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A Highly Stereoselective Synthesis of (E,E)-1,5-Dienes

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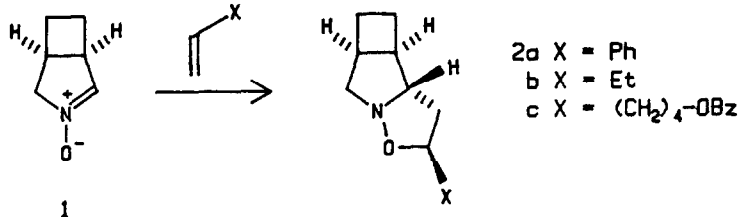
Abstract - Several representative 1,5-dienes were synthesized, with a high degree of regioselectivity, by a series of nitrone cycloadditions and subsequent deamination of the adducts.

Through the use of nitrone cycloaddition chemistry, numerous nitrogenous natural products have been synthesized with excellent stereochemical control;[1] however, very few examples exist which utilize nitrones to generate nitrogen-free products.[2-5] The sesquiterpenes represent a biologically important class of compounds, many of which contain a (E,E)-1,5-diene system. The focus of our recent work has been to synthesize several model compounds containing 1,5-dienes in a highly stereoselective manner by using nitrone cycloaddition chemistry followed by a stereospecific deamination process.

In the proceding communication, we described the synthesis and stereospecific cycloaddition reactions of the bicyclic nitrone **1**, leading to adducts in which the product was formed by cycloaddition from the α-face of the nitrone.[6]



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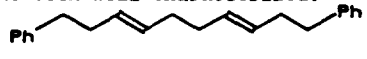
Further manipulation of these adducts allowed us to synthesize the 1,5-dienes, **3-6**, with a high degree of stereoselectivity, where **6** is an isomer of the pink bollworm moth sex pheromone which has been well characterized.[7,8]



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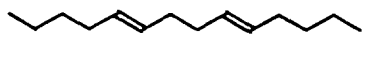

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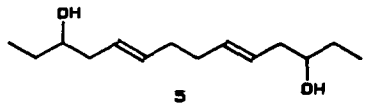

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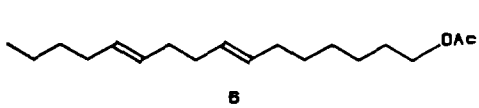

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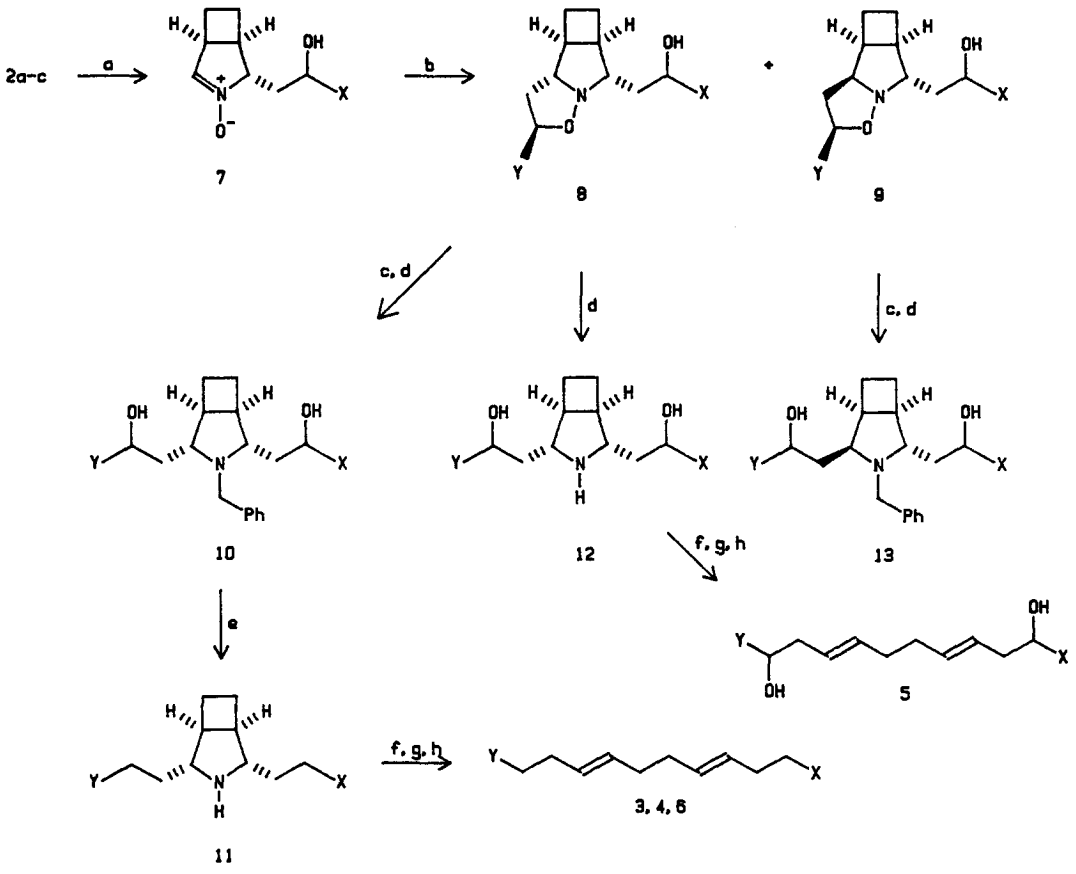
Our general synthetic route is outlined in Scheme I.



