

The Development and Use of Ketene Equivalents in [4+2] Cycloadditions for Organic Synthesis

Varinder K. Aggarwal*, Amjad Ali and Michael P. Coogan

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF, United Kingdom.

E-mail: V.Aggarwal@Sheffield.ac.uk; fax: 44 (0)114 2738673

Received 30 September 1998

Key words: ketene equivalents, [4+2] cycloaddition, enantiomerically pure bicyclic ketones

Contents

1.	Introduction and Scope	293
2.	Mechanistic Considerations	294
3.	Captodative Olefins as Ketene Equivalents	294
	(i) α -Substituted acrylonitriles	294
	(a) α -Acetoxyacrylonitrile	294
	(b) α -Chloroacrylonitrile	296
	(c) α -Alkylthio and α -alkylaminoacrylonitriles	297
	(ii) α -Substituted acrylates	297
	(a) 2-Alkyl-5-methylene-1,3-dioxolan-4-ones	297
	(b) α -Amidoacrylates	298
4.	Sulfoxides	299
	(a) α,β -Unsaturated sulfoxides	299
	(b) Vinyl sulfonium salts	301
5.	Sulfones and Sulfonates	302
6.	Vinyl Sulfoximines	303
7.	Allenes	303
8.	Miscellaneous	304
	(a) Vinyl boranes	304
	(b) Selenoacetylenes	305
9.	Ketene Equivalents in Natural Product Synthesis	305
10.	Conclusions	307

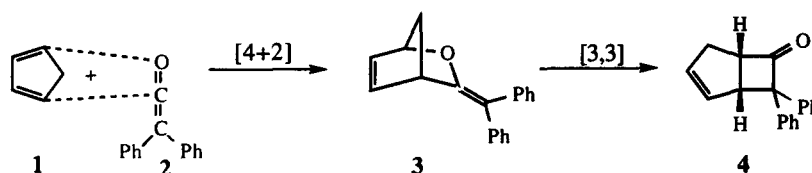
1) Introduction and Scope

The inability of ketenes to undergo satisfactory [4+2] cycloadditions with 1,3 dienes has been established since the pioneering work of Staudinger in the early 1910s.¹⁻⁴ In recent years the attention paid to ketene equivalents has increased dramatically⁴⁻⁸ culminating in the advent of chiral ketene equivalents.⁹

The first reports of chiral ketene equivalents (based on α , β -unsaturated sulfoxides) were received in the early 1980s. Since then chiral ketene equivalents have received much attention. Many of the examples reported herein involve vinyl sulfoxides,¹⁰ which offer high levels of diastereocontrol and ease of conversion to the carbonyl group. What follows is a survey of the literature up to the end of 1997 with emphasis given to novel chiral ketene equivalents and especially their applications in Diels-Alder reactions. Earlier non-chiral methods were reviewed comprehensively by Ranganathan⁵ through to the end of 1977 and so the discussion on non-chiral methods will be selective, focusing on α -acrylonitrile derivatives not presented in that review.

2) Mechanistic Considerations

The current state of mechanistic theory regarding ketene [2+2] vs [4+2] has been highlighted recently by Yamabe,¹¹ who has shown by a series of *ab initio* calculations¹² that for the reaction of ketene **2** with **1**, the [4+2] addition is calculated to have the smallest activation energy amongst all the computationally obtained cycloadditions. This work has led to a new proposal by Yamabe¹¹ that ketenes undergo a two-step reaction mechanism with 1,3 cyclopentadiene: initial [4+2] cycloaddition at low temperature followed by [3,3] sigmatropic rearrangement (Scheme 1) to give the cyclobutanone **4**.



Scheme 1

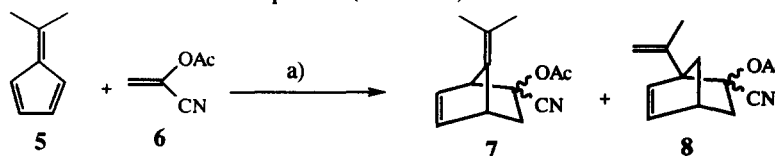
Validation for these theoretical studies has been provided by experimental studies leading most recently to the spectroscopic observation of the [4+2] adduct **3** at low temperature.¹¹

3) Captodative Olefins as Ketene Equivalents

(i) α -Substituted Acrylonitriles

a) α -Acetoxyacrylonitrile

The first example of a ketene equivalent was reported in 1956 by Bartlett,¹³ and involved the reaction of α -acetoxyacrylonitrile with cyclopentadiene. Although satisfactory yields of the ketene adduct were obtained, subsequent conversion to the ketone required forcing conditions (NaOH, reflux, 100°C). Another limitation of α -acetoxyacrylonitrile is its long reaction times (the reaction with 6,6-dimethylfulvene, for example, is reported to take 15 days to completion).¹⁴ Oku *et. al.*, however, have reported that pyridine can be used as an effective promoter in the reaction of fulvene with α -acetoxyacrylonitrile (Scheme 2).¹⁵ The modest yields previously reported for this reaction¹⁴ were greatly improved as a result of the addition of pyridine and, furthermore, the formation of the unwanted adduct **8** was suppressed (Scheme 2)

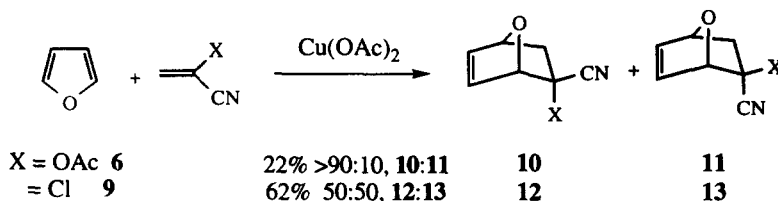


Reagents: a) pyridine (0.5 eq), 70°C, 28 h, **7** 80%, **8** 0%

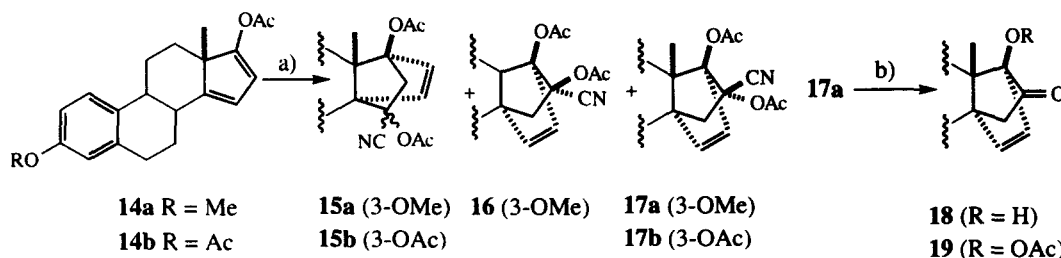
Scheme 2

Lewis acids (in particular Cu(I) and Cu(II) catalysts) also promote the Diels-Alder reactions of α -acetoxyacrylonitrile and α -chloroacrylonitrile giving cycloadducts in 20–62% yield with furan (Scheme 3).¹⁶ The highest yields were obtained with the more reactive dienophile^{17–25} α -chloroacrylonitrile.

α -Acetoxyacrylonitrile was used in the synthesis of a range of 16-functionalized 14 α , 17 α -ethano-19-norsteroids.²⁶ The cycloaddition to the dienyl acetate **14a** initially gave a complex mixture of cycloadducts **15a** (13%), **16** (4%) and **17a** (32%). Optimisation (Scheme 4) gave an 81% yield of a single cycloadduct **17a** together with 16% starting material.



Scheme 3



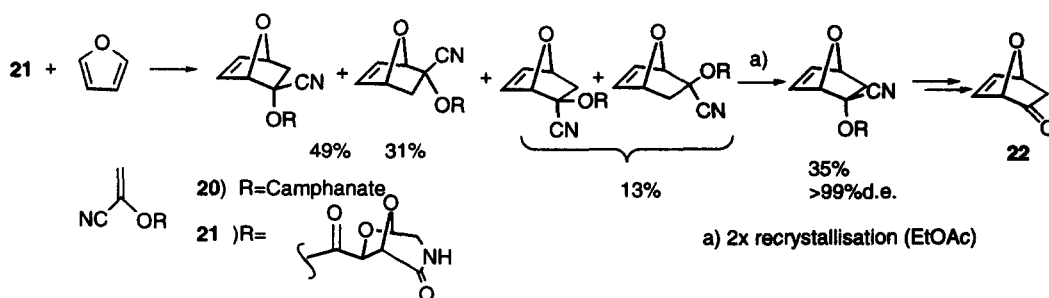
Reagents: a) $\text{H}_2\text{C}=\text{C}(\text{OAc})\text{CN}$, 100–180° C; b) KOH, H_2O , DMSO, THF, 0° C

Scheme 4

Alkaline hydrolysis of **17a** furnished the 17 β hydroxy 16-ketone **18** (Scheme 4) in excellent yield (82%).

