

A METHOD FOR DIASTEREOSELECTIVE
 SYNTHESIS OF UNSATURATED ACYCLIC AMINES

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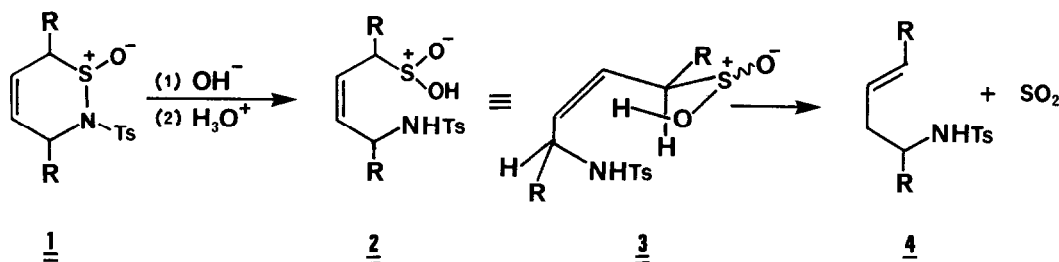
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Summary: Diels-Alder adducts of dienes and N-sulfinyltoluenesulfonamide can be used in synthesis of homoallylic amine derivatives having predictable stereochemistry and double bond geometry.

One of the most active areas of synthetic organic chemistry during the past several years has been in the development of methods for controlling stereochemistry in acyclic systems.¹ Although there has been extensive work on synthesis of oxygenated acyclics, particularly via aldol or aldol-like processes,^{1,2} relatively little general methodology has been reported for diastereoselective synthesis of acyclic amines. We now describe a novel procedure for stereorational construction of diastereomeric homoallylic amines having predictable double bond geometry.

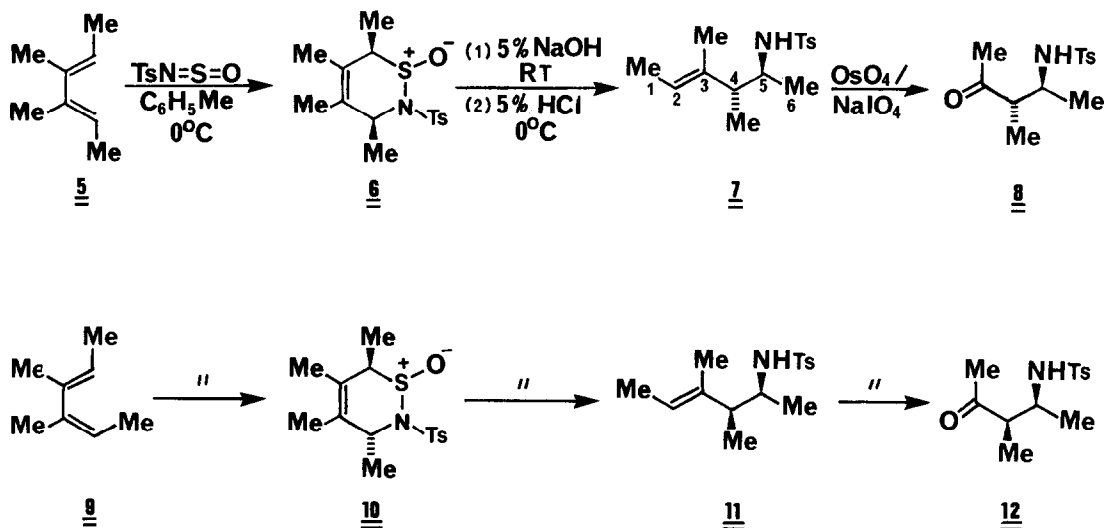
Diels-Alder cycloadditions of various N-sulfinyl imines with 1,3-dienes to produce adducts of type 1 under mild conditions are well documented and are known to show good regio- and stereo-selectivity.^{3,4} To date, however, these readily available heterocycles have found little application in sophisticated synthesis. One known reaction of this sort of adduct which appeared to us to be potentially valuable is the hydrolysis of 1 to unsaturated amine 4 via sulfinic acid 2 (Scheme I).^{3,5} Recently, Mock and Nugent investigated the mechanism of this

Scheme I



transformation.⁶ Based upon some deuterium labeling experiments, they postulated that conversion of 2 to 4 probably involves a concerted retro-ene reaction which occurs through a six-membered chair-like transition state (cf 3). Due to the nature of their experiments, these workers could not answer some important questions. In particular, it could not be determined quantitatively how important a concerted retro-ene reaction was vis-à-vis non-concerted or solvent assisted processes. Also, because of the isotope methods and the substrates used, it was not possible to determine product configurations. The experiments described below both clarify these mechanistic points and demonstrate the synthetic potential of this methodology.

Treatment of E,E-tetramethylbutadiene 5⁷ with *N*-sulfinyltoluenesulfonamide⁸ (0°C, toluene, 0.5 h) rapidly gave Diels-Alder adduct 6, which without purification was hydrolyzed (5% NaOH, room temperature, 12 h; 5% HCl, 0°C) to afford 7 as a single stereoisomer (85% purified yield from 5). No other diastereomer or double bond isomer was detected within the limits of NMR analysis in the crude reaction mixture.



