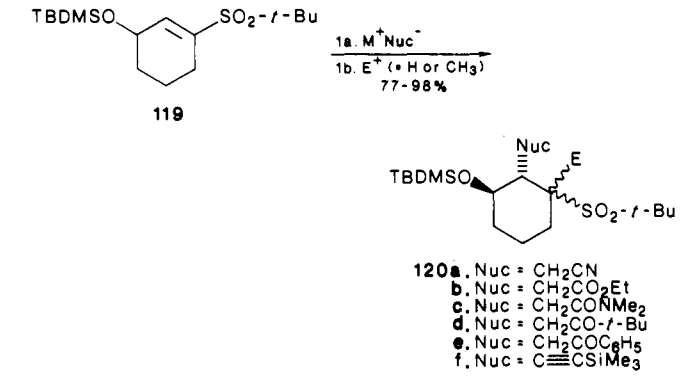
moiety produces cis adduct *d*-**113** while treatment of the same substrate under conditions where the methylating agent is expected not to be associated with the epoxy group affords trans adduct *d*-**114**.[34]

Efforts to extend this strategy to a variety of other carbon nucleophiles are not at all successful. Fortunately, an equally easily available substrate **115** (the *tert-butyldiphenylsilyl* analogue of chiral vinyl sulfone *l*-**73**) provides a general solution to this problem.[21] For example, reaction of amino vinyl sulfone **115** with a variety (see Table I) of organolithium reagents affords adducts **116a–f** which can be quaternized to produce ammonium salts **117a–f**. Treatment of these ammo-

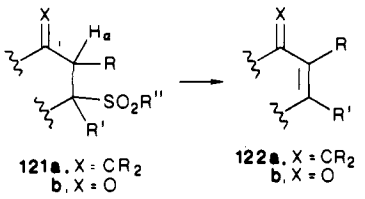
SCHEME 18



SCHEME 19



SCHEME 20



nium salts with DBU smoothly generates vinyl sulfones *trans*-**118a–f** with excellent stereocontrol. More importantly, the ammonium salt **74** derived from **115** reacts with "soft" organometallic reagents (see Table I) to directly afford *cis*-**118a–f**.[21]

D. Additions of Moderately Soft Anions to a Vinyl Sulfone

Since our overall goal is to further functionalize α-sulfonyl anions produced by the conjugate addition to vinyl sulfones, our early synthetic studies had been guided by the dictum that only anions having pK_a values greater than 25 would be expected to undergo facile addition to the vinyl sulfone moiety. Recent results suggest that under appropriate conditions, "softer" anions such as those derived from nitriles, esters, amides, ketones, and acetylenes undergo efficient addition to vinyl sulfones. Examples of these reactions are seen in the **119** to **120a–f** transformation. A significant observation in this study is that the *potassium* counterion is essential in many cases to provide useful reaction rates.[35]

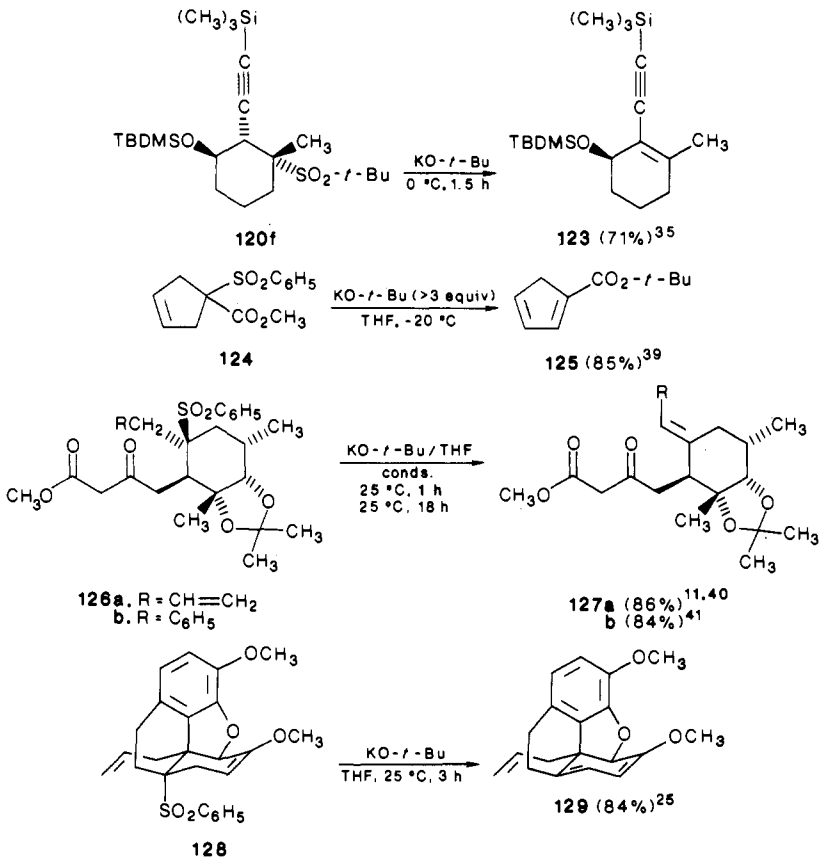
E. 1,2-Eliminations of Sulfinic Acid To Afford Olefins

