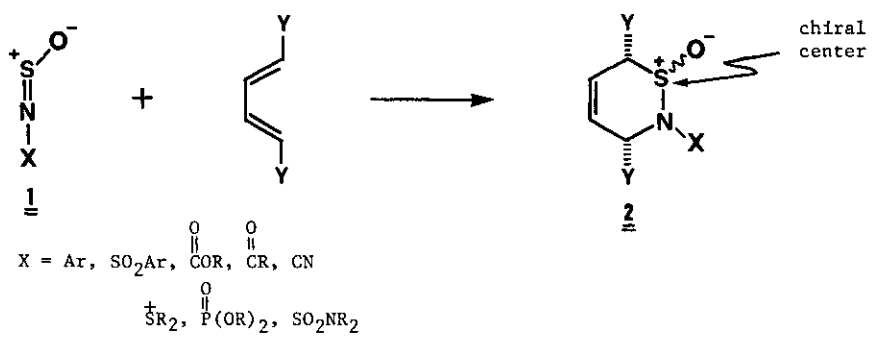
NATURAL PRODUCT SYNTHESIS VIA CYCLOADDITIONS WITH N-SULFINYL DIENOPHILES

Steven M. Weinreb*, Ravi S. Garigipati, and James A. Gainor
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, USA

Abstract—Diels-Alder cycloadducts derived from N-sulfinyl dienophiles have been used for stereospecific preparation of acyclic unsaturated amines and in stereospecific syntheses of threo-sphingosine (31) and erythro-sphingosine (32). Methodology based upon these cycloadducts is also currently being developed for total synthesis of the microbial metabolite staurosporine (46).

Diels-Alder type [4+2]-cycloadditions of various N-sulfinyl compounds 1 with 1,3-dienes to form 3,6-dihydrothiazine-1-oxides (2) have been known for many years (Scheme I)[1] In general, when X is an electron withdrawing group in 1 these reactions proceed rapidly at relatively low temperatures and are often exothermic. A wide variety of substituted N-sulfinyl compounds participate in the process and some representative examples are indicated in Scheme I. Most commonly

Scheme I

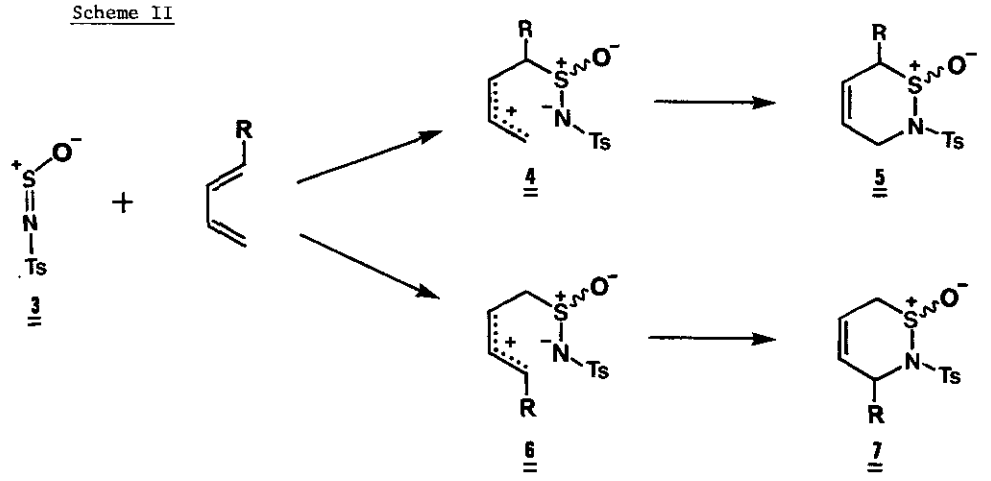


a sulfinyl dienophile is generated from the parent primary aniline,[2] amide or carbamate by treatment with thionyl chloride/pyridine, and can usually be used in situ.[1]

These cycloadditions usually show excellent orientational specificity when using unsymmetrical dienes. Mock and Nugent[3] have investigated the mechanism of the addition of N-sulfinyltoluenesulfonamide (3) with conjugated dienes (Scheme II) and have presented a convincing argu-

ment that this reaction proceeds via a stepwise process involving a dipolar intermediate (eg 4, 6). The regiospecificity of N-sulfinyl dienophile cycloadditions can generally be rationalized by considering the relative stability of dipolar species such as 4 and 6 which lead to dihydrothiazine oxide isomers 5 and 7, respectively. If an electron donating substituent R

Scheme II

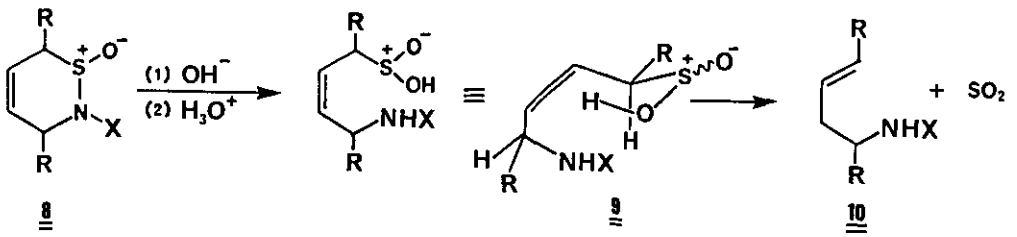


is present which will stabilize the intermediate allylic carbonium ion, a product such as 7 will result. If R is electron withdrawing (eg CO_2R') isomer 5 will be produced as the kinetic product of the addition. It should be noted that these N-sulfinyl dienophile cycloadditions are often readily reversible,[4] and occasionally the reaction temperature will affect the product regiochemistry. It is conceivable that the Mock mechanism of cycloaddition of sulfinyl sulfonamide 3 is not general for all of the other variously substituted sulfinyl compounds 1. However, the observed orientation for sulfinyl dienophiles appears to be in line with FMO theory[5] and concerted processes cannot yet be completely ruled out.

