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Studies of intramolecular Diels–Alder reactions of nitroalkenes for the stereocontrolled synthesis of *trans*-decalin ring systems

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Dedicated in honor of Professor Harry Wasserman on the occasion of his 90th birthday.

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ABSTRACT

Studies of thermal IMDA cyclizations of (1*E*,7*E*)-1-nitro-deca-1,7,9-trienes and (1*E*,3*Z*,7*E*)-1-nitro-deca-1,3,7,9-tetraenes have been examined. Reactions of these nitroalkenes proceed via transition states featuring characteristics of asymmetric stretch asynchronicity and result in stereoselective formation of *trans*-fused decalin products. Substantial rate acceleration is observed for IMDA cyclizations exemplified by triene **14** due to steric repulsions of substituents in the tethering chain which promote facile stereocontrolled formation of *trans*-fused **26**.

The intramolecular Diels–Alder reaction (IMDA) has been extensively utilized as a powerful strategy for the efficient construction of polycyclic systems.[1] Applications of transannular versions of IMDA reactions, as well as a number of creative IMDA strategies, have been featured for natural product synthesis.[2] Nevertheless, there are surprisingly few examples of IMDA processes which describe the use of nitroalkenes as dienophilic components. An early precedent illustrated the thermal cyclizations of 1-nitro-1,6,8-decatrienes for the synthesis of hexahydroindenes,[3] and Kunesch and Tillequin described the cycloaddition of a 1,1-dinitroalkene with a tethered furan to produce 3,7-dinitro-11-oxatricycloundec-9-ene.[4] In 2000, we reported the first study of IMDA reactions of (*E*)-1-nitro-1,7,9-decatrienes leading to substituted decalins as a preliminary investigation toward the synthesis of the AB ring system of norzoanthamine.[5] Alternatively, the use of the nitroalkene moiety as a heterodiene in formal [4 + 2] cyclizations leading to nitronates has been extensively exploited by Denmark and coworkers as an effective strategy for the synthesis of alkaloids.[6] In this communication, we describe studies of IMDA reactions of nitroalkenes which detail factors affecting the relative reactivity of these substrates as well as the observed stereoselectivity of the cyclization process.

A comparative summary is compiled in Table 1 for reports of thermal IMDA cyclizations of several representative decatrienes **1a–d**. Houk has previously noted that the unactivated and unsubstituted (*E*)-deca-1,3,9-triene (**1a**) displays very little stereoselectivity in the production of nearly equal amounts of *trans*-fused and *cis*-fused decalins **2a** and **3a**.[7] Four concerted synchronous transition state arrangements stemming from **4–7** are feasible in which the staggered conformations of the tethering carbon chain are compatible with a minimization of ring strain in the developing chair-like B-ring. Thus *cis*-fused decalins are derived from arrangements **5** and **6** in which the transition state positions the diene in an axial orientation with respect to the developing cyclohexane of the tether. The incorporation of the ester in methyl (*E*,*E*)-undeca-2,8,10-trienoate (**1b**) does not significantly alter the product distribution even though this electron-withdrawing functionality increases the relative rate of the IMDA process.[8] Further enhancement of the rate of the reaction is observed by the inclusion of the terminal nitro group in **1c** and **1d**, and these examples display a modest improvement in stereoselectivity which favors the *trans*-fused products **2c** and **2d**.[5] Finally, the precoordination of Lewis acids results in powerful electron-withdrawing effects which dramatically alter the LUMO of the dienophile in **1e**, and result in high *trans*-stereoselectivity (**2e**:**3e** ratio 97:3).[9] These aspects of stereocontrol appear to correlate with a change from a concerted and highly synchronous reaction to a concerted, asynchronous pathway with increasing polarization of the dienophile. Indeed, Houk and Brown first described asymmetric stretch asynchronicity[10] as a relevant concept leading to internal compression of the reacting C_2 and C_7 loci which proceeds to a greater preference for the *trans*-fused *endo*-transition states from **4** and **7**.

Our recent studies have examined the intramolecular [4Π + 2Π] cycloaddition of the 1-nitro-deca-1,3,6,8-tetraene system **8** (Scheme 1).[11]

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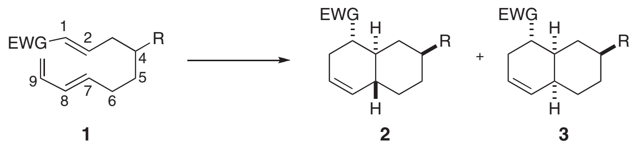
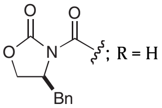
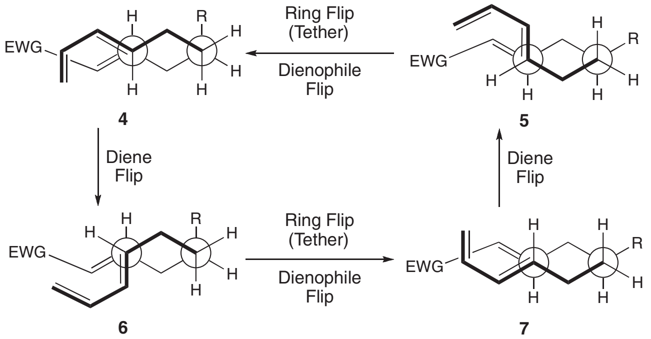
Table 1
A comparison study of the formation of *trans*- and *cis*-decalins via thermal IMDA cyclizations