Although examples of base-catalyzed and thermal eliminations of simple nonactivated sulfones are known,[36] the reaction is currently of synthetic significance only in those cases in which the hydrogen β to the sulfone moiety is activated by the presence of an adjacent π-system, typically a ketone or olefin group. Thus, treatment of a homoallylic sulfone (**121a**) or a β-sulfonyl ketone (**121b**) with base usually smoothly affords a 1,3-diene (**122a**)[37] or an enone (**122b**),[38] respectively.

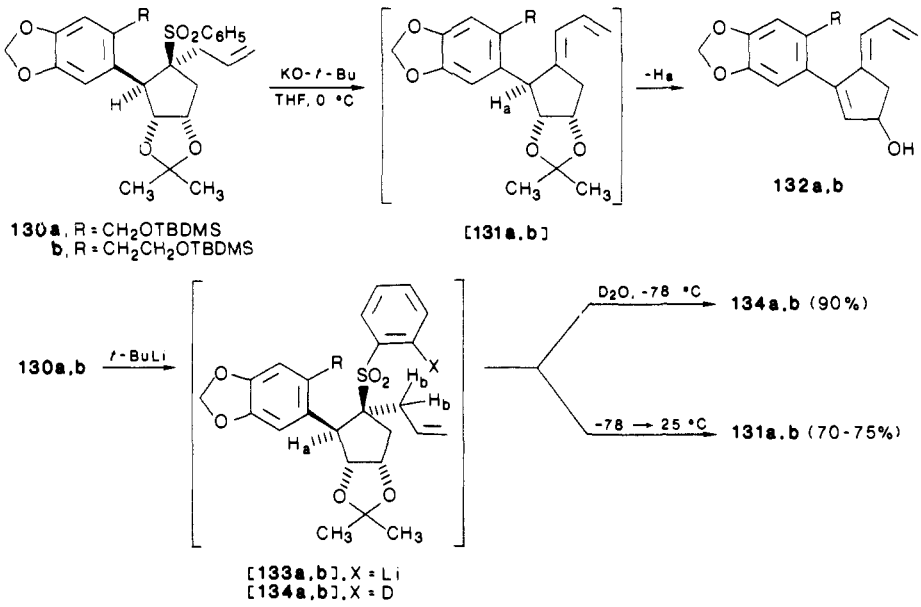
The standard conditions to effect the olefin-forming reaction[37] employ potassium *tert*-butoxide, a reagent which is generally compatible with a reasonably large range of functional groups. Examples of this reaction involving homopropargyl, homoallyl, and homobenzyl sulfones are shown in the following scheme.

We have observed several instances where the above olefin forming reaction fails. For example, treatment of acetonide **130a,b** with potassium *tert*-butoxide affords the unstable trienyl alcohols **132a,b** in very low

SCHEME 21



SCHEME 22



yield. Presumably the desired product **131a,b** undergoes further elimination of the acetonide moiety because of the activated nature of H_a.[42]