Chiral α -acyloxyacetonitriles

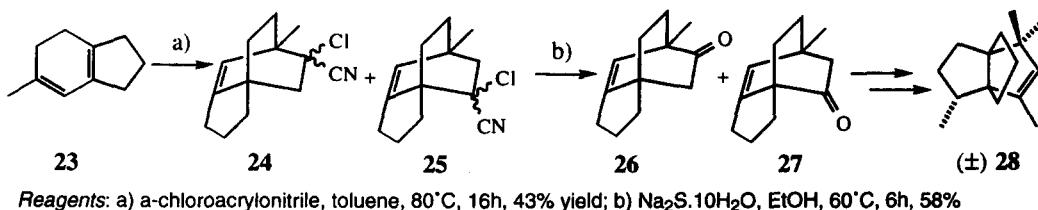
Vogel has developed a class of chiral acetoxyacetonitrile analogues. Their Diels-Alder reactions with furan provide (after recrystallisation) single isomers of compounds which have been referred to as "naked sugars" due to their ability to act as synthons for hexoses, whilst lower in functional density. Two systems have been used, one based upon camphanates²⁷ **20** and an improved analogue bearing a tartrate-derived chiral auxiliary **21**.²⁸ Although the diastereoselectivities in the Diels-Alder reaction are moderate, diastereomerically pure products are readily obtainable *via* recrystallisation. The ketone functionality is realised by mild saponification to recover the chiral auxiliary and furnish optically pure (-)-7-oxabicyclo[2.2.1]hept-5-en-2-one **22** (Scheme 5), which was subsequently elaborated to a range of sugars and nucleosides.



Scheme 5

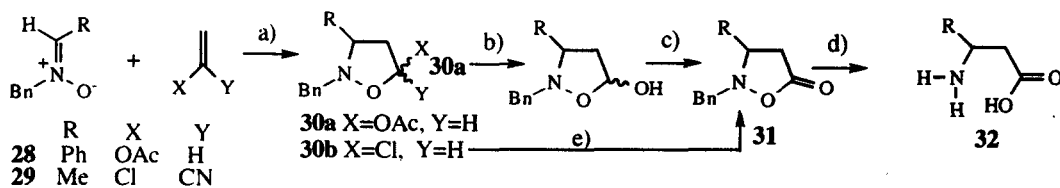
3 (i) (b) α -Chloroacrylonitrile

The versatility of α -chloroacrylonitrile as a ketene equivalent is demonstrated in the construction of the [3.3.3] propellane and tricyclo [5.3.1.0]^{4,11} undecane ring systems. Mehta and coworkers have shown in studies directed towards the total synthesis of the sesquiterpene (\pm)- modiphene **28** that α -chloroacrylonitrile is superior to nitroethylene as a ketene equivalent, particularly in terms of ease of conversion to the carbonyl compound.²⁹ Thus, diene **23** was subjected to cycloaddition in the presence of α -chloroacrylonitrile to afford a mixture of the adducts **24** and **25** in 40% yield (Scheme 9). Conversion to the carbonyl functionality proved trouble free using Evans methodology (sodium sulfide nonahydrate in refluxing ethanol)³⁰ giving a mixture of β,γ unsaturated ketones **26** and **27** (58% yield) in a 4:1 ratio, respectively (Scheme 6).



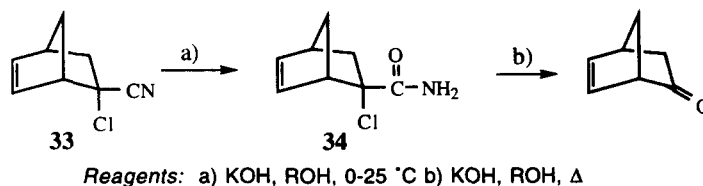
Scheme 6

The syntheses of β -amino acids (including asymmetric syntheses using α -methylbenzyl instead of benzyl), *via* nitron cycloaddition to ketene equivalents including α -chloroacrylonitrile have been reported by Overton.³¹ The reaction is significant in that the cycloadducts are easily converted (by hydrolysis either directly to the isoxazolidinone, or *via* the lactol and oxidation) to β -amino acids *e.g.* **32** (Scheme 7) which are themselves useful synthetic intermediates.^{32,33}



Scheme 7

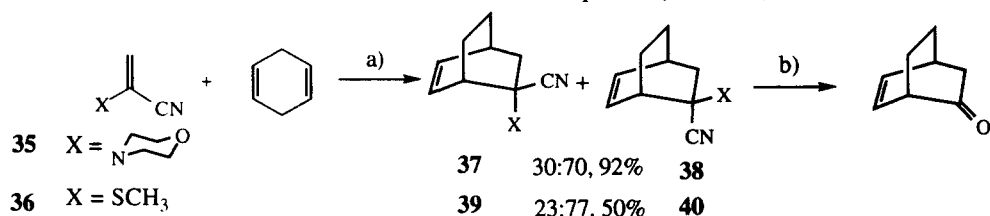
The successful conversion to the ketone group represents a pivotal step in the use of any ketene equivalent and Shiner and coworkers³⁴ have undertaken an extensive study of the hydrolysis of α -chloronitriles. The authors surmise that although pathways involving nucleophilic displacement of chloride or cyanide have been proposed,³⁵ they are unlikely.³⁴ A more likely scenario is the formation of α -chloro amides **34** followed by base-induced conversion to ketones (Scheme 8) and indeed α -chloroamides have been isolated as intermediates.³⁴



Scheme 8

3 (i) α -Alkylthio and α -alkylaminoacrylonitriles

Stella *et. al.*³⁶ investigated the captodative olefins **35**, **36** as ketene equivalents. α -Morpholinoacrylonitrile **35** and α -methylthioacrylonitrile **36**³⁷ are both easily prepared and have been shown to react with dienes to afford [4+2] cycloadducts in good yields (62-92%) (Scheme 9). The conversion of α -aminonitriles³⁸ and α -thionitriles³⁹ to ketones has been accomplished (Scheme 9)



Scheme 9

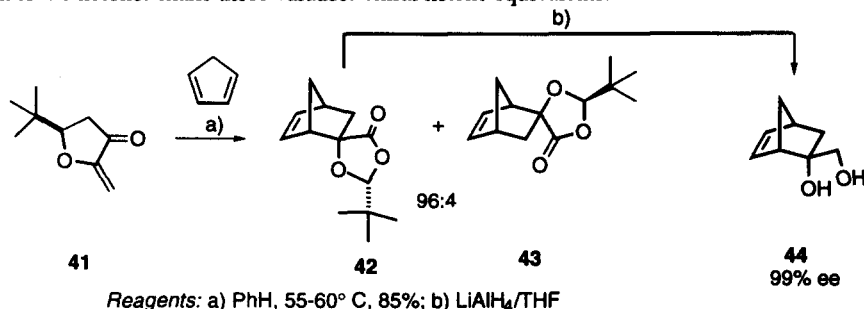
Also noteworthy is work by Ahlbrect *et. al.*⁴⁰ who has shown that 1-cyanoenamines are effective ketene equivalents and add to cyclohexenone enolates in a tandem-Michael addition fashion to provide bicyclo [2.2.2]octanones.

3 (ii) α -Substituted Acrylates

a) 2-Alkyl-5-methylene-1,3-dioxolan-4-ones

It has been demonstrated that the Diels-Alder reactions of 2-alkyl-5-methylene-1,3-dioxolan-4-ones proceed with high *exo* selectivity, in contrast to the normally favoured *endo* addition. This applies to both their thermal and Lewis acid catalysed reactions, with both cyclic⁴¹ and acyclic⁴² dienes. The Diels Alder reactions of chiral 2-alkyl-5-methylene-1,3-dioxolan-4-ones, in addition to the high *exo* selectivity, also show high diastereoselectivity. The work of Roush, while mainly directed towards natural product synthesis in which the dioxalanone is otherwise transformed, has also demonstrated the use of these compounds as chiral ketene equivalents.⁴³ Thus the chiral dienophile **41** reacts with cyclopentadiene to give only two products **42**, **43**, the *exo* isomer **42** being favoured by a ratio of 94:6. Metal hydride reduction of the chromatographically purified *exo*

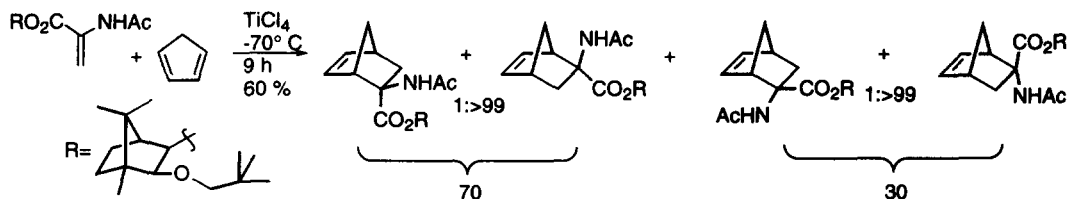
isomer gave the diol **44** (Scheme 10). As (+)-**44** has previously been converted⁴⁴ to norbornenone, it was possible to assign the absolute configuration of the product (-) and calculate the e.e. (99 %), while formally demonstrating the potential of these dienophiles to act as chiral ketene equivalents. The high selectivities and ease of conversion to the ketones make these valuable chiral ketene equivalents.