These cycloadditions show the usual high Diels-Alder stereoselectivity with respect to the diene component. Thus, if a dipolar intermediate is actually involved in the reaction, it must close to a dihydrothiazine oxide faster than loss of allyl cation stereochemistry occurs. Dihydrothiazine oxides 2 possess chirality at sulfur. At times a single or predominant sulfur stereoisomer is formed in these reactions, but often mixtures of isomers are produced. It is not presently clear what factors control sulfur configuration, although Mock's experiments seem to indicate that secondary orbital effects are probably not important in these systems.[3]

Little chemistry had been described for the dihydrothiazine oxide products of these cycloadditions at the time we began work in this area. It was well known that hydrolysis of these adducts generally produced unsaturated amine derivatives 10 (Scheme III).[1] On the basis of

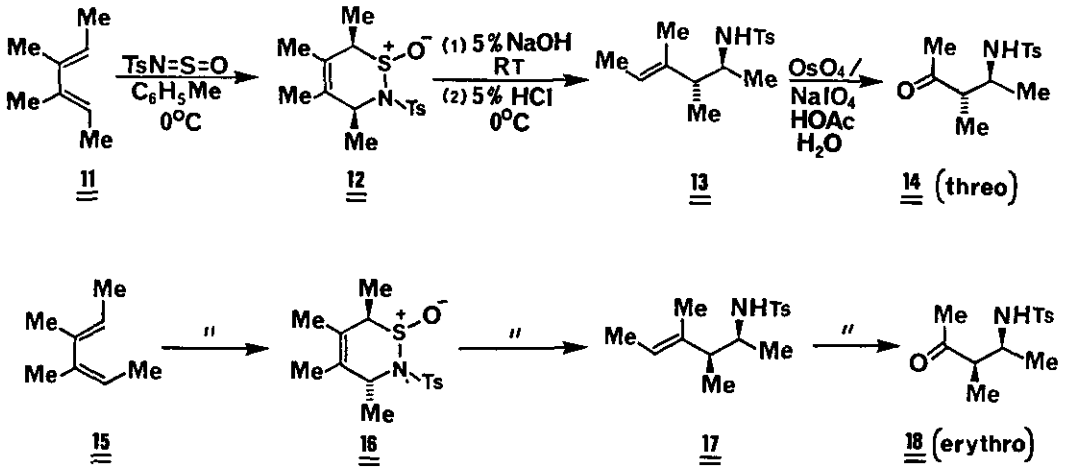
Scheme III



deuterium labelling experiments, Mock and Nugent suggested that conversion of 8 (X = Ts,R = Me) to 10 proceeds via an allylic sulfenic acid 9, which subsequently loses SO_2 in a concerted retro-ene reaction.[6] These workers proposed that proton transfer occurs through a six-membered chair-like transition state with the R group in an equatorial position.

This interesting transformation of N-sulfinyl dienophile Diels-Alder products appeared to us to be a potentially useful method for establishing relative and double bond stereochemistry in unsaturated acyclic amines. However, there were a few ambiguities in the mechanistic studies on the conversion of 8 to 10.[6] Thus, we decided to conclusively establish whether the Mock-Nugent retro-ene mechanism was correct by the experiments shown in Scheme IV.[7]

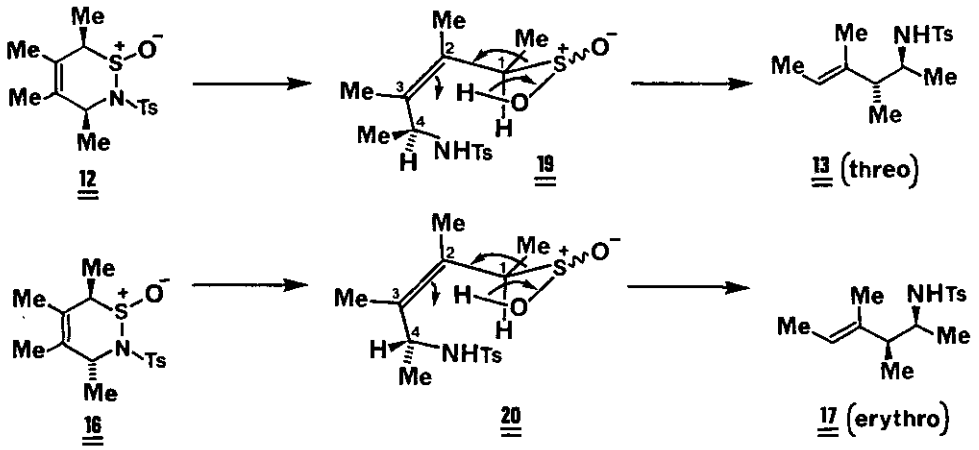
Scheme IV



Cycloaddition of N-sulfinyl-p-toluenesulfonamide and E,E-tetramethylbutadiene (11) gave adduct 12 which upon hydrolysis afforded exclusively sulfonamide 13 having an E-double bond[8] and the threo configuration (85% from 12). Similarly, E,Z-tetramethylbutadiene (15) afforded adduct 16, which upon hydrolysis yielded only the diastereomeric erythro derivative 17 also having an E-double bond (83% from 15).[8] In neither series of reactions was any other stereoisomer detected, and thus both transformations were found to be totally stereospecific. These results

do in fact conform nicely to a concerted retro-ene process (Scheme V) as shown in diastereomeric transition states 19 and 20. An important feature of this mechanism is that the substituent on the sulfur-bearing carbon assumes an equatorial position to avoid $A^{1,3}$-strain with the substi-