In an effort to deal with the above problem, we sought an alternative strategy for elimination of the sulfone moiety. Since it was well-known that directed metalation of aryl sulfones with organolithium reagents affords ortho lithio sulfones,[43] we felt that metalation of homoallyl sulfones **130a,b** would afford intermediates **133a,b**, which could undergo "self-immolative" intramolecular metalation (with removal of the geometrically more accessable proton H_b) to afford the desired dienes **131a,b**. Treatment of **130a,b** with excess *tert*-butyllithium affords the desired intermediates [**133a,b**] as evidenced by recovery of ortho-deuterated sulfones **134a,b** in high yield by quenching the reaction with D_2O at low temperature. Replacement of the quenching step by warming to room temperature produces the desired dienes **131a,b** in yields of 70–75%.[42]

IV. Synthetic Applications of the Vinyl Sulfone Strategy

A. Synthesis of Highly Functionalized α,β-Unsaturated Cyclic Ketones[14,18,23,32,34,45]

Conjugate addition of aryl anions **135a–c** to vinyl sulfone **89b** followed by treatment of the resultant α-sulfonyl anion with 3-silyloxypropyl iodide **136** and deprotection of the primary isopropyldimethylsilyl ether affords triply converged adducts **137a–c** in 68–86% overall yield.[14] Activation and displacement of the primary alcohol smoothly affords the corresponding primary azides which are desilylated, oxidized, and treated with base to effect β-elimination of the sulfone moiety, thus generating enones **138a–c** in a four-step overall yield of 66–68%.[14]

An even more streamlined version of this strategy utilizes the dioxygenated vinyl sulfone **54** as substrate. Conjugate addition of aryl anion **135b**, followed by alkylation with iodopropyl azide **139**, and subsequent acetonide removal provides diol **140** (68% overall). Bis oxidation of this diol with the sulfur trioxide–pyridine complex affords enolized dione **141** in 75% yield.[14]

Chiral reactants extend the versatility of this enone synthesis. Addition of the heteroallyl anions *d*-**143**[34] and *l*-**144**[44] to vinyl sulfones *l*-**114** and *l*-**142** affords the chiral enones *l*-**145**[34] and *l*-**146**[18] after oxidation and elimination.

As can be seen in the following scheme, combining the nucleophile and electrophile into a single structure, the ((β-bromoethyl)aryl)lithium reagent **147** provides an effective annulation sequence affording tricyclic adducts **148a,b** in very good yield.[45] Deprotection, oxidation, and β-elimination of the sulfone moiety then completes the construction of the dihydronaphthalene-fused cycloalkanones **149a,b** in 68–70% yield.[45]

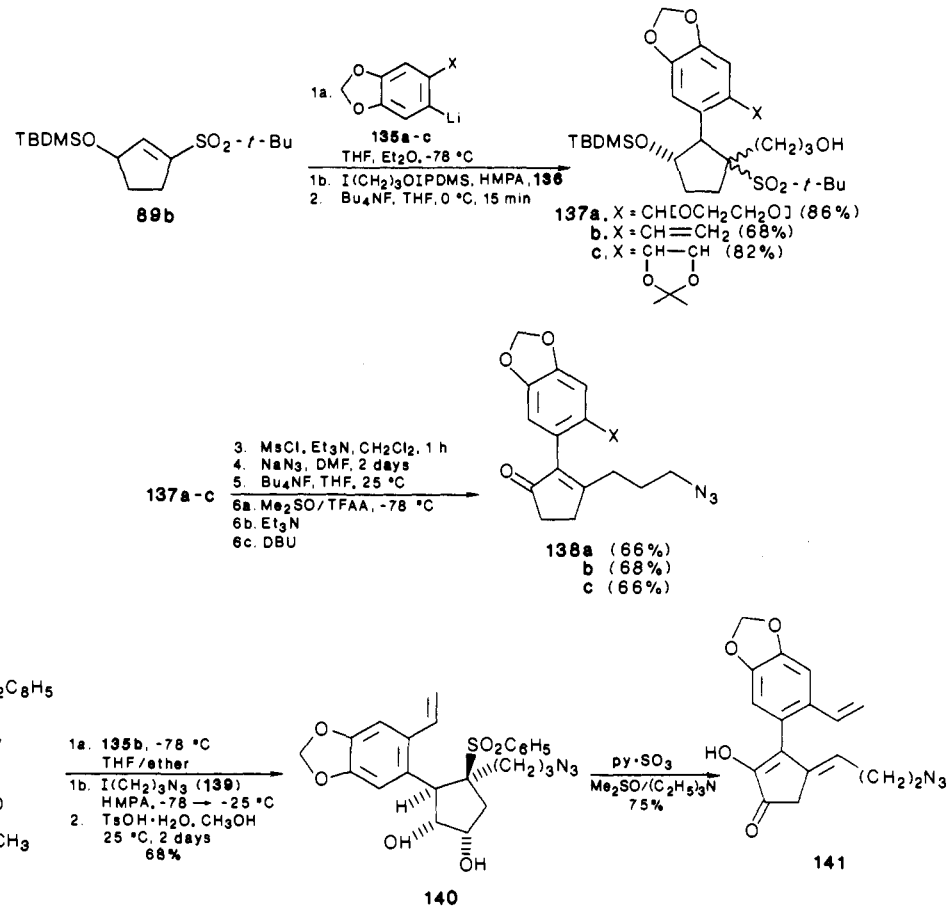
B. Synthesis of a Chiral Cytochalasin C Intermediate[9,11,40,46,47]