Scheme 10

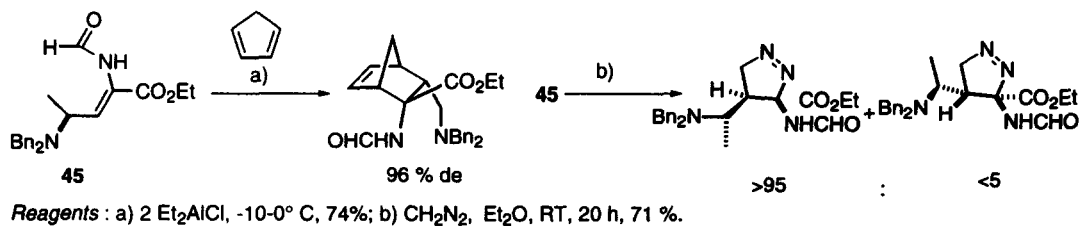
3 (ii) α -Amidoacrylates

α -Amidoacrylate esters of chiral alcohols,⁴⁵ have also been used in cycloaddition reactions, notably by CatiViela, to give norbornane amino acids with total diastereoselectivity and reversible *endo/exo* selectivity depending upon the chiral alcohol chosen.⁴⁶ A study of the effect of differing nitrogen substituents, and the factors effecting stereoselectivity has also been undertaken which includes the use of M.O. calculations.⁴⁷ This work is illustrated by the *endo* selective case in Scheme 11.



Scheme 11

Studies on the selectivity in cycloadditions of a different class of chiral α -amidoacrylate were undertaken by Reetz, in which the chirality was located at the allylic position.⁴⁸ These γ -amino- α,β -didehydroamino esters **45** (prepared from aminoacids, *via* reduction to the aldehyde and olefination by the Schöllkopf isonitrile method⁴⁹) gave adducts with both cyclopentadiene and diazomethane in generally good yields and excellent diastereoisomer ratios.



Scheme 12

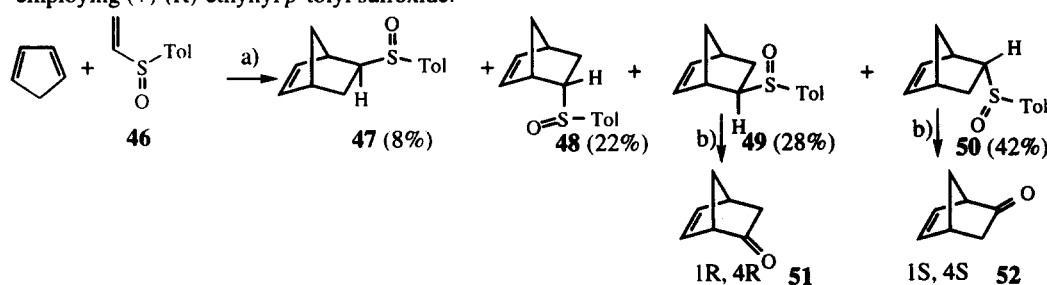
Whilst in these examples the latent ketone was not liberated, the methodology exists for the conversion,³⁹ and thus for these compounds to act as chiral ketene equivalents.

4) Sulfoxides

4 (a) α,β -Unsaturated sulfoxides

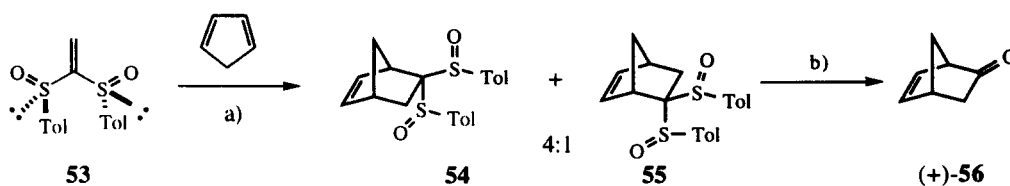
The emphasis in recent years towards homochiral synthesis prompted the development of chiral ketene equivalents. Initial attempts focused on the use of enantiomerically pure α,β -unsaturated sulfoxides¹⁰ and the first successful case was reported by Maignan *et. al* in 1983.⁵⁰ Reaction of (+)-(*R*)-*p*-tolyl vinyl sulfoxide **46** with cyclopentadiene gave a mixture of four separable diastereoisomers **47–50**, two of which were transformed to the two enantiomers of dehydronorcamphor (bicyclo[2.2.2]hept-5-enone) **51** and **52** possessing very high enantiomeric purity (Scheme 13).

Koizumi⁵¹ reported the use of (*S,S*)-1,1-*bis*(*p*-tolylsulfinyl)ethene **53** which possesses C_2 symmetry and thus leads to only two diastereomeric adducts. The reaction between (*S,S*)-1,1-*bis*(*p*-tolylsulfinyl)ethene and cyclopentadiene gave two diastereomeric adducts **54** and **55** (4:1), which were converted to the known norbornenone **56** with 54% ee (Scheme 14). A similar approach towards (+)-**56** was adopted by Maignan *et. al*⁵² employing (+)-(*R*)-ethynyl *p*-tolyl sulfoxide.



Reagents: a) 115° C, 15 h, neat; b) i) NCS, CCl₄, ii) H₂O, CuCl₂, CuO, 49% 2 steps.

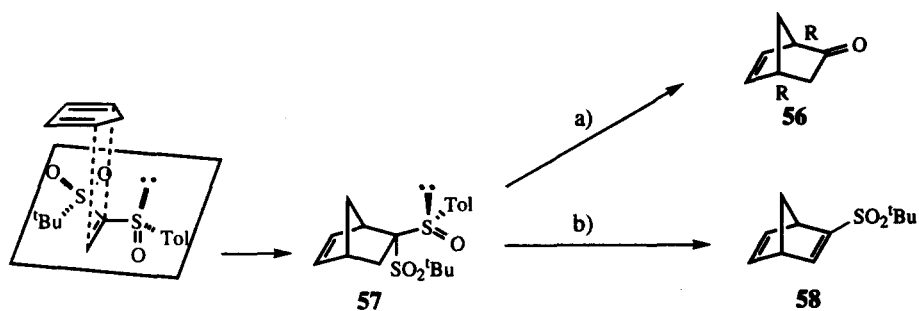
Scheme 13



Reagents: a) sealed tube, 60-70°C, 98 %; b) TiCl₃, AcOH, 36 %, 54 % ee.

Scheme 14

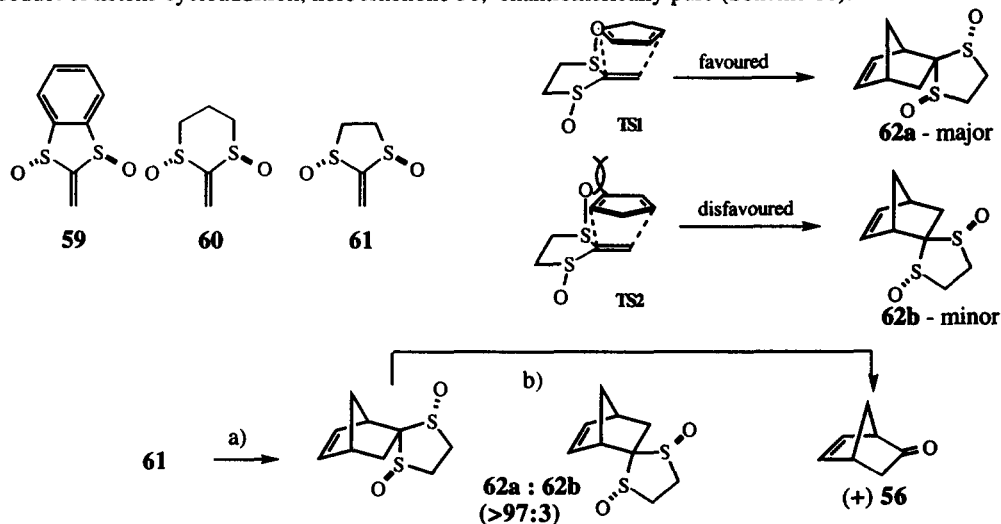
Although these studies clearly demonstrated the viability of such a process, the full potential of the approach was not realized until 1991 when Carretero⁵³ demonstrated that the Diels-Alder reactions of (+)-(*S*)-*t*-butylsulfonyl-1-*p*-tolylsulfinylethene with cyclopentadiene proceeded with very high stereoselectivity (Scheme 15). The reactions generally required mild Lewis acid catalysis (ZnBr₂, Eu(fod)₃ and SiO₂) and gave good yields of the major diastereomer **57** (62% yield, 92:8) (Scheme 15). The reaction is thought to proceed *via* an *endo* approach of the diene, with respect to the *t*-butylsulfonyl group, to the less hindered face of the *S-cis* conformation of the dieneophile.⁵⁴



Reagents: a) TiCl_3 (15% in water), AcOH, r.t., 5 days, 60% b) $\text{P}(\text{OMe})_3$ (2 eq.), toluene, 70°C , 4 days, 62%.

