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The Geometry of Dienes from 2,3-Substituted-3-Sulfolenes and the Stereoselectivity of their Intramolecular Diels-Alder Cyclisations

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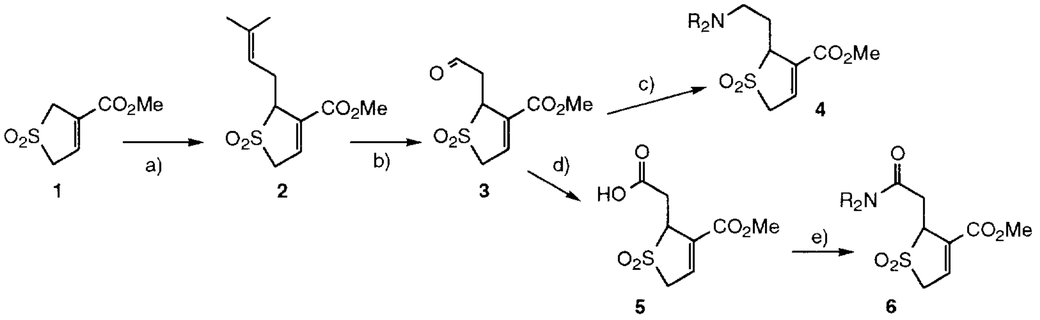
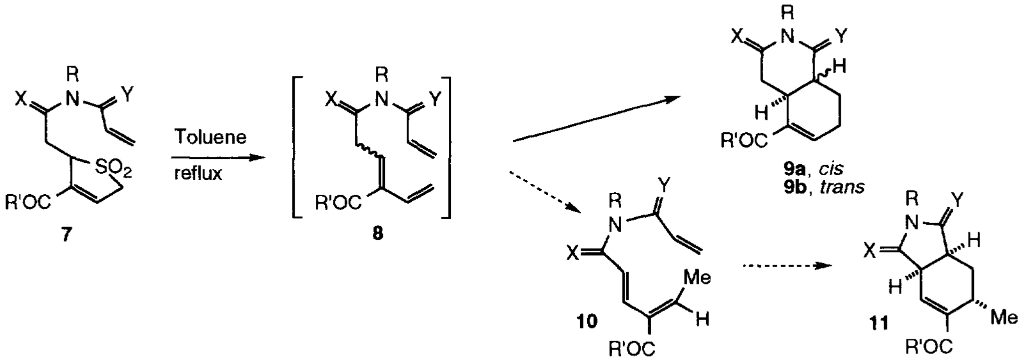
Abstract: The geometry of dienes obtained from 2,3-substituted sulfolenes bearing a 3-carboxyl derivative is dependent on the nature of the 3-carboxy group and on the functionality of the 2-substituent. These factors therefore have a crucial influence on the stereoselectivity of subsequent Diels-Alder reactions. © 1997 Published by Elsevier Science Ltd.

We have been exploring synthetic routes to yohimbine and manzamine-type alkaloids involving intramolecular Diels-Alder reactions of 2,3-disubstituted sulpholene masked diene precursors.[1-3] Such routes are short and effective because of the ready availability of the 2,3-disubstituted sulpholene precursors *via* alkylation of the dianion of 3-carbomethoxy-3-sulpholene **1**. In particular, a range of methods have been developed for installing dienophiles linked through a nitrogen atom (Scheme 1).[1,4]



Scheme 1: a) i) BuLi (2eq)/ THF/ -78°, ii) $Me_2C{=}CHCH_2Br$ (84%); b) i) O_3/ CH_2Cl_2, ii) Me_2S (96%); c) R_2NH/ $NaBH_3CN$/ MeOH; d) Jones' reagent (90%); e) R_2NH/ DCC/ CH_2Cl_2.