The triply convergent strategy comprises a central theme in our cytochalasin program. Addition of dipotassium methyl acetoacetate dianion (the dilithium reagent is not sufficiently reactive to undergo effective addition with the γ,γ-disubstituted vinyl sulfone) to *d*-**50** followed by subsequent reaction with allyl bromide affords adduct **126a** in over 90% yield.[11] Treatment of homoallyl sulfone **126a** with potassium *tert*-butoxide affords **127** as described in section IIIE. Transamidation of this material with chiral dienyl amine *d*-**150**[46,47] provides β-keto amide **151** in 90% yield.[40] Reaction of **151** with methyl glyoxylate followed by acylation and elimination of the aldol adduct provides amide **153** in a highly satisfying yield of 97%.[40] This cyclization employs a seldom-used variant of the intramolecular Diels–Alder reaction, that of using a (*Z*)-diene.[11,40,46,47] As can be seen from transition-state [**152**], the C3–C4 stereochemistry is determined by the asymmetric center at C3 (diastereofacial selectivity), while the C4–C9 selectivity is enforced by the lack of an alternate exo transition state.

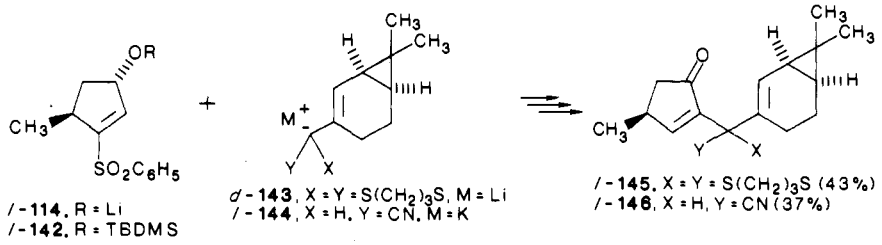
C. Total Synthesis of *l*-(−)-Prostaglandin E_2[17]

Vinyl sulfone *d*-**75**, which had been prepared in >40% overall yield by the enantioconvergent metho-