Scheme 15

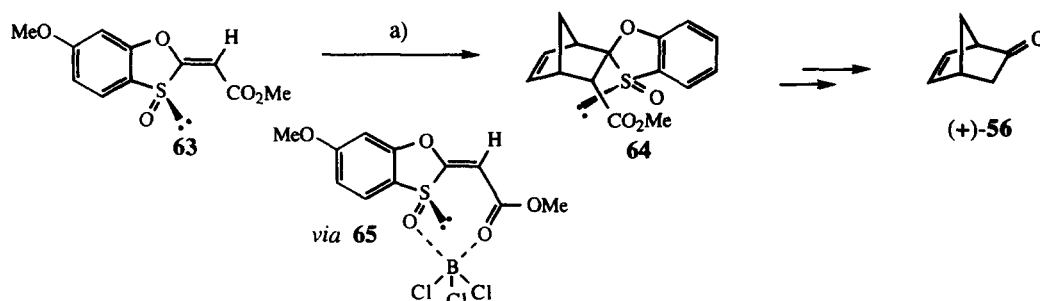
The use of *trans*-dioxides of cyclic ketene thioacetals as highly selective chiral ketene equivalents have been reported by the Aggarwal group. Cyclic ketene thioacetals **59**, **60** and **61** have been studied and it has been found that⁵⁵ **61** is more reactive and more selective than both **59** and **60**. Dienophile **61** was prepared in four steps (52%, overall) from readily available starting materials and found to undergo cycloaddition with a range of dienes with excellent selectivities ($>97:3$). The reaction of **61** with cyclopentadiene at -78°C using $\text{BF}_3 \cdot \text{OEt}_2$ gave **62a** as a single diastereomer. This high selectivity is rationalised partly in terms of non-bonded steric interactions destabilising **TS2**, and partly by invoking a repulsive interaction between the lone pairs on the sulfonyl oxygen and alkene π system further destabilising **TS2**. The ketone is unmasked in two steps (82%) to give the formal product of ketene cycloaddition, norbornenone **56**, enantiomerically pure (Scheme 16).



Reagents: a) cyclopentadiene, $\text{BF}_3 \cdot \text{OEt}_2$, -78°C , 20 min., 74%; b) i) PBr_3/DCM ii) CuCl_2 , SiO_2 , $\text{H}_2\text{O}/\text{DCM}$ (82% 2 steps).

Scheme 16

One further example of a sulfoxide based ketene equivalent was reported by Fallis:⁵⁶ the reaction of (+)-6-methoxy-1,3-benzoxathiolan-(Z)-2-carbomethoxypropenyl-3-oxide **63** with cyclopentadiene. Optimum conditions required boron trichloride catalysis at -78°C to afford diastereomerically pure **64** in 77% yield (Scheme 17).



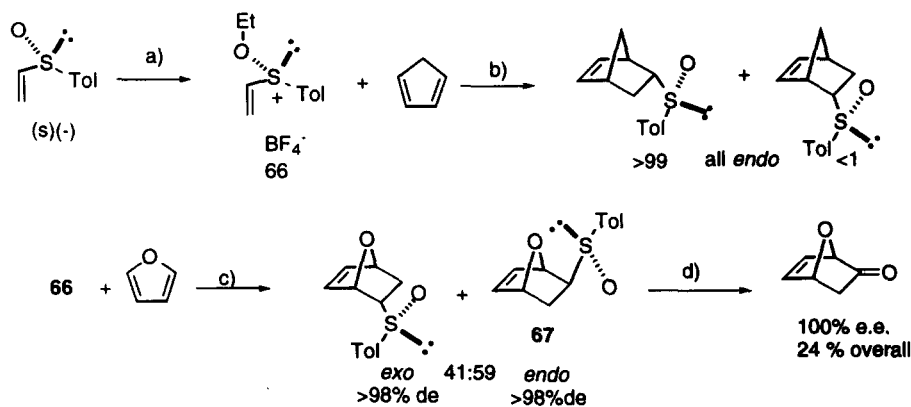
Reagents: a) cyclopentadiene, BCl_3 , -78°C , 5h, CH_2Cl_2 , 77%

Scheme 17


Since the reaction proceeds with complete π -facial control *syn* to the sulfoxide lone-pair, as illustrated in **65**, it seems likely that the boron is coordinated to the sulfoxide oxygen and the carbonyl group. This leaves the opposite face exposed and hence leads to the selectivity observed. Hydrolysis of the acetals proved troublesome and required four steps to convert **64** into (+)-(1R,4R)-norbornenone **56** in 60% yield.

4 (b) Vinyl sulfonium salts

Some inspired work by Kagan⁵⁷ has demonstrated that *O*-alkylation of chiral vinyl sulfoxides (with trialkyl oxonium salts) activates them towards reaction with dienes, allowing a low temperature Diels-Alder to occur which shows very high selectivity. The reaction of (*S*)-(-)-*p*-tolyl vinyl sulfoxide with cyclopentadiene is sluggish, requires high temperatures (115°C) and gives a mixture of all four possible isomers. The salt obtained upon *O*-ethylation of (*S*)-(-)-*p*-tolyl vinyl sulfoxide, **66**, however, reacts with cyclopentadiene at low temperature (-78°C) to give (after hydrolytic dealkylation of oxygen) only the *endo* isomer in 62% yield, with >99% de (Scheme 18). Reaction of the same salt with furan at -20°C gives the corresponding oxobicyclic with poorer *endo/exo* selectivity (59:41) but again with >98% de for each isomer. The ketene equivalence is unmasked by the conversion of the *endo* isomer **67** into (+)-oxanorbornenone with 100% ee.

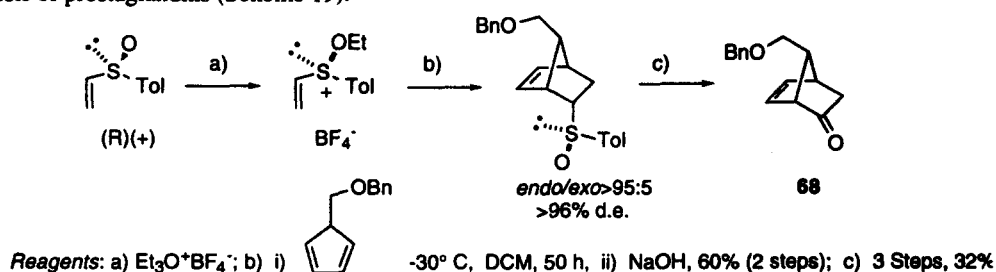


Reagents: a) $\text{Et}_3\text{O}^+\text{BF}_4^-$; b) i) -78°C , 36h, ii) NaOH , 62%, (2 steps); c) i) -20° , 30 h, ii) NaOH , 35% (2 steps);

d) i)  PCl , py, PhH; ii) NaOH ; iii) NCS ; iv) Cu(II) .

Scheme 18

This method was used⁵⁸ to prepare the bicyclic ketone **68** which is an important intermediate in the synthesis of prostaglandins (Scheme 19).⁵⁹

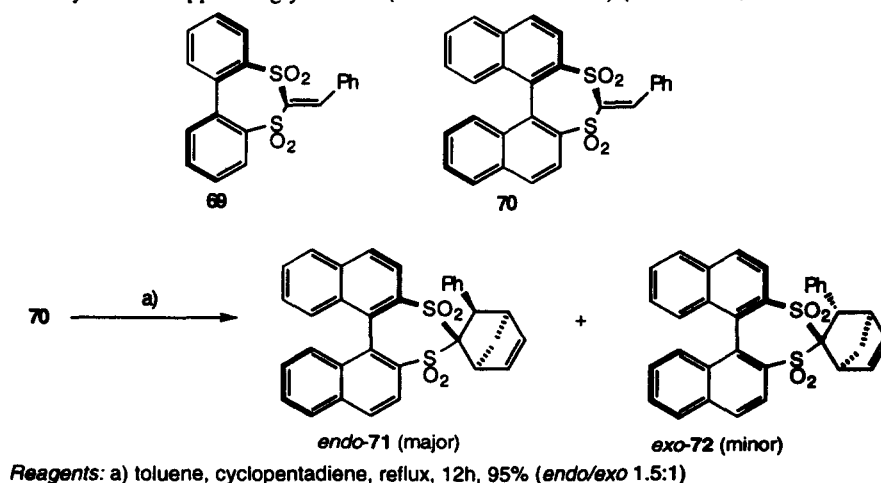


Scheme 19

5) Sulfones and Sulfonates.