Entry	Triene	Conditions	Yield (%) (ratio **2**:**3**)	Literature reference
1	**1a** EWG = H; R = H	220 °C/cyclohex	92 (48:52)	Ref. 7
2	**1b** EWG = COOMe; R = H	155 °C/toluene	92 (51:49)	Ref. 8
3	**1c** EWG = NO_2; R = H	85 °C/benzene	63 (73:27)	Ref. 5
4	**1d** EWG = NO_2; R = CH_3	85 °C/benzene	80 (73:27)	Ref. 5
5	**1e** EWG =  ; R = H	Me_2AlCl (1.4 equiv) −30 °C/CH_2Cl_2	88 (97:3)	Ref. 9



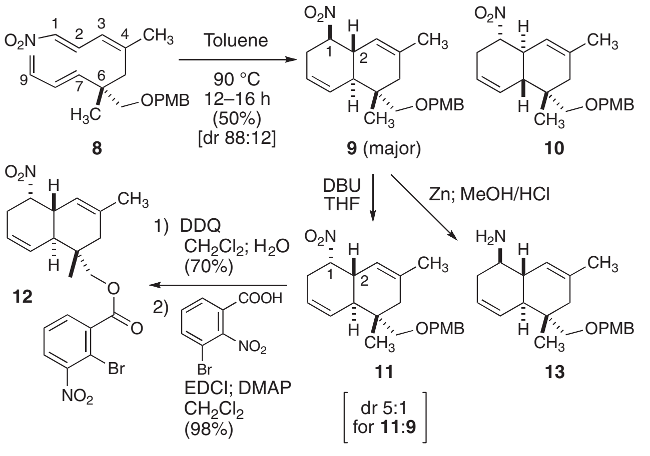
Investigations of IMDA reactions of related tetraenes have not been previously explored. However, the incorporation of the (*Z*)-C_3–C_4 double bond in **8** was expected to provide an important element of conformational constraint which, in addition to the presence of the fully substituted C_6 carbon, would facilitate the cyclization process. One caveat is posed by the potential for thermal (*Z*) → (*E*) isomerization in **8**. Mulzer and coworkers have recently addressed this issue by the design of an *exo*-selective transannular Diels–Alder reaction yielding *cis*-decalin products.[12]

In the event, we have observed slow cyclizations of **8** proceeding to 50% conversion upon heating at 90 °C under argon atmosphere in toluene (or xylenes) over a period of 12–15 h. Small quantities of BHT are added to curtail radical decomposition processes, but longer reaction times lead to side products from destruction of the starting tetraene. In practice, we have routinely isolated a 50% yield of the substituted decalins **9** and **10** as a 88:12 ratio of diastereomers with the recovery of 45% yield of the starting material. In this fashion, approximately 72% yield of the *trans*-decalins **9** and **10** can be achieved after one recycle of starting tetraene.

Purification by flash silica gel chromatography afforded complete characterizations of **9** and **10**, and NMR studies showed key NOESY correlations as depicted in Figure 1, which led to the assignments of relative stereochemistry.

Under basic conditions, product **9** underwent isomerization to give a separable mixture of C_1 epimers (99%, dr 5:1) in which the axial diastereomer **11** was identified as the major component. A number of bases produced the same unanticipated result. Indeed, our calculations confirm that **11** is less stable than the starting equatorial **9** by approximately 2.0 kcal/mol. This outcome suggests that the accumulation of **11** is the result of an unanticipated kinetic effect. Removal of the PMB ether and esterification yielded a highly crystalline sample of **12** (mp 111–112 °C), and X-ray diffraction studies of **12** provided an unambiguous stereochemical assignment.[13] In addition, selective reduction with zinc in methanolic HCl yields the amino-substituted *trans*-decalins, such as **13** (70%) for further derivations.

Based on the cyclization results, we postulate that features of extended conjugation in tetraene **8**, which lower the LUMO energy of the nitroalkene dienophile, have very little effect on the rate of



Scheme 1. Studies of tetraene **8**.

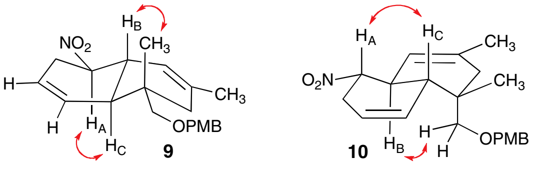


Figure 1. Key NOESY correlations for **9** and **10**.