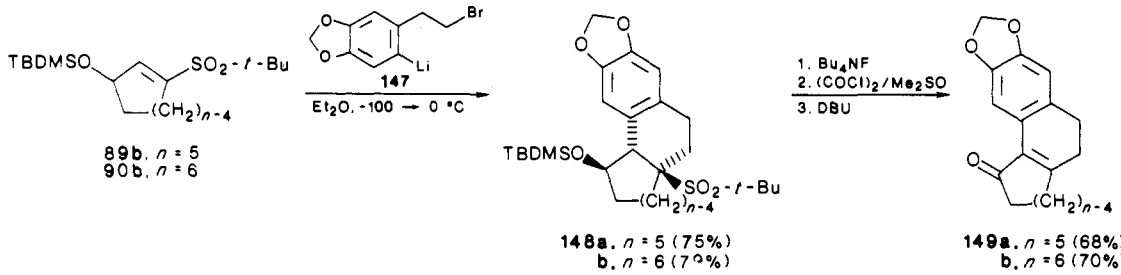
SCHEME 23



SCHEME 24

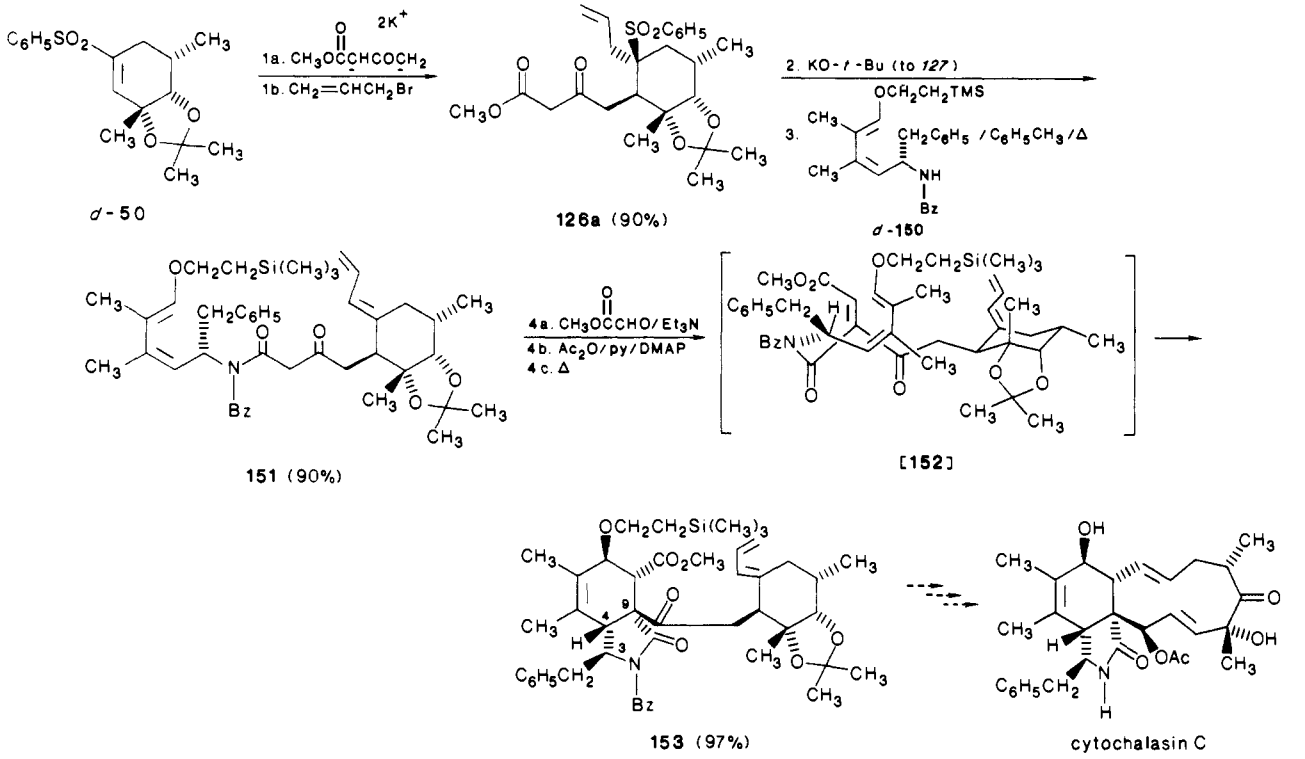


SCHEME 25

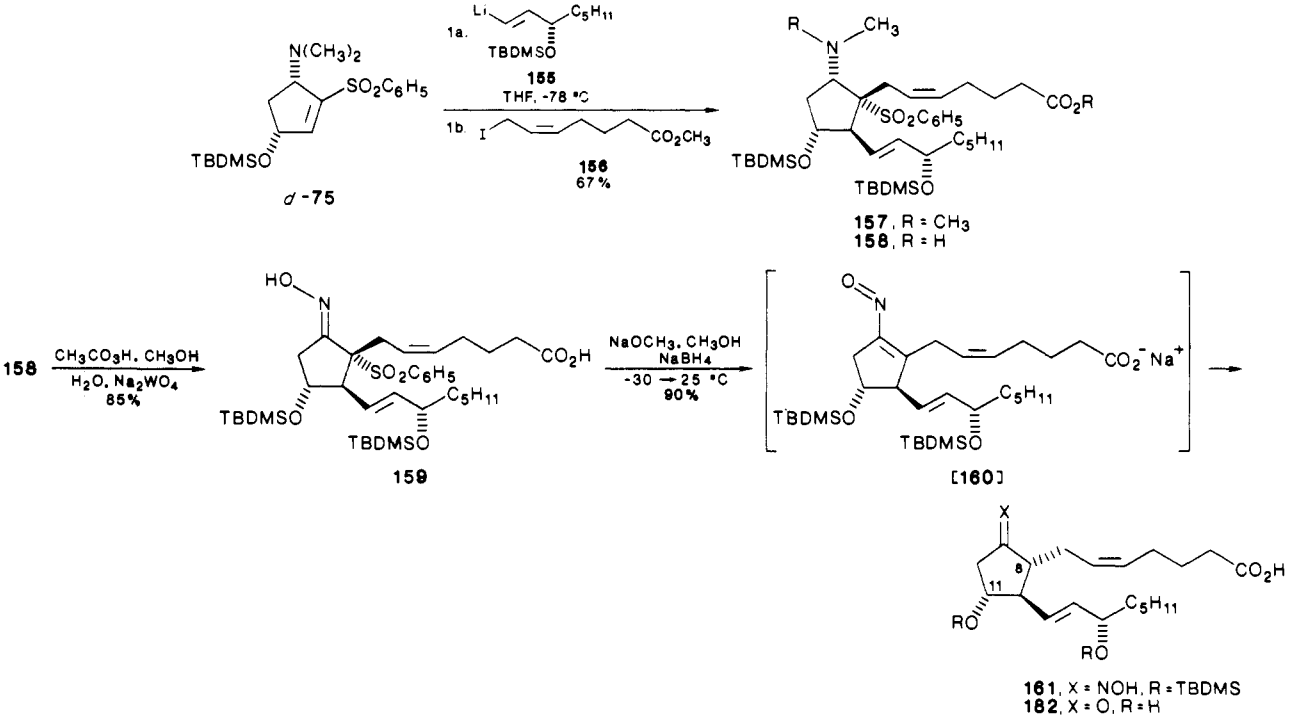


dology previously described in sections IIB and IIC, served as the pivotal component in our synthesis of PGE_2. Treatment of this material (75-mmol scale) with the chiral vinyl anion **155** at −78 °C followed by subsequent alkylation with allyl iodide **156** provides 67% of the nicely crystalline sulfone **157**.[17] Conversion of this material to the secondary amino carboxylic acid **158** was smoothly accomplished by dealkylation [(trichloroethyl)urethane] and saponification (87.5% overall). Oxidation of amine **158** yields oxime **159** which was suitably functionalized for stereospecific establishment of the carboxylic acid bearing side chain. Cautious treatment of this oxime with sodium methoxide in the presence of excess borohydride provides desulfonylated oxime **161** as a single C-8 stereoisomer. Presumably this reaction occurs via hydride conjugate addition to vinyl nitroso intermediate [**160**]. The stereocontrol being elicited by virtue of the hydrophobic C-11 silyloxy moiety shielding the α-face in methanol solution. Final conversion of **161** to PGE_2 **162** was accomplished by reaction with aqueous formaldehyde in the presence of boron trifluoride. The *overall yield for this process*,