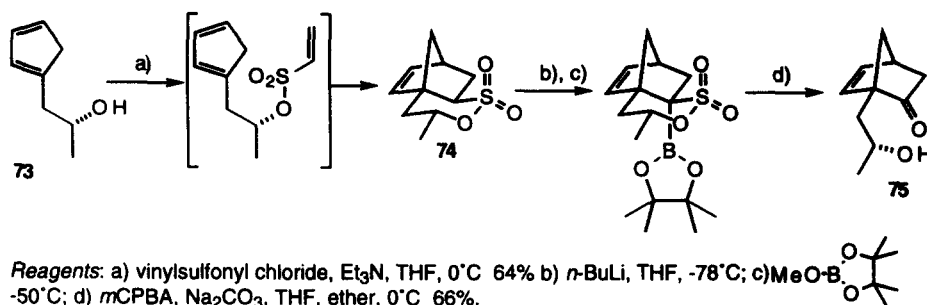
The demonstration by Little⁶⁰ that anions derived from cyclic sulfones undergo oxidation to ketones, either with molecular oxygen (**CAUTION** the authors report a "moderate" explosion), or oxodiperoxymolybdenum (pyridine)(hexamethylphosphoric triamide) (MoOPH)⁶¹ allows us to regard vinyl sulfones as dienophiles which act as ketene equivalents. Little applied this technology to a small range of dienes and 2-alkylidene-1,3-diyis. However, the wealth of examples of vinyl sulfones acting as dienophiles⁶² imply that this methodology could prove valuable.

De Lucchi *et al.*⁶³ considered a number of aryl substituted ketenedithioacetal tetroxides as potential dienophiles. These include dienophiles **69** and **70** which are atropisomeric chiral molecules, but the levels of diastereoselectivity were disappointingly modest (*endo*-**71**:*exo*-**72** 1.5:1) (Scheme 20).



Scheme 20

Metz *et al.*,⁶⁴ described the use of vinylsulfonyl chloride,⁶⁵⁻⁶⁸ in reaction with dienol **73**, to give an intermediate vinyl sulfonate which readily cyclises to the corresponding sultone **74** in good yield and excellent diastereoselectivity. The sultones are degraded to hydroxy ketones **75** (formalising the ketene equivalency) via a deprotonation-borylation-oxidation hydrolysis sequence (Scheme 21).



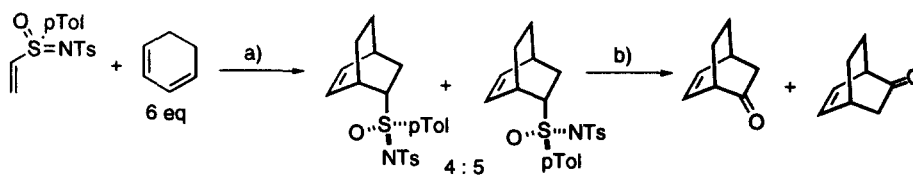
Scheme 21

The high level of regio- and stereocontrol of this method was contrasted with the Diels-Alder reaction of the same cyclopentadiene **73** with the standard ketene equivalent, 2-acetoxyacrylonitrile, which gave a mixture of ten isomers, and subsequent basic hydrolysis yielded a mixture of **75** with virtually all of its regio- and stereoisomers.

6) Vinyl Sulfoximines

In addition to the reactions of vinyl sulfones, a small number of aryl vinyl sulfoximines, which have a potential advantage over sulfones in that they are intrinsically chiral, have been prepared in both racemic and optically pure form and their Diels-Alder reactions investigated.⁶⁹ While the *endo/exo* selectivities in these reactions are good, little or no diastereoselectivity has been observed. Fortunately, the diastereoisomers are separable by HPLC, so that the use of homochiral vinyl sulfoximines potentially provides access to homochiral products of the formal addition of ketenes to dienes [the ketone is revealed in the same manner as for sulfones, i.e. *via* deprotonation-oxidation (with MoOPH)](Scheme 22).

N-tosyl sulfoximines seem to be more reactive dienophiles than the analogous sulfones, reacting with a range of cyclic and acyclic dienes in good yields. This reactivity, taken along with their ease of cleavage and the possibility of access to enantiomerically pure products (albeit *via* diastereoseparation) makes them a promising, if underexploited, addition to the field of ketene equivalents.



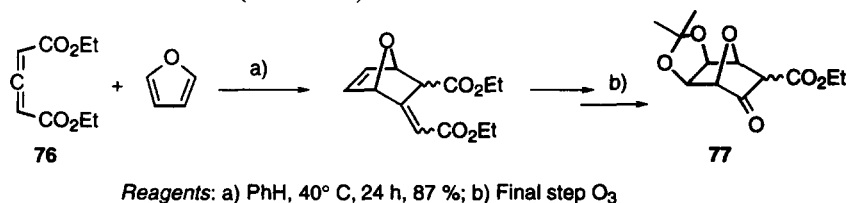
Reagents: a) CHCl₃ D, 50 h, 96 %, *endo:exo* , 97:3; b) i) LDA; ii) MoOPH, 37 %, oxidation performed on mixed isomers.

Scheme 22

7) Allenes

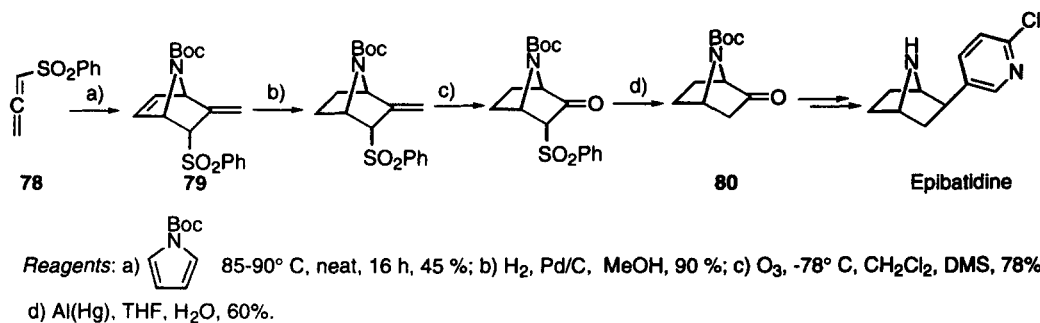
As it can be envisaged that the double bond which would remain after an allene had participated in a Diels-Alder reaction could be oxidatively cleaved to a ketone, it is surprising that there exist only a few examples of the use of allenes as ketene equivalents in organic synthesis. Kozikowski⁷⁰ reported the cycloadditions of 1,3 diethoxycarbonyllallene **76** with a range of cyclic dienes, including cyclopentadiene and both furanyl and pyrrol

heterocyclic dienes. The yields obtained in these reactions were generally good, although the authors noted that the products were isolated as mixtures of isomers (ratios unreported). The conversion to a ketone was realised (after other functional group manipulations) by ozonolysis, furnishing a key intermediate **77** in a projected synthesis of antibiotic C-nucleosides (Scheme 23).



Scheme 23

More recently Trudell⁷¹ applied the same chemistry to a formal synthesis of racemic epibatidine. Although a variety of allenic diesters were successfully subjected to cycloaddition with pyrroles, yields in the liberation of the ketone were low, so attention was turned to an allenic sulfone. Benzenesulfonyl allene **78** was found to undergo a Diels-Alder reaction with *N*-Boc pyrrole to give a single product **79** in 45% yield. The ketone was liberated and the product transformed into the epibatidine precursor **80** in three further high yielding steps (19 % overall, four steps, Scheme 24).

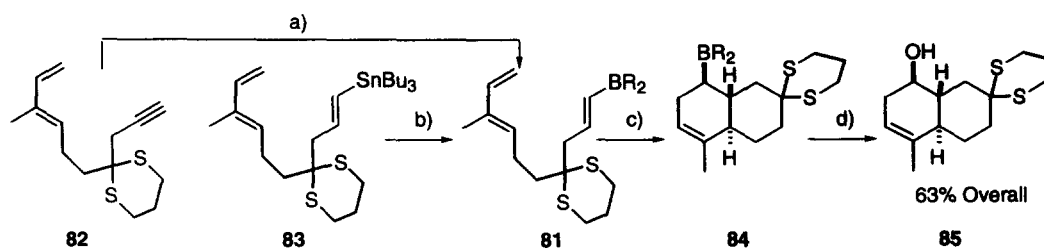


Scheme 24

8) Miscellaneous

a) Vinyl Boranes

Vinyl boranes have been shown to be highly reactive and *endo* selective dienophiles.⁷² In particular their synthetic potential is demonstrated in the intramolecular Diels-Alder reactions of the vinyl borane **81** obtained by either hydroboration of dieneynes **82** or tin-boron exchange of diene vinylstannanes **83**.⁷³ The Diels-Alder adduct **84** is formed as a single isomer and readily oxidised to the alcohol **85** (Scheme 25). Although the transformation to the ketone was not undertaken, this simple oxidation would allow these vinylboronic species to be regarded as ketene equivalents.