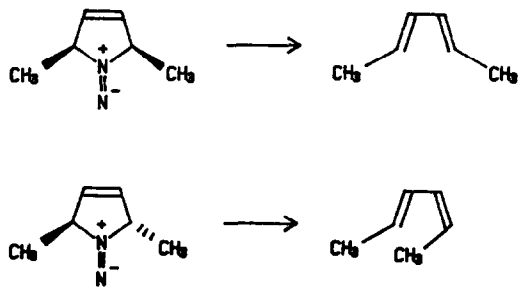
Scheme 1: a. MCPBA; b. H_2C=CH-Y; c. BzBr; d. Zn/HOAc; e. see text; f. HO_3SONO; g. $LiAlH_4$; h. HgO

In order to further functionalize our system the initial adducts were reconverted into nitrones and permitted to react with a second dipolarophile. The oxidative ring opening reaction of isoxazolidine adducts of this type has been shown to produce the less substituted of the two possible nitrones (ie, nitrone **7**) with high regioselectivity. Evidence for the formation of this nitrone is provided by the presence of the proton signal at δ 6.90-7.00 ppm. The cycloaddition of the nitrones **7a-c** with the required dipolarophiles produced separable mixtures of the two stereoisomeric adducts resulting from the addition to the α- or β-face of the nitrone. The reaction of **7a** with styrene (Y = Ph), produced a 67% yield of **8a** and **9a** in a 9:1 ratio. The reaction of **7b** with 1-butene (Y = Et), produced a 77% yield of **8b** and **9b** in a 3:1 ratio. Similarly, the reaction of **7c** with 1-butene (Y = Et) afforded a 77% yield of **8c** and **9c** in a 7:3 ratio. The cycloaddition reactions proceded with good stereoselectivity, providing us with the desired α-face adducts (ie. **8a-c**).