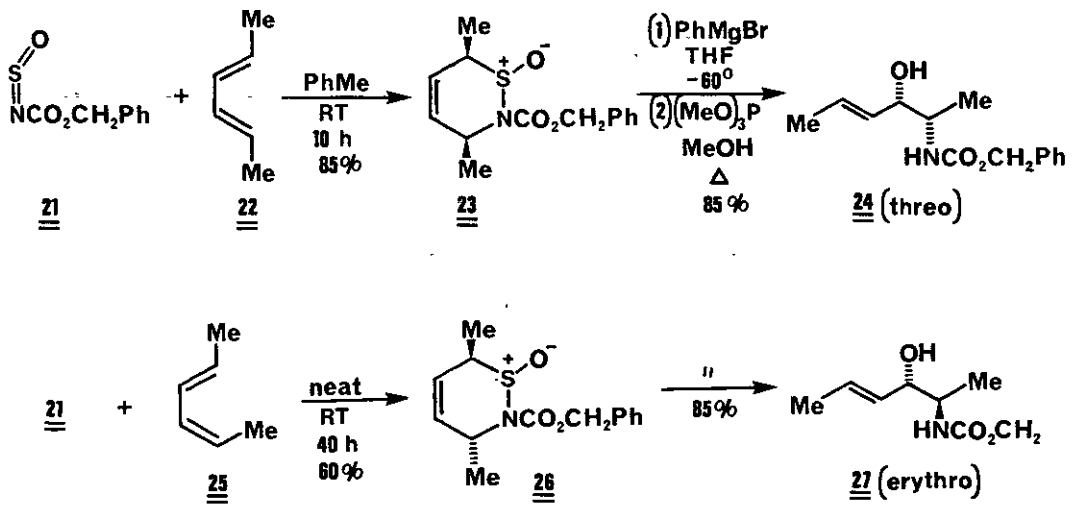
Scheme V



tuents on C-4. This "anchor effect" controls to which face of the double bond a proton is transferred, and establishes the geometry of the newly formed double bond. Compounds 13 and 17 could also be further converted to threo-ketone 14 and erythro-ketone 18, respectively. We are currently attempting to use this methodology in synthesis of some stereochemically complex alkaloids.

Since the above transformations proceeded so cleanly, we considered extensions of the methodology which might involve transition states similar to that for the retro-ene reaction. We have now developed a simple procedure for stereospecific synthesis of acyclic unsaturated

Scheme VI

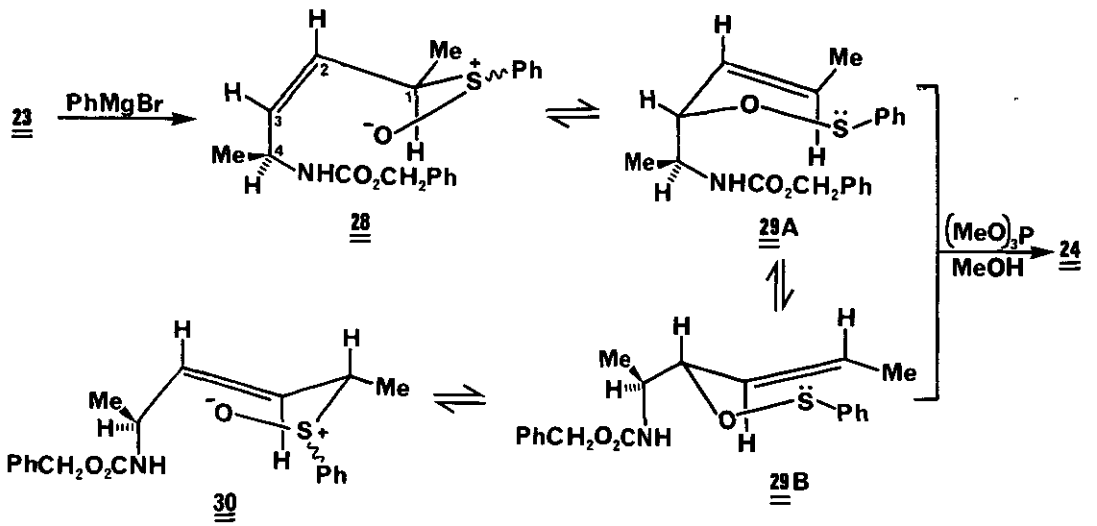


vicinal amino alcohols which, as above, totally controls relative and double bond configuration (Scheme VI).[9] Some exploratory experiments to test the proposed methodology were first carried out on dihydrothiazine oxides 23 and 26, prepared from N-sulfinyl carbamate 21 and isomeric dienes 22 and 25, respectively. Diels-Alder adduct 23 was a 20:1 mixture of sulfur stereoisomers which was not separated. Adduct 26 was a single stereoisomer. In neither case was sulfur configuration determined. Sulfinyl compound 21, easily prepared in situ from benzyl carbamate and thionyl chloride/pyridine, was used here since we anticipated that eventual nitrogen deprotection would be facile with this group.

Treatment of adduct 23 with phenylmagnesium bromide at low temperature gave an allylic sulfoxide[10] which was heated overnight with trimethyl phosphite in refluxing methanol to afford E-threo hydroxy carbamate 24 (85% yield). Similarly, adduct 26 produced the E-erythro isomer 27 (85% yield). No other stereoisomers could be detected by ^{1}H NMR in either series of reactions.

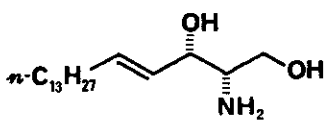
The transformation of Diels-Alder adduct 23, derived from E,E-2,4-hexadiene (22), to the E-threo product 24 is rationalized in Scheme VII. Opening of the dihydrothiazine oxide ring with phenylmagnesium bromide initially affords allylic sulfoxide 28. It is well established that such allylic sulfoxides undergo rapid reversible [2,3]-sigmatropic rearrangement to sulfenate esters.[11] One would anticipate that 28 would rearrange to 29 via an envelope-like transition state[11] in which the methyl group on the sulfur bearing carbon would occupy a quasi-equatorial position to avoid $A^{1,3}$-strain with the C-4 groups. The product of such a rearrangement, after desulfurization, would have the E-threo configuration observed in the experiments. However, the formation of 24 is actually more complex as was seen by ^{1}H NMR studies. The initially formed

Scheme VII

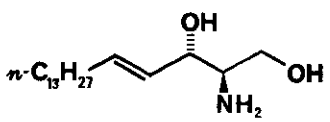


sulfoxide 28, having the expected cis double bond, was found to totally rearrange in 4 hours at 50°C to the trans-sulfoxide 30. This reaction is faster than sulfenate ester desulfurization by phosphite which required heating at 60°C for 12 hours. Such an isomerization of a cis allylic sulfoxide to the trans compound is precedented.[12] Formation of 30 from 28 probably occurs through a reversible rearrangement via sulfenate ester conformers 29A and 29B (Scheme VII). Treatment of pure sulfoxide 30 with trimethyl phosphite in refluxing methanol afforded only E -threo carbamate alcohol 24. Therefore, the formation of 24 occurs stereospecifically from both allylic sulfoxides 28 and 30.[12] The E-erythro compound 27 is presumably derived from adduct 26 by a similar route through an intermediate sulfoxide epimeric to 28 at C-4.