SCHEME 26



SCHEME 27

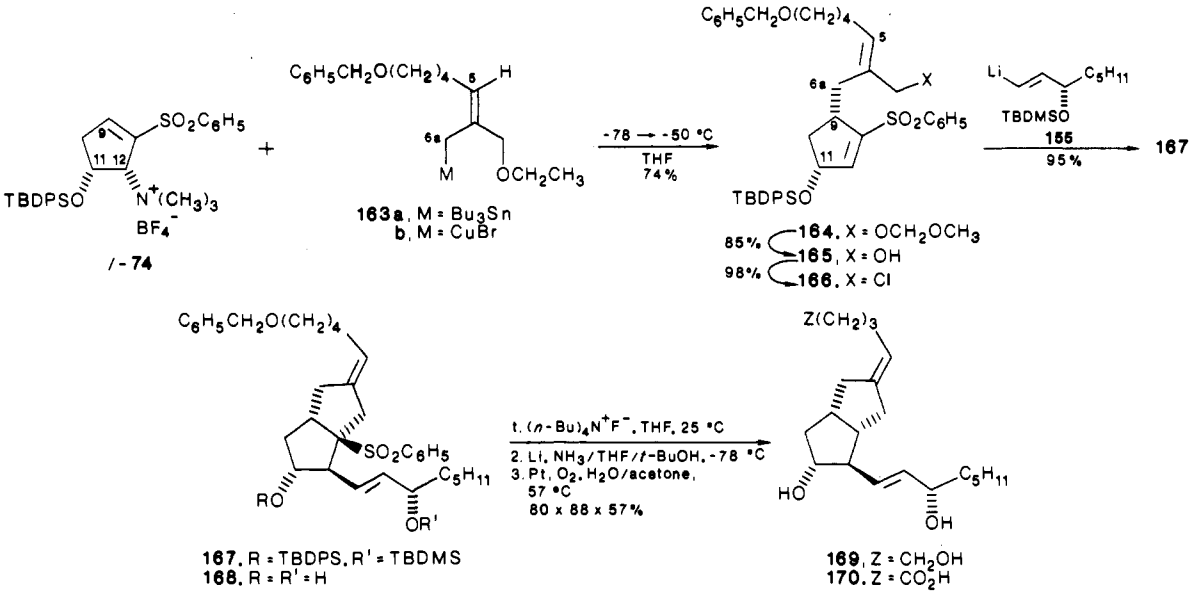


including the resolution steps, was 13%.[17]

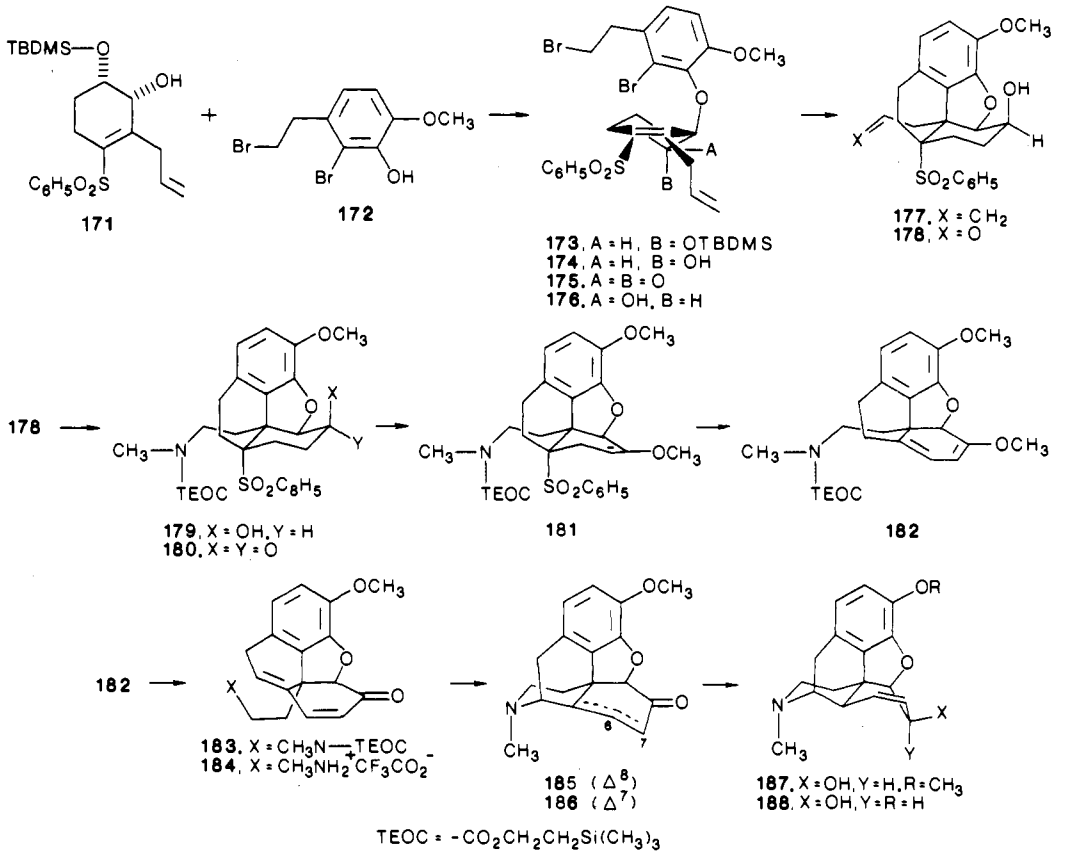
D. Synthesis of *d*-(+)-Carbacyclin[48]