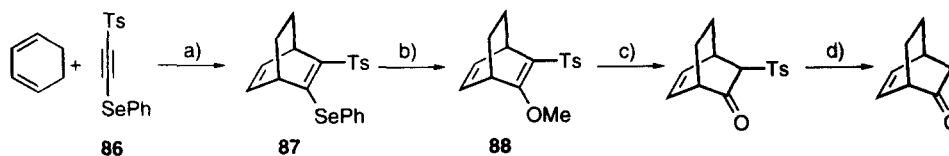


Reagents: a) $\text{HB}(\text{C}_6\text{H}_{11})_2$ b) Br-9BBN c) 75°C , 2 h d) $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$, 63% Overall (3 steps)

Scheme 25

b) Selenoacetylenes

1-(Phenylseleno)-2-p-toluenesulfonylethyne **86**⁷⁴ has been shown to act as a dienophile giving selenocyclohexenes **87** in excellent yields with a range of dienes. Subsequent oxidation to the selenoxide, followed by addition-elimination with methoxide ion gives an enol ether **88**, which upon hydrolysis unmasks the ketone, and confirms the ketene equivalence (Scheme 26). The α -tosyl group can remain ($\text{TsHC}=\text{C}=\text{O}$ equivalent), be reductively cleaved to a methylene group ($\text{H}_2\text{C}=\text{C}=\text{O}$ equivalent), substituted with an electrophile before reductive cleavage ($\text{RHC}=\text{C}=\text{O}$ equivalent) or even potentially oxidised to another ketone by the methods described in the section on vinyl sulfones ($\text{O}=\text{C}=\text{C}=\text{O}$ equivalent). These potential transformations and the high yields may offer a very versatile ketene equivalent.

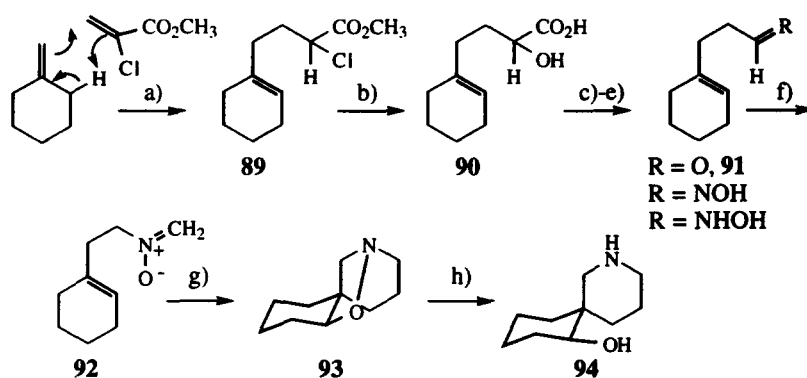


Reagents: a) PhMe , 60°C , 6 h, 90%; b) (i) mCPBA , CHCl_3 (ii) NaOMe/MeOH , 91%; c) HCl , $\text{THF/H}_2\text{O}$, 95%; d) 5% $\text{Na}(\text{Hg})$, Na_2HPO_4 , THF-MeOH , 75%.

Scheme 26

9) Ketene Equivalents in Natural Product Synthesis

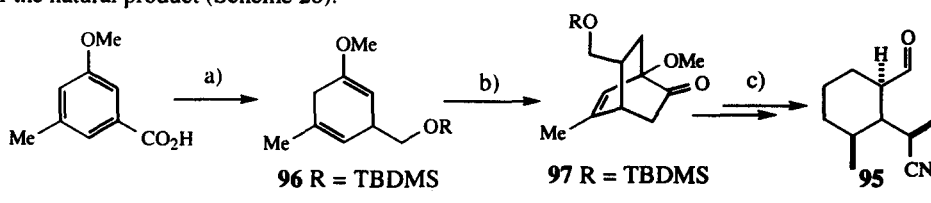
Early experiments in this area were largely concerned with the total syntheses of racemic alkaloids and involved the use of simple ketene equivalents. For example, Snider and coworker have described the synthesis of (\pm)-nitramine **94** in seven steps (33% overall yield) which incorporates methyl α -chloroacrylate as a ketene equivalent in an ene reaction (Scheme 27).⁷⁵ Chloro ester **89** derived from methylene cyclohexane and methyl α -chloroacrylate was converted first to the hydroxy acid **90** and then to the aldehyde **91** in 71% overall yield. Further manipulation to the nitron **92** was achieved by oxime formation, reduction to the hydroxylamine and condensation with formaldehyde. Intramolecular cycloaddition of nitron **92** proceeded smoothly to give **93** (the formation of **93** is favored by entropic effects in C-C bond formation of a six-membered ring) which was converted to (\pm)-nitramine **94** by hydrogenolysis (Scheme 27).



Reagents: a) EtAlCl₂, C₆H₆, 25°C, 20h, 95%; b) Na₂CO₃, Δ, 89%; c) Pb(OAc)₄, pyridine, 2h, 25°C, 84%; d) NH₂OH.HCl, Na₂CO₃, 99%; e) NaCNBH₃, HCl, 80%; f) H₂CO, PhMe, 1 h, not isolated g) PhMe, Δ, 24 h, 70% 2 steps; h) H₂/Pd, EtOH, 96%.

Scheme 27

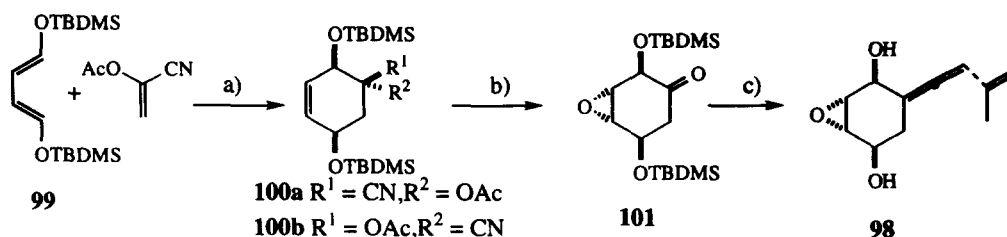
Yoshi^{76,77} has utilized α -acetoxyacrylonitrile as a ketene equivalent in the synthesis of (+)-tetronomycin, a novel tetrionic acid ionophore antibiotic (Scheme 28). Construction of the left-hand cyclohexane sub-unit **95** commenced with Diels-Alder reaction of diene **96**, derived from 3-methoxy-5-methylbenzoic acid, with α -acetoxyacrylonitrile (Scheme 28). Treatment of the resulting cycloadduct with 1.1 equivalents of NaOMe in MeOH afforded a 4:1 mixture of bicyclic ketone **97** and its C8 epimer in 68% yield. The stereochemistry of the major product **97** presumably arises from the approach of the dienophile to the less hindered face of **96**, and was confirmed by the authors. A further nine steps yielded the key cyclohexyl aldehyde subunit **95** which constitutes ring C of the natural product (Scheme 28).



Reagents: a) 3 steps, 84%; b) (i) $\text{AcO}-\text{C}(\text{CN})=\text{C}=\text{C}=\text{O}$ (ii) NaOH, MeOH, 52% 2 steps; c) 9 steps including resolution.

Scheme 28

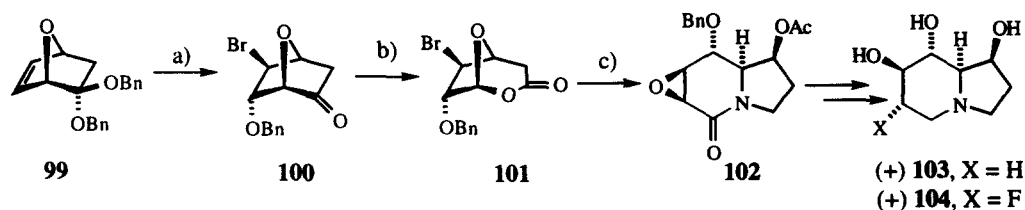
Tabacchi and coworker⁷⁹ have also utilized α -acetoxyacrylonitrile in the stereoselective synthesis of the novel allenic cyclohexanoid epoxide **98** produced by the fungus *Eutypa lata*. Reaction between the diene **99** and α -acetoxyacrylonitrile gave the cycloadducts **100a** and **100b** (ca. 8:1). The major isomer **100a** obtained in 50–65% yield by recrystallisation, was transformed over three steps to the epoxy ketone **101** and then to the desired allenic cyclohexanoid epoxide **98** over a further three steps (seven steps in total, 7.4% overall yield) (Scheme 29).



Reagents: a) 110°, 4 days; b) (i) mCPBA, (ii) NaBH₄, (iii) CrO₃.py₂; c) 6 steps, 7.4% overall.