We have now carried out a variety of intramolecular Diels-Alder reactions involving the 2,3-substituted sulfolene precursors, and although the reactions usually proceed with a high degree of stereoselectivity, it is sometimes difficult to predict which stereoisomer will be favoured. We have also observed that apparently minor differences in the structures of the sulfolene precursors can lead to dramatic changes in the stereochemical outcome of the Diels-Alder reactions. Thus, in order to clarify the factors which govern the stereoselectivity of such processes, we decided to carry out a detailed comparative study on a range of related Diels-Alder precursors **7a-h** (Scheme 2, Table 1). This range of Diels-Alder precursors was chosen because we had noticed: firstly, that the nature of the carboxyl derivative attached to the diene had an influence on the stereochemistry of the cyclisation; and secondly, that the nature of X and Y in such precursors was highly influential, but not in a way which was predictable on the simple assumption that an *endo* transition state (leading to *cis* stereochemistry) would be favoured where Y is a carbonyl.



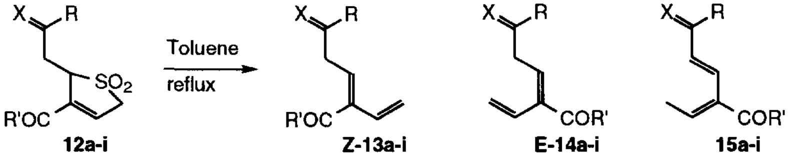
Scheme 2

	Sulfolene precursor				Time	Products - 9a/9b		11
	R	R'	X	Y		Yld%	cis:trans	Yld%
7a	Allyl	OMe	H_2	H_2	24h	100	1:15	0
7b	Bn	OMe	H_2	H_2	24h	100	1:15	0
7c	Bn	NMe_2	H_2	H_2	70h	80	1:15	0
7d	Bn	OMe	H_2	O	23h	55	1:1	0
7e	Bn	NMe_2	H_2	O	24h	100	1:7	0
7f	Bn	OMe	O	H_2	3.5h	75	3:1	~5
7g	Ind-3-$(CH_2)_2$	OMe	O	H_2	3.5h	79	4:1	11
7h	Ind-3-$(CH_2)_2$	NMe_2	O	H_2	96h	68	1:1	10

Table 1

The general trends which should be noted are: as expected on geometric grounds, *trans* products are formed almost exclusively from amine precursors **7a-c** (X = Y = H_2); for amides where Y = O there is a surprising difference in stereoselectivity between the diene ester (R' = OMe) and the diene amide (R' = NMe_2), but the expected predominance of *cis* products formed *via endo* transition states was not observed; *cis* products predominated from amide precursors where X = O and the diene group is an ester, but there was again a surprising change in stereoselectivity on changing to an amide group on the diene.

One of the most important factors which could influence the stereochemical outcome of these reactions is the geometry of the intermediate dienes **8a-h**. For 2,3-disubstituted sulfolenes either geometrical diene isomer could in principle be formed *via* alternative symmetry allowed disrotatory cheletropic processes. There is ample president that 2,3-substituted sulfolenes bearing simple alkyl substituents, open selectively to give dienes with the substituents *cis* to one another.[5-8] Sulfolenes with SPh and $SiMe_3$ groups in the 3- position also open in the same manner but with less selectivity,[9,10] and 2,3-dicarbomethoxy-3-sulfolene opens to give a 1:1 mixture of *E*- and *Z*-dienes.[11] Since very little was known about the geometry of ring opening of 3-carboxy sulfolene derivatives, it was crucial to establish which diene isomer was involved in our Diels-Alder cyclisations. Thus, in a parallel study, we investigated cheletropic SO_2 extrusion reactions for a range of sulfolenes **12a-i**, analogous to **7a-h** but lacking an internal dieneophile, in order to establish the general preferences of such processes.



Scheme 3

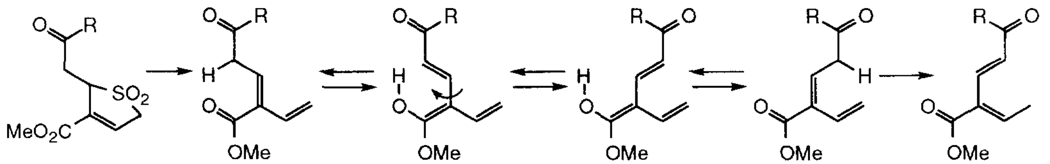
	X	R	R'	Z-13	E-14	15
a	$(OMe)_2$	H	NMe_2	1	0	0
b	$(OMe)_2$	H	N(Me)OMe	1	0	0
c	$=CMe_2$	H	NMe_2	1	0	0
d	O	OMe	NMe_2	1	0	0
e	O	NMe_2	NMe_2	>96	<2	<2
f	H_2	NMeBn	OMe	>98	<2	0
g	$=CMe_2$	H	OMe	>96	<2	<2
h	O	NMe_2	OMe	1	1	3*
i	$(OMe)_2$	H	OMe		mixture containing **15**	