Treatment of chiral allylammonium salt *l*-**74** with bromocuprate reagent **163b** (which is in turn readily prepared by sequential reaction of allyl stannane **163a** with *n*-butyllithium and cuprous bromide–dimethyl sulfide complex in the presence of lithium bromide) affords vinyl sulfone **164** in 74% yield. (See section IIIC for additional S_N2' reactions of allyl sulfone **74**.) It should be noted that this reaction simultaneously controls two stereocenters (C9,11 and olefin geometry) and two regiocenters (C9 vs. C12 and C5 vs. C6a) in a single step! Deprotection of the acetal moiety of **164** yields alcohol **165** which undergoes smooth conversion to allyl chloride **166** (83% overall). Reaction of this substrate with **155**, the same chiral vinyllithium reagent employed in the above PGE_2 synthesis, affords bicyclooctyl sulfone **167** in 95% yield. Completion of the synthesis is accomplished by bis desilylation (to **167**), Birch reduction (effecting desulfonylation concurrently with debenzylation to provide **169**), and selective oxidation of the primary alcohol moiety to afford *d*-(+)-carbacy-

SCHEME 28



SCHEME 29



clin **170** in 5.1% overall yield.[48] The best previously reported yield for total synthesis of chiral carbacyclin is 1.3%.[49]

E. Total Synthesis of *dl*-Morphine[25,28]

Coupling of phenol **172** with alcohol **171** (both available in 40% overall yields from readily available starting materials) affords *trans*-aryloxy silyl ether **173** which is smoothly desilylated to alcohol **174** in 80% overall yield. Oxidation (to **175**) and reduction provides cis alcohol **176** in 90% yield. Treatment of alcohol **176** with 2.2 equiv of *n*-butyllithium in THF at −78 °C followed by warming and quenching with ammonium chloride provides tetracyclic sulfone **177** as a beautiful crystalline material (57%).

Catalytic osmylation of **177** followed by lead tetraacetate cleavage of the resulting diols affords aldehyde **178** in 85% overall yield. Reaction of **178** with methylamine hydrochloride and sodium cyanoborohydride in methanol followed by acylation of the resultant secondary amine with [((trimethylsilyl)ethyl)oxy]-chloroformate (TEOC–Cl) provides urethane **179** in 85% yield for the two-step process. Swern oxidation of the secondary alcohol followed by treatment of the resulting ketone **180** with trimethyl orthoformate in

acidic methanol affords enol ether **181** (75% overall). Reaction of **178** with potassium *tert*-butoxide in THF at room temperature smoothly affords dienyl ether **182** in 85% yield. Oxidation of this material with DDQ provided the racemic TEOC–dienone **183** (40%) which was identical in all respects (except rotation) with an authentic sample prepared from natural thebaine.[50] Deacylation of **183** followed by neutralization of the resultant dienone–ammonium salt **184** affords a mixture of neopinone **185** and codeinone **186** in 63% yield.[50] Further isomerization of the neopinone to codeinone was accomplished by the method of Rapoport.[51] Sodium borohydride reduction[52] of codeinone **186** to codeine **187** (95%) followed by demethylation[53] affords racemic morphine **188** (50%). Thus, the overall yield of morphine **188** from 2-allylcyclohexane-1,3-dione and isovanillin (precursors of **171** and **172**) was 1.1%.[25,28]

V. Conclusion

This review explores various aspects of the chemistry of conjugate-addition reactions to vinyl sulfones. The ability of this functional group to serve as a substrate for the execution of multiply convergent syntheses promises considerable potential for future applications.

Acknowledgments. P.L.F. wishes to express his appreciation to the superb group of research associates who are named as coauthors in the papers cited in this review. Special thanks are due to the "vinyl sulfone team" whose primary research focus was the development and application of the vinyl sulfone strategy; this group includes P. C. Conrad, R. E. Donaldson, J. C. Saddler, D. L. Barton, P. R. Hamann, P. L. Kwiatkowski, T. F. Braish, D. K. Hutchinson, J. E. Toth, S. A. Hardinger, X. Radisson, and T. P. Burkholder. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (PRF 9941-AC1; PRF 11617-AC1; PRF 13341-AC1). We also thank the National Institutes of Health for their continuing support of this program (NIH CA 19689; NIH GM 32693).

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