This method thus allows one to efficiently transform the double bond geometry of a 1,3-diene via a dihydrothiazine oxide to an unsaturated amino alcohol derivative having predictable double bond geometry and relative configuration. Application of this methodology to synthesis of the sphingolipid bases threo-sphingosine (31) and erythro-sphingosine (32) was investigated next. Although several syntheses of these compounds have been previously reported,[13] none completely control both double bond geometry and relative configuration of the two chiral centers in 31 and



31 (threo)



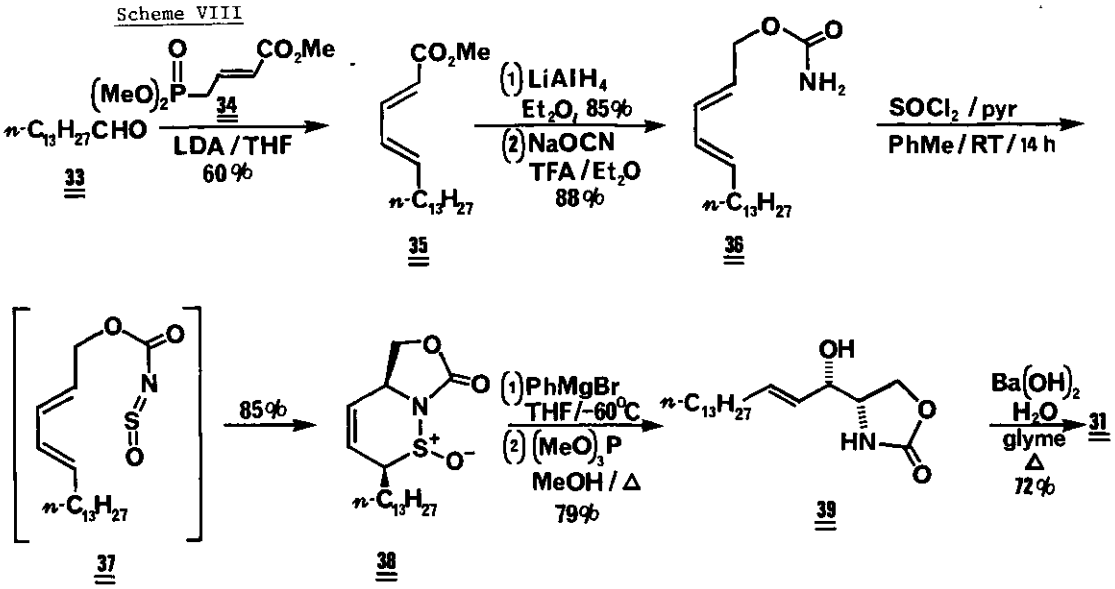
32 (erythro)

32. In considering possible unsymmetrical 1,3-dienes for use in synthesis of the sphingosines, it became evident that regiochemical problems would probably result in the initial Diels-Alder steps. We have solved these potential difficulties by employing intramolecular N-sulfinyl dienophile cycloadditions. Such intramolecular cyclizations have not previously been reported.[1]

The synthesis of threo-sphingosine (31) starting from n-tetradecanal (33) is shown in Scheme VIII. Conversion of 33 with the anion of crotyl phosphonate 34 gave diene ester 35 having exclusively the requisite E,E-geometry. This compound was transformed to the primary carbamate 36 in two additional steps. Treatment of 36 with thionyl chloride gave the N-sulfinyl carbamate 37 which cyclized overnight to afford Diels-Alder adduct 38 in high yield.

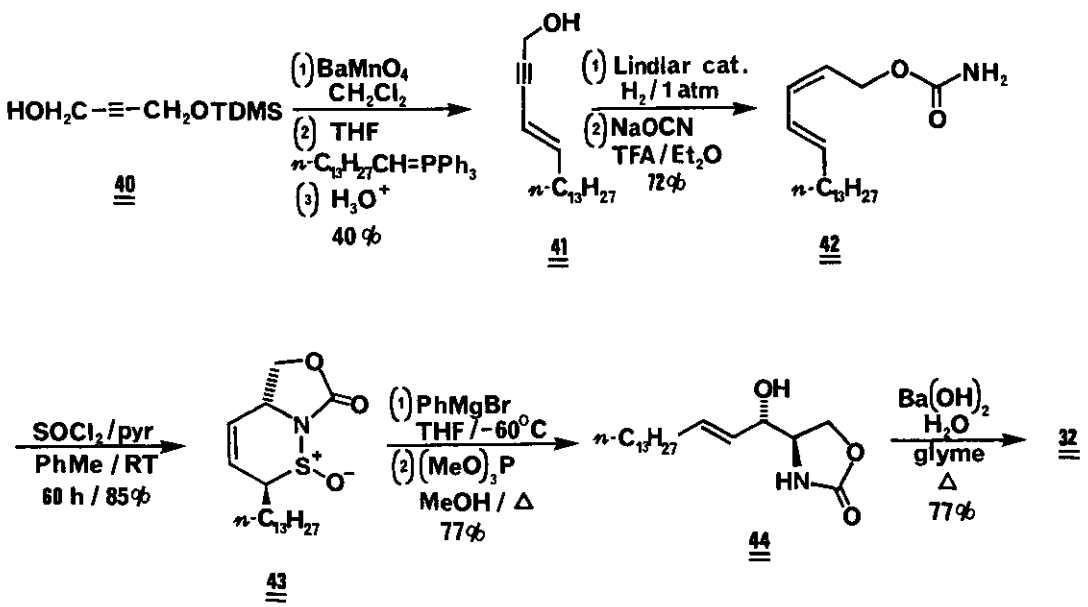
The two-step sequence used in the above model studies served to convert 38 to the unsaturated carbamate alcohol 39. Only the stereoisomer shown was detected in this process. Hydrolysis of 39 afforded threo-sphingosine (31).