Scheme 29

Vogel has utilized his chiral ketene equivalent technology in the asymmetric syntheses of (+)-6-deoxycastanospermine and (+)-6-deoxy-6-fluorocastanospermine.⁸⁰ Both syntheses rely on the "naked sugar" (-)-(1S,4S)-7-oxabicyclo[2.2.1]hept-5-en-2-one (-)-**22** referred to earlier in the section on chiral α -acyloxynitriles. Naked sugar (-)-**22** allows ready access (*via* its dibenzoyl ketal **99**) to epoxy lactam **102** in four steps (Scheme 30), a further two steps affords the indolizidine alkaloid 6-deoxycastanospermine (+)-**103**. Epoxy lactam **102** is also an intermediate for 6-deoxy-6-fluorocastanospermine (+)-**104** (Scheme 30).



Reagents: a) Br₂ (1.1 equiv), CH₂Cl₂, NaHCO₃, -90°C, 98%; b) 85%-*m*-chloroperbenzoic acid, NaHCO₃, CH₂Cl₂, 5°C, 96%; c) see ref. 80b, overall yield : 43%.

Scheme 30

10) Conclusions

Ever since the discovery by Staudinger in the early 1910s that ketenes do not undergo [4+2] Diels-Alder cycloadditions, the development of new ketene equivalents has inspired many researchers around the world. From the early use of α -acetoxyacrylonitrile and α -chloroacrylonitrile through to the use of enantiomerically pure dienophiles as ketene equivalents many ingenious methods of circumventing the failure of ketene to react as desired have been developed. With the continued emphasis on homochiral synthesis set to continue well into the new millennium there is little doubt that the development of new chiral ketene equivalents will continue to attract great interest.

Acknowledgments: We thank the EPSRC for support and the Nuffield Foundation for a Fellowship (VKA).

References and Notes

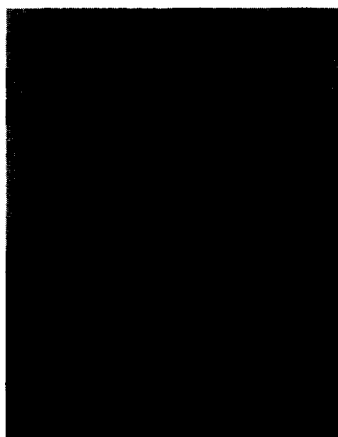
1. Staudinger, H. *Die Ketene*, F. Enke, Stuttgart, 1912.
2. Staudinger, H.; Suter, E. *Chem. Ber.*, **1920**, *53B*, 1092-1105.
3. Dryden, H.L. *J. Am. Chem. Soc.*, **1954**, *76*, 2841.
4. Blomquist, A.T.; Kwiatek, J. *J. Am. Chem. Soc.*, **1951**, *73*, 2098.

5. For an earlier review on ketene equivalents, see: Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K., *Synthesis*, **1977**, 289-296.
6. Hyatt, J.; Reynolds, R.W. *Org. React.*, **1994**, *45*, 159-646.
7. Tidwell, T.T. *Ketenes*; Wiley: New York, 1995.
8. *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; The Chemistry of Functional Groups; Wiley: Chichester, U.K., 1980; Parts 1 and 2.
9. See sections 4) and 5) of reference 8 and references cited therein.
10. For the use of sulfur functionalities as control elements in Diels-Alder reactions, see: DeLucchi, O.; Pasquato, L. *Tetrahedron*, **1988**, *44*, 6755-6794.
11. Yamabe, S.; Tatsuo, D. *J. Am. Chem. Soc.*, **1996**, *118*, 6518-6519.
For earlier studies see e.g. Holder, R.W.; Graf, N.A.; Duesler, E.; Moss, J.C. *J. Am. Chem. Soc.*, **1983**, *105*, 2929-2931. Al-Husaini, A.H.; Moore, H.W. *J. Org. Chem.*, **1985**, *50*, 2595-2597. Hegedus, L.S.; Montgomery, J.; Narukawa, Y.; Snustad, D.C. *J. Am. Chem. Soc.*, **1991**, *113*, 5784-5791. Burke, L.A. *J. Org. Chem.*, **1985**, *50*, 3149-3155. Bernardi, F.; Boltoni, A.; Olivucci, M.; Robb, M.A.; Schlegel, H.B.; Tonachini, G. *J. Am. Chem. Soc.*, **1988**, *110*, 5993-5995. Bernardi, F.; Bottoni, A.; Robb, M.A.; Venturini, A. *J. Am. Chem. Soc.*, **1990**, *112*, 2106-2114. Valenti, E.; Pericas, M.A.; Moyano, A. *J. Org. Chem.*, **1990**, *55*, 3582-3593. For other examples of [2+2] pathways between cyclopentadiene and ketene, see: Salzner, U.; Bachrach, S.M. *J. Org. Chem.*, **1996**, *61*, 237-242. Yamabe, S.; Minato, T.; Osamura, Y. *J. Chem. Soc., Chem. Commun.*, **1993**, 450-452. The transition state of the [2+2] cycloaddition was determined by Wang and Houk: Wang, X.; Houk, K.N. *J. Am. Chem. Soc.*, **1990**, *112*, 1754-1756.
12. GAUSSIAN 92 was used for calculations. Frisch, M.J.; Trucks, G.W.; Head-Gordon, M.; Gill, P.M.W.; Wong, M.W.; Foresman, J.B.; Johnson, B.G.; Schlegel, H.B.; Robb, M.A.; Replogle, E.S.; Gomperts, R.; Andres, J.L.; Ragavachari, K.; Binkley, J.S.; Gonzalez, C.; Martin, R.L.; Fox, D.J.; DeFrees, D.J.; Baker, J.; Stewart, J.J.P.; Pople, J.A. GAUSSIAN 92, Revision C; Gaussian, Inc.: Pittsburgh, PA, 1992.
13. Bartlett, P.D.; Tate, B.E. *J. Am. Chem. Soc.*, **1956**, *78*, 2473.
14. Dupuy, C.H.; Story, P.R. *J. Am. Chem. Soc.*, **1960**, *82*, 627.
15. Oku, A.; Nozaki, Y.; Hasegawa, H.; Nishimura, J.; Harada, T. *J. Org. Chem.*, **1983**, *48*, 4374-4377.
16. Vieira, E.; Vogel, P. *Helv. Chim. Acta*, **1982**, *65*, 1700.
17. Paasivirta, J.; Kreiger, H. *Suom. Kemistil B*, **1965**, *38*, 182.
18. Corey, E.J.; Koelliker, U.; Neuffer, J. *J. Am. Chem. Soc.*, **1971**, *93*, 1489.
19. Corey, E.J.; Weinshenker, N.M.; Schaaf, T.K.; Huber, W. *J. Am. Chem. Soc.*, **1969**, *91*, 5675.
20. Brown, E.D.; Clarkson, R.; Leeney, T.J.; Robinson, G.E. *J. Chem. Soc. Chem. Commun.*, **1974**, 642.
21. Brown, E.D.; Leeney, T.J.; *J. Chem. Soc. Chem. Commun.*, **1975**, 39.
22. Ipautschi, J. *Chem. Ber.*, **1972**, *105*, 1840.
23. Krieger, H.; Nakajima, F. *Suom. Kemistil.B*, **1969**, *42*, 314.
24. Goering, H.L.; Chang, C.S. *J. Org. Chem.*, **1975**, *40*, 2565.
25. Kreiger, H. *Suom. Kemistil B*, **1970**, *43*, 318.
26. Bull, J.R.; Grundler, C. *Tetrahedron*, **1994**, *50*, 6347-6362.