Adducts **8a-c** and **9a-c** were independently N-benzylated with benzyl bromide in greater than 90% yield, and the isoxazolidines were reductively opened with zinc in acetic acid in almost quantitative yield to produce the N-benzyl amino diols **10a-c** and **13a-c.** NMR analysis of the benzylic methylene protons of these compounds confirmed the stereochemical relationship of the side chains. It has been previously shown that a cis relationship between the side chains on a 5-membered ring produces a singlet for the N-benzyl methylene protons, while a trans relationship results in the appearance an AB quartet.[9,10] Compounds **10a-c** exhibit a singlet attributable to the methylene protons at 3.86, 3.83 and 3.90 ppm respectively. The diols with a trans side chain relationship, **13a-c**, show AB quartets centered about 3.64, 3.68 and 3.70 ppm, respectively, with coupling constants all in the range of 12-14 Hz. Aside from confirming the relative stereochemistry of the side chains, the N-benzyl group also protected the nitrogen during the dehydroxylation sequence. Mesylation of **10b** and **10c** with methanesulfonyl chloride and triethylamine gave the dimesylates (91% from **10b** and 97% from **10c**). An S_N2 displacement by Super Hydride efficiently removed the hydroxyl groups in 72 and 86% respective yield. Removal of the N-benzyl protecting group (and the O-benzyl group for **10c**) was accomplished by hydrogenation in acidic ethanol with a mixture of 10% Pd/C and PdO at 1500 psi, thereby providing **11b** and **11c.** The hydroxyl groups could not be removed from **10a** in the same manner due to the instability of the benzylic mesylate.[11] Alternativly, it has been reported that benzylic hydroxyls can be removed by hydrogenation in acidic media using a palladium catalyst.[12] This procedure removed both the hydroxyl groups and the N-benzyl group to give **11a** in 75% yield.

The crucial reaction sequence in our synthesis involved the deamination of **11a-c** in a stereospecific manner to give the all trans 1,5-dienes. It has been demonstrated that diazenes formed from 3-pyrrolines undergo a stereospecific sigmasymmetric fragmentation, producing 1,3-dienes[13] as shown in Scheme II.

Scheme II



The amino compounds **11a-c** were N-nitrosated, using nitroso sulfuric acid,[14] and converted to the corresponding N-amino compounds by reduction with lithium aluminum hydride. Oxidation of the hydrazines using yellow mercuric oxide[15] provides the all trans-1,5-dienes **3, 4** and **6** (after acetylation with acetyl chloride and pyridine) as the sole products formed in greater than 90% overall yield for all three cases. The structures and stereochemistry of **3** and **4** were confirmed by an independent synthesis of the corresponding diacetylenic compounds and subsequent reduction

with sodium and ammonia[16] to provide the trans,trans dienes. Partial reduction with Pd on $BaSO_4$ in the presence of quinoline[17] afforded the cis,cis isomers. Analysis of the ^{13}C-NMR data for **3** and **4** showed it to be identical to the ^{13}C-NMR data for the dienes obtained by the sodium/ammonia reduction, but drastically different from the partially hydrogenated products obtained from the diacetylene precursors, unambiguously confirming that we had synthesized the (E,E)-dienes.[18] All four isomers of the pheromone, (Z,E)-7,11-hexadecadienyl-1-acetate, have been previously synthesized and fully characterized. Analysis of the ^{13}C-NMR data of **6** indicated it corresponded to the (E,E)-isomer.[19]

Reductive cleavage of **8b** with zinc and acetic acid afforded the amino diol **12** quantitatively. When **12** was subjected to the nitrosation, reduction, oxidation sequence, the dihydroxy diene **5** was exclusively obtained in 61% yield, demonstrating that functionality can be incorporated into various parts of the diene. We are currently using this method as an integral part of a synthetic approach directed toward several sesquiterpenes.

Acknowledgement:

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19. ^{13}C-NMR data; for **6**: 13.9, 20.9, 22.1, 25.9, 28.7, 28.7, 29.5, 31.9, 32.2, 32.4, 32.7, 32.7, 64.6, 129.7, 130.0, 130.4, 130.7, 169.5; for **7,11-(E,E)-hexadecadienyl-1-acetate**[8]: 13.9, 20.9, 22.2, 25.9, 28.7, 28.7, 29.5, 31.8, 32.3, 32.3, 32.8, 32.8, 64.5, 129.6, 129.8, 130.2, 130.5, 170.7

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