Table 2 *After 6 hours

Simply changing between an ester group and a dimethylamide group in the 3-position of the sulfolene can have a significant effect on both the SO_2 extrusion and on subsequent Diels-Alder reactions. Interestingly, whenever the 3-substituent was an amide (**12a-e**), a Z-diene (**13a-e**) was obtained in a highly selective manner upon heating in toluene at reflux. The dienes were formed in high yields (>90%), were stable to the reaction conditions and did not rearrange or dimerise by intermolecular Diels-Alder reactions. Only in the case of **12e** was any trace of the rearranged conjugated diene **15** detected. The geometry of the dienes was established by nOe studies. In the *E*-dienes the vinyl methyne proton had a positive nOe with the allylic methylene protons, but not with the down field conjugated alkene proton. Whereas, the Z-dienes, had a positive nOes between the vinyl methyne proton and the conjugated alkene proton. The conjugated diene was distinguished by a methyl doublet at δ1.7, which had a positive nOe to the methyne proton at the other end of the diene.

The sulfolene esters **12f-i** gave a distinctly different range of SO_2 extrusion products from their amide counterparts. Compounds **12f** and **12g**, gave one diene product almost exclusively and that was the Z-isomer **13**. When X was an amide carbonyl the two geometrical diene isomers Z-**13h** and *E*-**14h** were formed, as well as the conjugated diene **15h**. The progress of the reaction was monitored by ^1H NMR. At an early stage the Z-diene **13h** was predominant, but as the reaction progressed the proportion of *E*-diene **14h** and rearranged diene **15h** increased. Eventually, after 6h no sulfolene remained and **15h** was the major product. Although the dienes were not particularly stable, they could be isolated and their geometry confirmed by nOe studies. When compound **12i** was subjected to SO_2 extrusion a complex, inseparable mixture of products was always formed which appeared to contain all three dienes by NMR.

From the results above it is clear that, in the case of the 3-dimethylamido sulfolenes, Diels-Alder reactions proceed *via* Z-dienes and it would appear that this is the kinetically formed diene in all cases. The picture with the 3-carbomethoxy derivatives is more difficult to interpret, not least because the dienes formed are quite unstable, but there are several features of their Diels-Alder reactions which require explanation. The ester acrylamide **7d** cyclises to give a much higher proportion of *cis* product (formed *via* an *endo* transition state) than the amide **7e** and this could be accounted for by a stronger tendency for secondary orbital overlap with the ester diene, competing with the inherent geometrical constraints of the system. It is more difficult to identify a reason for the distinct change in stereoselectivity between ester **7f** and amide **7h**, but the SO_2 extrusion from sulfolene **12h** may provide clues. Since there appears to be equilibration between the *Z*- and *E*-isomers, stereocontrol may be dependant on the relative rates of Diels-Alder cyclisations of each diene. The *E*-rearranged conjugated diene **15** appears to be formed with high stereoselectivity and, although there are several different mechanisms which could lead to this, one possibility is that it is formed from *E*-diene **14** by a [1.5]-hydrogen shift. The proton adjacent to the ester in **13** is particularly acidic and it is possible that formation of the *E*-diene in this case could also involve a [1.5]-hydrogen shift, followed by a tautomerisation (Scheme 4).



12 ***Z*-13** ***E*-14** **15**

Scheme 4

In summary, we have determined the geometry of dienes obtained from 2,3-sulfolenes bearing 3-carboxy groups and shown that amide and ester derivatives behave quite differently. It is clear from these results that subsequent intramolecular Diels-Alder reactions can lead to the selective formation of hydroisoquinolines with either *cis* or *trans* ring junction stereochemistry, by careful choice of appropriate functionality around the nitrogen tether, and at the diene carboxyl group. The practical application of such complementary stereoselectivity is illustrated by our synthetic routes to both *allo*- and *normal*-series yohimbine alkaloids, as reported in the following paper.

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