Scheme VIII

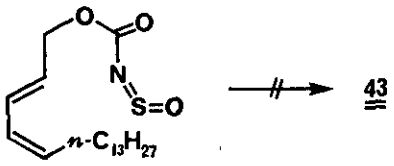


Synthesis of erythro-sphingosine required a starting E,Z-1,3-diene, and the successful synthetic route is shown in Scheme IX. Acetylenic alcohol 40 was converted to E-olefin 41 by standard chemistry.[14] Hydrogenation of 41 afforded a diene alcohol with the desired stereochemistry which was transformed to carbamate 42. This carbamate, on treatment with thionyl chloride/pyridine, formed a N-sulfinyl carbamate intermediate which slowly cyclized at room

Scheme IX



temperature to dihydrothiazine oxide 43. That this cycloaddition was sluggish relative to the E,E-diene (Scheme VIII) is not surprising, since it is well known that E,Z-dienes such as 42 have difficulty in attaining the requisite s-cis conformation. In this regard, it might be noted that compound 45 was also prepared, but could not be induced to cyclize to 43. This lack of Diels-Alder reactivity is probably due to the inability of 45 to attain an s-cis conformation because of the bulky n-alkyl chain.



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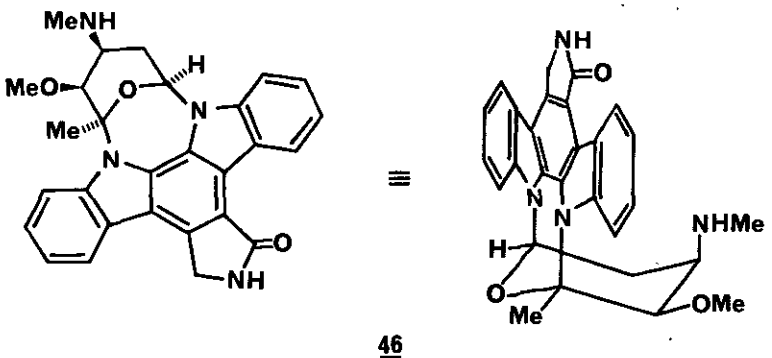
To complete the sphingosine synthesis, adduct 43 was rearranged using the usual procedure cleanly affording erythro-carbamate alcohol 44. Basic hydrolysis of 44 yielded erythro-sphingosine (32).

Recently, we have begun to apply N-sulfinyl dienophile Diels-Alder chemistry to synthesis of the structurally unique microbial metabolite staurosporine (46).[15] This compound is produced by Streptomyces staurosporeus[16] and its structure was elucidated in 1978 by X-ray crystallography.[17] Interest in this molecule has been heightened by its reported antibiotic and antihypertensive activity.[16] Staurosporine is most likely constructed in Nature from a tryptophan-derived aromatic unit and an amino sugar moiety which are connected by an unusual double N-glycosidic



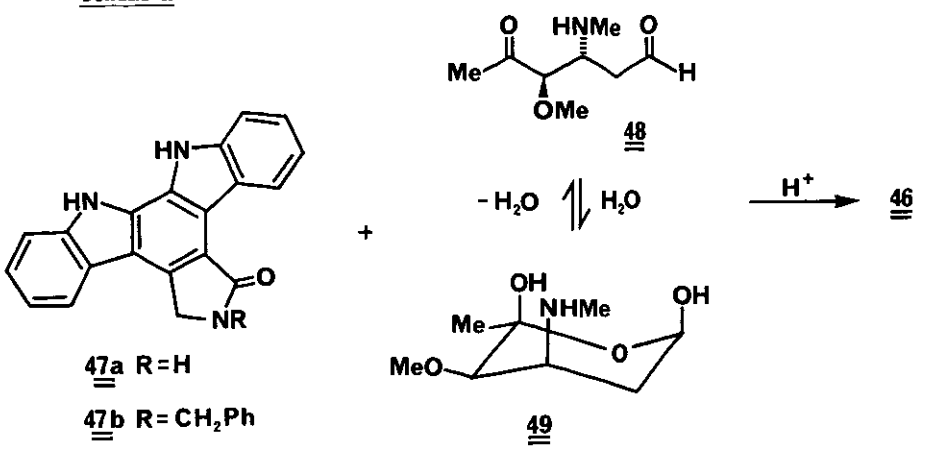
46

linkage.

Our overall synthetic strategy for eventual construction of staurosporine is shown in Scheme X, and is based upon coupling of an aromatic indolocarbazole 47a with an amino sugar-like moiety 48 or 49. It is important to note that there are regio- and stereochemical

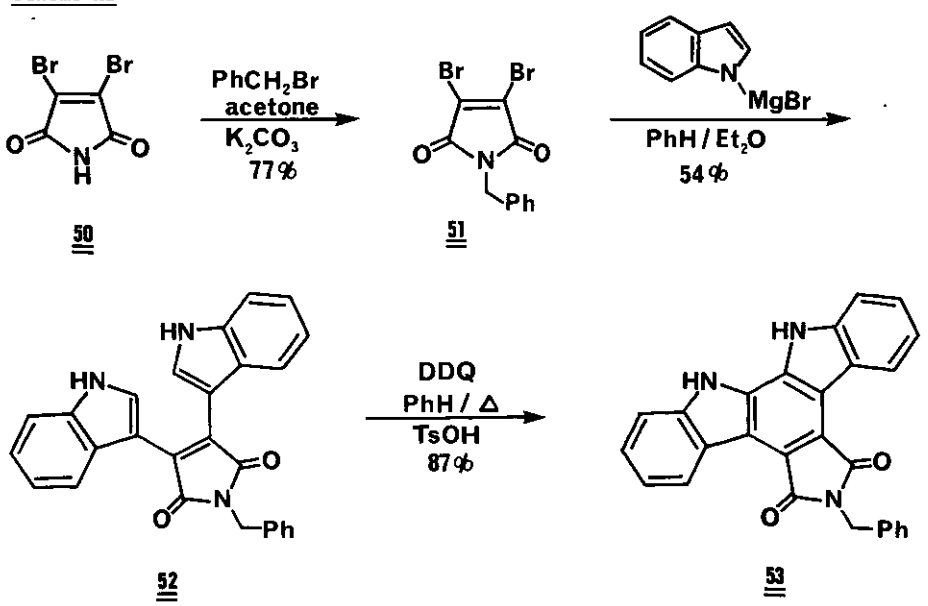
problems inherent in this approach which will ultimately have to be addressed. At present, however, we have been primarily concerned with syntheses of the appropriate individual components.