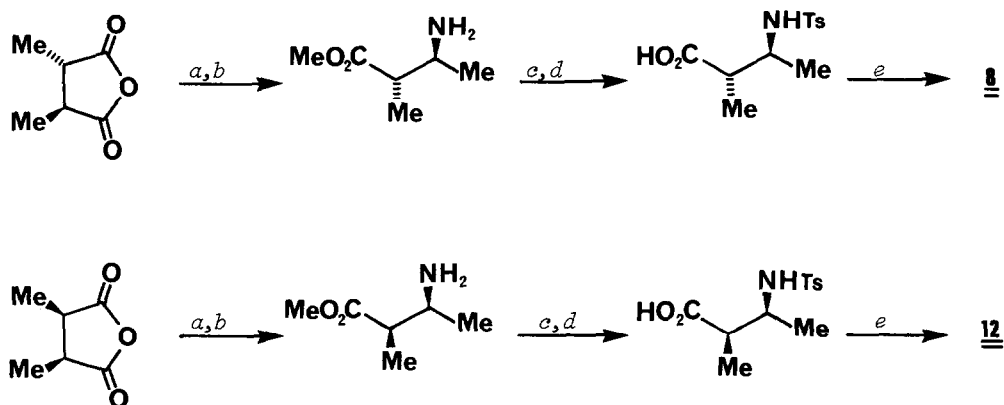
Similarly, E,Z-diene 9⁷ afforded 11 via adduct 10 in 83% yield under the identical reaction conditions used for the E,E-diene series. Once again, 11 was found to be exclusively one stereoisomer, but was different from 7.

Both 7 and 11 were shown to have the E-double bond geometry by nuclear Overhauser effect difference spectroscopy (NOEDS). For example, irradiation of the C-2 vinyl proton of 7 gave a 3% enhancement of the C-4 allylic methine proton, but no enhancement of the C-3 methyl signal. In addition, irradiation of the C-3 methyl group produced no enhancement of the vinyl proton.⁹

The relative configurations of the chiral centers in 7 and 11 were established unambiguously by chemical correlation with compounds of known stereochemistry as shown in Scheme II. Thus,

dl-dimethylsuccinic anhydride and meso-dimethylsuccinic anhydride were cleanly converted

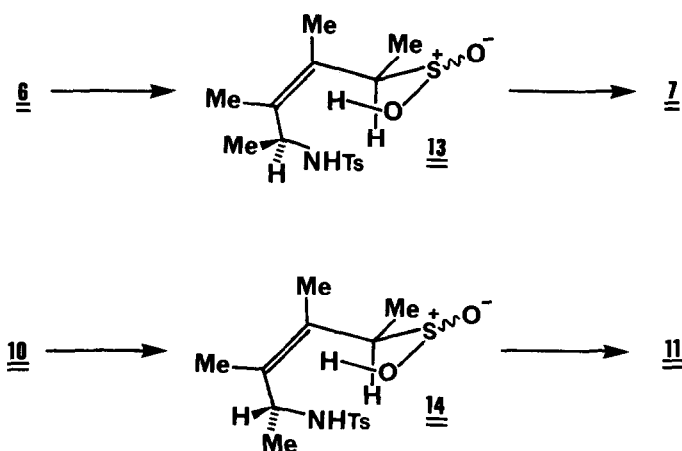
Scheme II^a



^a Key: (a) CH_3OH , room temperature (b) NEt_3 , ClCO_2Et , acetone; $\text{NaN}_3, \text{H}_2\text{O}$; ϕCH_3 , 80°C ; 5% HCl , room temperature (c) TsCl , NEt_3 , CH_2Cl_2 (d) K_2CO_3 , CH_3OH (e) CH_3Li , room temperature, ether.

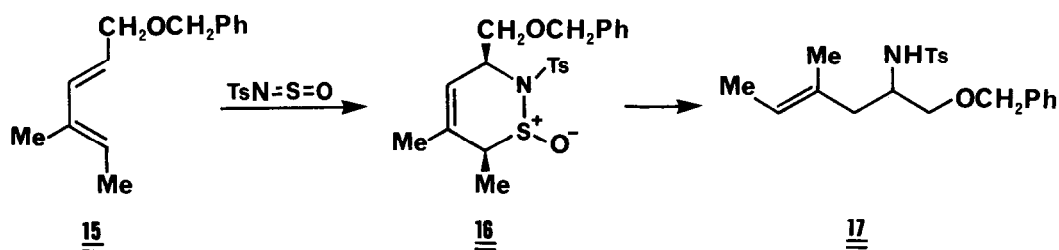
to threo-ketone 8 and erythro-ketone 12, respectively, using standard chemistry.¹⁰ Cleavage of retro-ene product 7 with osmium tetroxide/sodium meta-periodate ($\text{HOAc}/\text{H}_2\text{O}$, room temperature) gave threo-ketone 8 (58%) identical with an authentic sample. Likewise, compound 11 was oxidatively cleaved to afford erythro-ketone 12 (60%) indistinguishable from authentic material.

It is evident from the above discussion that the conversions of 6 to 7 and 10 to 11 are totally stereospecific and are nicely rationalized by a concerted retro-ene mechanism. Thus,



the diastereomeric transition states shown in 13 and 14 lead to the observed product stereochemistry. The important feature of this mechanism is that a substituent on the sulfur-bearing carbon acts as an equatorial "anchor" and thus controls the proton transfer onto a single face of the double bond. We have found no evidence of product crossover, thus ruling out a non-concerted process or one involving proton transfer from solvent.

We believe such a mechanism generally holds for these transformations. Thus, N-sulfinyl-toluenesulfonamide added to diene 15¹¹ (-30°C , $\text{C}_6\text{H}_5\text{CH}_3$, 0.5 h) to afford only regioisomeric adduct 16 (90%),¹² which upon the usual hydrolysis (95%) gave exclusively the predicted E tri-substituted double bond isomer¹³ in 17, even though the product contains only one chiral center.



In conclusion, the chemistry described here provides a unique synthetic method for relating the double bond geometry of a 1,3-diene to relative stereochemistry in a β,γ -unsaturated acyclic amine derivative. We are presently exploring the scope of this procedure and its application to natural product synthesis.

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- (13) Double bond geometry was proven by NOESD methods.⁹
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