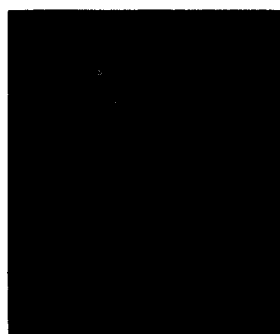
27. Vogel, P.; Fattori, D.; Gasparini, F.; LeDrain, C. *Synlett* **1990**, 173-185
28. Reymond, J-L.; Vogel, P. *Tetrahedron Asymm.*, **1990**, *1*, 729-736
29. Mehta, G.; Subrahmanyam, D. *J. Chem. Soc. Perkin Trans 1*, **1991**, 395.
30. Evans, D.A.; Scott, W.L.; Truesdale, L.K. *Tetrahedron Lett.*, **1972**, 121.
31. Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc. Perkin Trans.1*, **1991**, 1041.
32. Griffith, O.W. *Ann. Rev. Biochem.*, **1986**, *55*, 855.
33. Drey, C.N.C. *The Chemistry and Biochemistry of Amino Acids*, ed. B. Weinstein, Dekker, New York, 1976, Vol. 4., p 241.
34. Shiner, C.S.; Fisher, A.M.; Yacoby, F. *Tetrahedron Lett.*, **1983**, *51*, 5687-5690.
35. Freeman, P.K.; Balls, D.M.; Brown, D.J. *J. Org. Chem.*, **1968**, *33*, 2211.
36. Stella, L.; Boucher, J.L. *Tetrahedron Lett.*, **1982**, *23*, 953-956.
37. Gundermann, K.D.; Thomas, R. *Chem. Ber.*, **1956**, *89*, 1263.
38. Stella, L.; Boucher, J.L. *Tetrahedron*, **1985**, *41*, 875-887; Büchi, G.; Liang, P.H.; Wüest, H. *Tetrahedron Lett.*, **1978**, 2763; Trost, B.M.; Tamaru, Y. *J. Am. Chem. Soc.*, **1977**, *99*, 3101 and references therein.
39. Jung, M.E.; Yuk-Sun, P.; Mansuri, M.M. *J. Org. Chem.*, **1985**, *50*, 1087-1105.
40. Ahlbrecht, H.; Dietz, M.; Schon, C.; Baumann, V. *Synthesis*, **1991**, 135.
41. Fotiadu, F.; Michel, F.; Bueno, G. *Tetrahedron Lett.*, **1990**, *31*, 4863-4866
42. Roush, W.R.; Essenfield, A.P.; Warmus, J.S.; Brown, B.B. *Tetrahedron Lett.*, **1989**, *30*, 7305-7308
43. Roush, W.R.; Brown, B.B. *J. Org. Chem.*, **1992**, *57*, 3380-3387.
44. Matthey, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327
45. Cativiela, C.; de Villegas, D.; Galvez, J.A. *Synthesis*, **1990**, 198-199
46. Cativiela, C.; Lopez, P.; Mayoral, J.A. *Tetrahedron Asymm.*, **1991**, *2*, 449-456.
47. Bueno, M.P.; Cativiela, C.; Mayoral, J.A. *Can. J. Chem.*, **1987**, *65*, 2182
48. Kayser, F.; Harms, K.; Reetz, M. *Tetrahedron Lett.* **1992**, *33*, 3453-3456.
49. Schollkopf, U.; Gerhart, F.; Schroder, R.; Hoppe, D. *Leibigs Ann. Chem.* **1972**, 766, 116-129.
50. Maignan, C.; Raphael, R.A. *Tetrahedron*, **1983**, *39*, 3249.
51. Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Synth. Comm.* **1986**, *16*, 233-244.
52. Maignan, C.; Belkasmioui, F. *Tetrahedron Lett.*, **1988**, *29*, 2823-2824.
53. Lopez, R.; Carretero, J.C. *Tetrahedron Asymm.*, **1991**, *2*, 93-96.
54. For studies demonstrating the greater stability of the *s-cis* conformation with respect to the *s-trans* in related 1,1-disubstituted vinylsulfoxides see: Koizumi, T.; Aray, Y.; Takayama, H. *Tetrahedron Lett.*, **1987**, *28*, 3689.
55. Aggarwal, V.K.; Gültekin, Z.; Grainger, R.S.; Adams, H.; Spargo, P.L. *J. Chem. Soc. Perkin Trans 1*, **1998**, in press; Aggarwal, V.K.; Drabowicz, J.; Grainger, R.S.; Gültekin, Z.; Lightowler, M.; Spargo, P.L. *J. Org. Chem.*, **1995**, *60*, 4962; Aggarwal, V.K.; Lightowler, M.; Lindell, S.D. *Synlett*, **1992**, 730.
56. Martynow, J.; Dimitroff, M.; Fallis, A.G. *Tetrahedron Lett.*, **1993**, *34*, 8201-8204.
57. Ronan, B.; Kagan, H.B. *Tetrahedron Asymm.*, **1991**, *2*, 75-90.
58. Ronan, B.; Kagan, H.B. *Tetrahedron Asymm.*, **1992**, *3*, 115-122.
59. Corey, E.J.; Ensley, H.E. *J. Am. Chem. Soc.* **1997**, *97*, 6908-6926.

60. Little, R.D.; Myong, S.O. *Tetrahedron Lett.*, **1980**, *21*, 3339-3342.
61. Vedejs, E.; Englar, D.A.; Telschow, J.F. *J. Org. Chem.*, **1978**, *43*, 188-196.
62. See, for example, Carr, R.V.C.; Williams, R.V.; Paquette, L.A. *J. Org. Chem.*, **1983**, *48*, 4976-4986, and references therein.
63. De Lucchi, O.; Fabbri, D.; Lucchini, V. *Tetrahedron*, **1992**, *48*, 1485-1496.
64. Metz, P.; Fleischer, M.; Frohlich, R. *Tetrahedron*, **1995**, *51*, 711-732.
65. Bovenschulte, E.; Metz, P.; Henkel, G. *Angew. Chem.*, **1989**, *101*, 204-206; *Angew. Chem. Intd. Ed. Engl.*, **1989**, *28*, 202-203.
66. Metz, P.; Fleischer, M.; Frohlich, R. *Synlett*, **1992**, 985-987.
67. Metz, P.; Fleischer, M. *Synlett*, **1993**, 399-400.
68. Metz, P.; Cramer, E. *Tetrahedron Lett.*, **1993**, *34*, 6371-6374.
69. Glass, R.S.; Reineke, K.; Shankli, M. *J. Org. Chem.*, **1984**, *49*, 1527-1533.
70. Kozikowski, A.P.; Floyd, W.C.; Kuniak, M.P. *J. Chem. Soc. Chem. Commun.*, **1977**, 583.
71. Trudell, M.L.; Pavri, N.P., *Tetrahedron Lett.*, **1997**, *38*, 7993-7996.
72. Singleton, D.A.; Martinez, J.P. *J. Am. Chem. Soc.*, **1990**, *112*, 7423; Singleton, D.A.; Martinez, J.P. *Tetrahedron Lett.*, **1991**, *32*, 7365; Singleton, D.A.; Martinez, J.P.; Watson, J.V., *Tetrahedron Lett.*, **1992**, *33*, 1017; Singleton, D.A.; Martinez, J.P.; Watson, J.V., *Tetrahedron*, **1992**, *48*, 5831.
73. Singleton, D.A.; Lee, Y-K., *Tetrahedron Lett.*, **1995**, *36*, 3473-3476.
74. Black, T.G.; Wehrli, D. *Synlett*, **1995**, 1123-1124.
75. Snider, B.B.; Cartaya-Marin, C.P. *J. Org. Chem.*, **1984**, *49*, 1688-1691.
76. Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshi, E. *J. Org. Chem.*, **1992**, *57*, 2888-2902.
77. Hori, K.; Nomura, K.; Mori, S.; Yoshi, E. *J. Chem. Soc. Chem. Commun.*, **1989**, 713.
78. Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.*, **1988**, *53*, 5531-5534.
79. Gordon, J.; Tabacchi, R. *J. Org. Chem.*, **1992**, *57*, 4728-4731.
80. (a) Reymond, J.L.; Vogel, P. *J. Chem. Soc. Chem. Commun.*, **1990**, 1070 (b) Reymond, J.L.; Vogel, P. *Tetrahedron Lett.*, **1989**, *30*, 705.

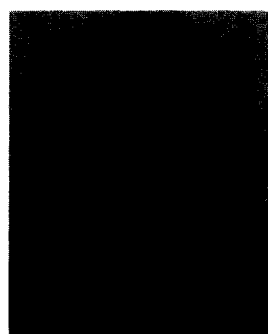
Biographical sketch



Varinder K. Aggarwal



Amjad Ali



Michael P. Coogan

Varinder Aggarwal was born in Kalianpur in the northern state of Punjab in India in 1961 and in 1963 his family emigrated to England. He received his BA in 1983 and PhD in 1986 from Cambridge University under the guidance of Stuart Warren. He then carried out post-doctoral research with Professor Gilbert Stork at Columbia University as a Harkness Fellow and returned to a lectureship at Bath University in 1988. In 1991 he moved to Sheffield University where, in 1997, he was promoted to Professor in Organic Chemistry.

Amjad Ali received his first degree from the University of Hertfordshire (Hatfield, UK) in 1986. He then moved to the University of Nottingham to read for his Ph.D. under the direction of Professor Gerald Pattenden where he investigated the development of novel cascade cyclization processes mediated by organocobalt reagents. Having successfully completed his Ph.D. in 1993 he moved to Austin, Texas (USA) as a Fulbright Postdoctoral Fellow to collaborate with Professor Stephen F. Martin on the total synthesis of the marine alkaloid, manzamine A. Two years later he returned to the UK to work with Prof. Varinder Aggarwal at the University of Sheffield, and he is currently a Senior Research Chemist at Merck Research Laboratories, Rahway, New Jersey (USA).

Mike Coogan was born in Birkenhead in 1969, graduated from Leicester University in 1990 and remained there for Ph.D. studies with Dr. R.S. Atkinson on quinazolinone based aziridinations. In 1994 he began post doctoral work with David Knight at the University of Nottingham in the area of reverse-Cope cyclisations, moving to Cardiff University upon the appointment of David Knight to the Distinguished Chair of Organic Synthesis. He returned to England in 1997 to work at Sheffield University with Prof. Varinder Aggarwal on the application of zinc carbenoids to epoxidations, and took up a Lectureship at Durham University in September 1998.