Scheme X



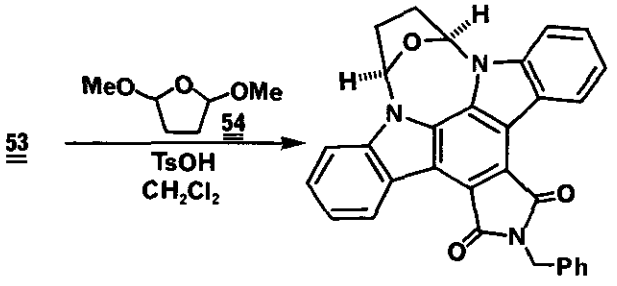
Aromatic systems similar to 47 have been isolated from some fungi by Steglich, et al.[18] These workers also described some synthetic studies on these compounds, and we have used a variation of their methodology to prepare hexacyclic imide 53 as outlined in Scheme XI. Dibromomaleimide (50) was N-benzylated to afford 51, which upon treatment with indolylmagnesium bromide gave 52. Oxidative cyclization of 52 was best achieved with p-toluenesulfonic acid/DDQ to provide 53 in excellent yield.[18]

Scheme XI



Raphael has recently described an elegant route to imide 53, which was subsequently reduced to the desired lactam 47b.[19] In addition, Winterfeldt has reported a biogenetically-patterned synthesis of 47a.[20]

In order to test that in fact the type of double N-glycosidic linkage found in staurosporine could be produced from 53, this compound was condensed under acid catalysis with model bis-acetal 54 to afford adduct 55 in good yield.



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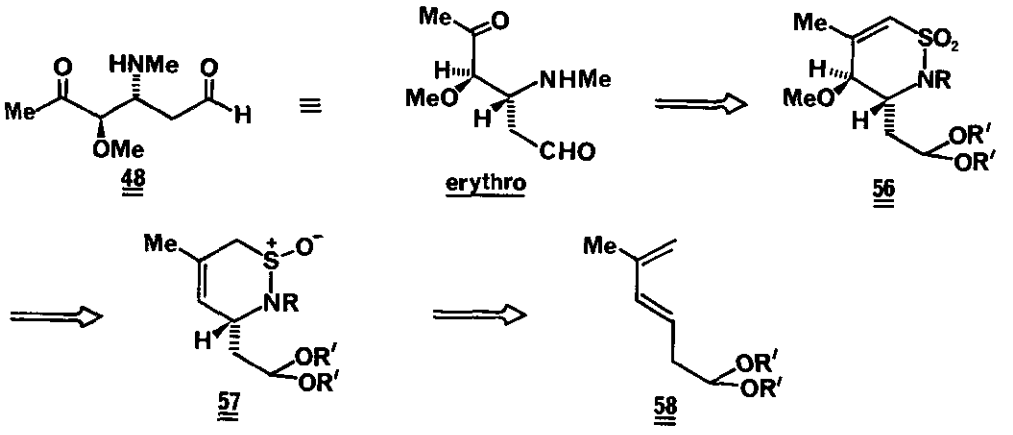
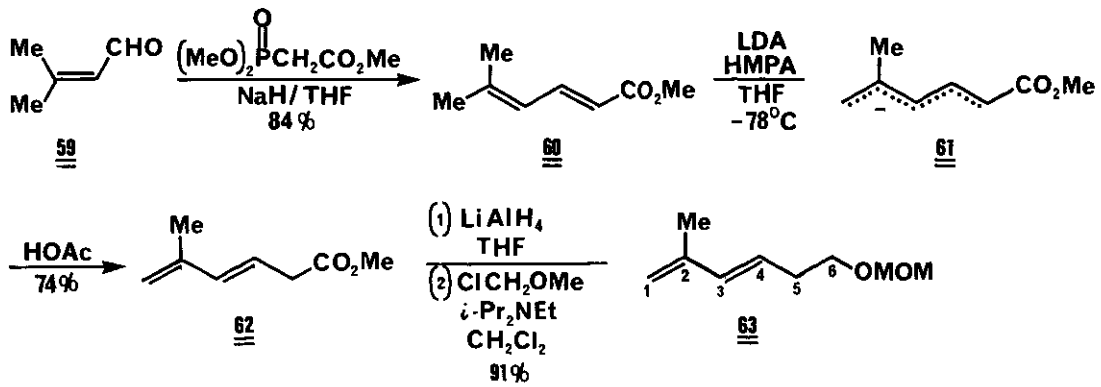
The planned construction of the required keto aldehyde 48 is shown in retrosynthetic form in Scheme XII. It is our intention to prepare 48 from compound 56 which contains the erythro relative stereochemistry present in the natural product aminoglycoside component. Vinyl sultam 56 might in turn be produced from dihydrothiazine oxide 57, presumably easily available by Diels-Alder cycloaddition of diene acetal 58 and an N-sulfinyl dienophile.

Scheme XII



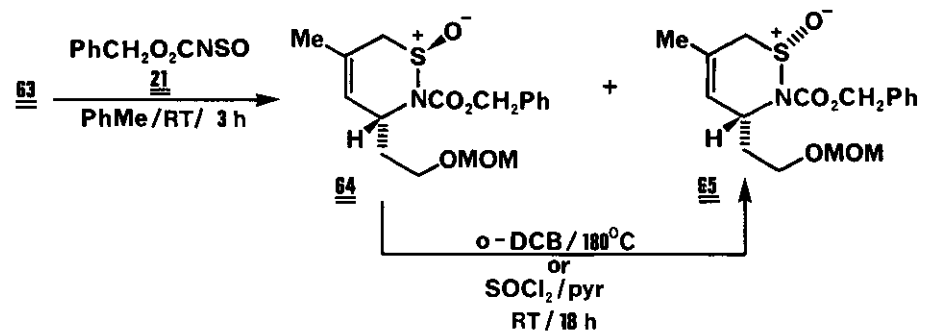
Towards this goal some model experiments have been conducted to test the validity of the approach. Thus, diene 63 was prepared as shown in Scheme XIII. Condensation of aldehyde 59 with trimethylphosphonoacetate gave diene ester 60. Deprotonation of 60 with LDA and reprotona-

tion afforded the deconjugated ester 62.[21,22] Hydride reduction of this ester, followed by



protection of the resulting alcohol, yielded O-methoxymethyl diene 63. Although ultimately C-6 of 63 will have to be adjusted to the aldehyde oxidation state (cf 48), model experiments have been conducted using this compound.

Treatment of 63 with N-sulfinyl carbamate 21 prepared in situ at room temperature (4 hours) gave a separable 2:1 mixture of adducts 64 and 65, respectively (91% yield), which differ only in their configuration at sulfur. No other regioisomers were detected in this reaction. We fully anticipated that the adduct orientation shown would be produced here based upon the mechanistic

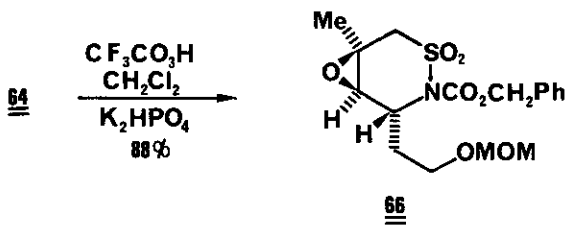


work of Mock previously outlined in Scheme II. It has not yet been possible to establish sulfur configuration in 64 and 65 in a completely unambiguous manner, but assignments have been tentatively made based upon subsequent chemistry (vide infra).

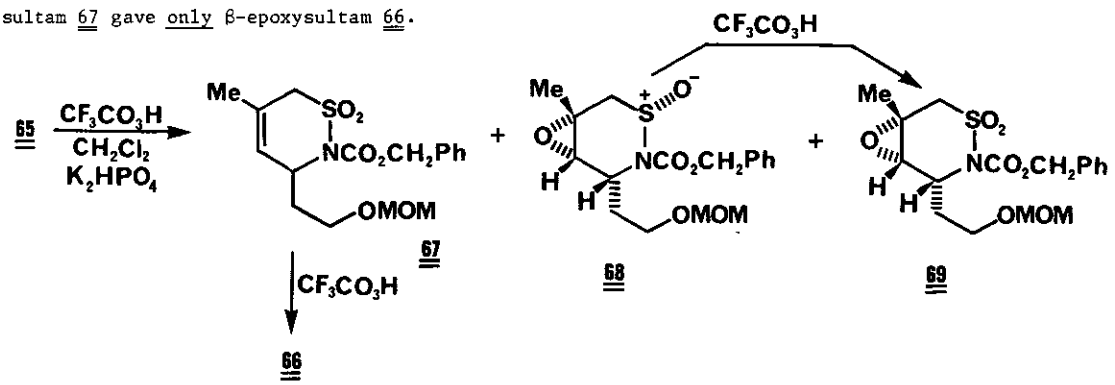
In order to determine whether this Diels-Alder cycloaddition of 63 and 21 might actually be producing a thermodynamic mixture of sulfur epimers 64 and 65, some equilibration experiments were performed. Upon heating at 180°C, adduct 64 was very slowly converted to 65. When 64 was stirred at room temperature with $SOCl_2$/pyridine under conditions approximating the Diels-Alder cycloaddition, 64 was cleanly transformed to 65 in about 18 hours.[21] Adduct 65 did not

afford any epimer 64 under identical conditions. Thus it appears that adduct 64 is a kinetic product of cycloaddition, but it is not clear just how much of 65 is formed by equilibration during the Diels-Alder reaction, and how much is kinetically derived.

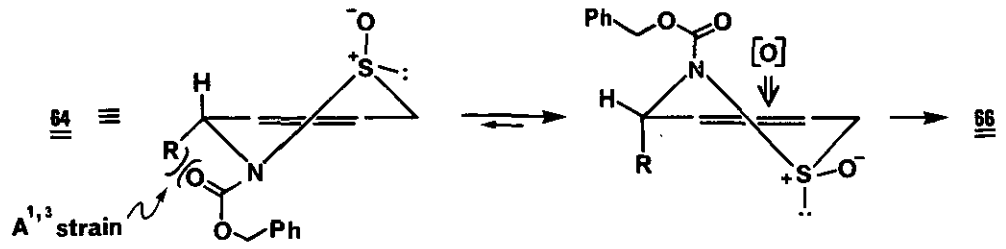
To continue the planned synthetic sequence (Scheme XII) adduct 64 was oxidized with pertrifluoroacetic acid to give exclusively epoxysultam 66. That 66 has the desired β-epoxide stereochemistry was eventually proven by a sequence of reactions to be discussed below.



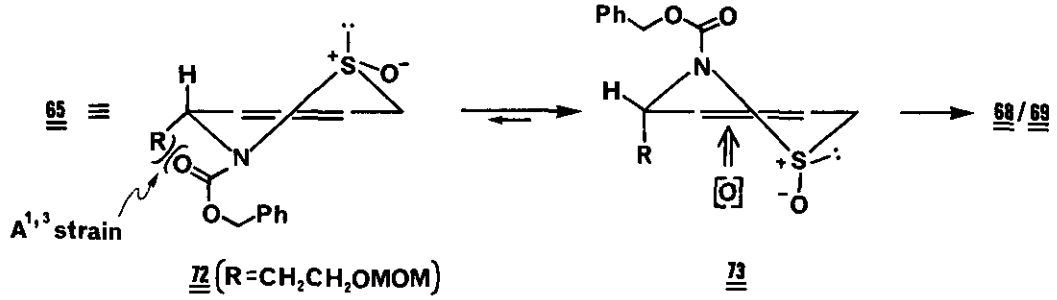
Identical oxidation of the epimeric Diels-Alder adduct 65 gave a mixture of sultam 67 (24%), epoxy-dihydrothiazine oxide 68 (18%), and epoxysultam 69 (51%). Compound 68 could be cleanly oxidized at sulfur to afford sultam 69. As indicated, epoxides 68 and 69 possess the undesired α-configuration, proven by the chemistry outlined below. Interestingly, oxidation of sultam 67 gave only β-epoxysultam 66.



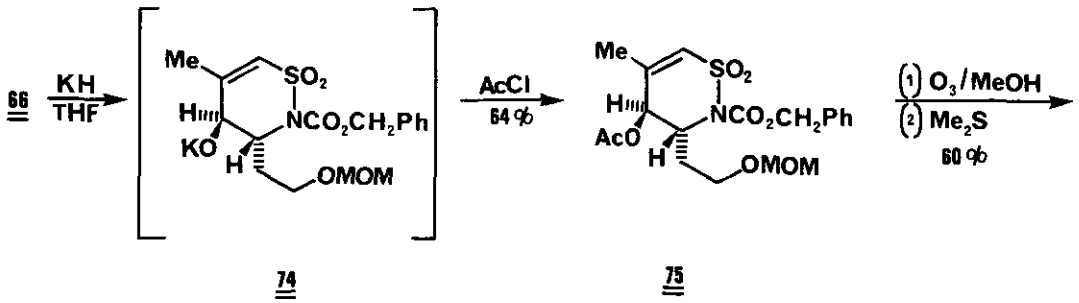
In order to attempt to explain the above epoxidation results, we have made some assumptions concerning the configuration at sulfur in adducts 64 and 65, and about their conformations. It seems reasonable to assume that the ground state conformation of 64 is a half chair and is probably 71. Such a conformation would avoid severe $A^{1,3}$-strain[23] between the dihydrothiazine oxide ring substituent and the carbamate group which is present in the alternative conformer 70. Epoxidation of 71 from the least hindered face would afford the β-epoxide 66 after oxidation at sulfur.

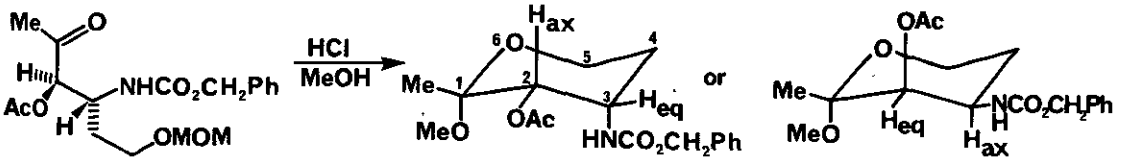


Similarly, adduct 65 would be expected to exist primarily in the half chair conformer 73 to avoid the $A^{1,3}$-strain found in 72. If epoxidation of 73 is directed by the quasi-axial oxygen on sulfur (Henbest effect)[24], then the observed α-epoxides 68 and 69 would be formed. These are tentative rationalizations and will hopefully be proven by future work.



Epoxide 66 was further transformed as shown in Scheme XIV in order to unambiguously establish epoxide stereochemistry and to test the feasibility of the synthetic plan leading to 48 outlined in Scheme XII. Treatment of 66 with potassium hydride gave the unsaturated sultam alkoxide 74 which was acetylated to afford 75. Ozonolysis of 75 produced methyl ketone 76 having the desired erythro stereochemistry (cf 48). This configuration was proven by conversion of 76 to a single tetrahydropyran which has either structure 77 or 78. The key feature of this

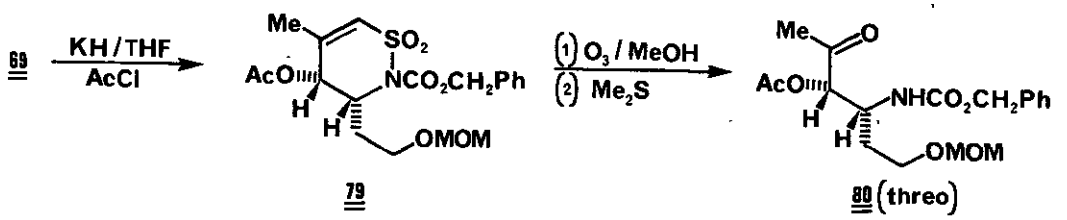




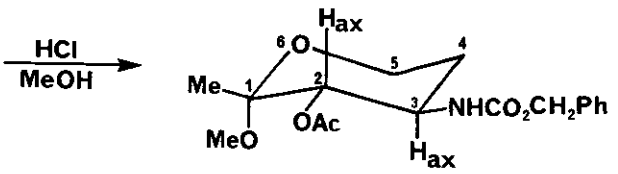
76 (erythro) 77 78

compound is the presence of protons having an axial/equatorial relationship on the acetoxy- and nitrogen-bearing carbons (C-2/C-3), as seen by ^{1}H NMR (J=3.1 Hz). Thus, compound 76 must have the erythro configuration found in staurosporine (46).

To confirm the above assignment, the α-epoxide 69 was similarly degraded. Conversion of 69 to acetate 79, followed by ozonization gave threo ketone 80. Treatment of 80 with methanolic HCl afforded 81, which showed the expected diaxial ^{1}H NMR coupling of protons on C-2 and C-3 (J=10.7 Hz).



79 80 (threo)



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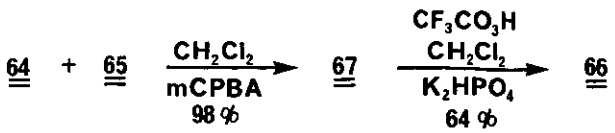
Since it is our intention to use β-epoxide 66 for preparation of 48 via sultam 56 (Scheme XII) it is important that we utilize both epimeric adducts 64 and 65 in the synthesis.



This can be easily done if the mixture of Diels-Alder cycloadducts is first oxidized at sulfur with m-chloroperbenzoic acid to sultam 67 followed by further oxidation with pertrifluoroacetic acid to β-epoxide 66. As mentioned above, epoxidation of sultam 67 had previously been found to be completely β-stereospecific. Work is currently in progress on completion of the total synthesis of staurosporine using the chemistry described here.

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