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Studies of intramolecular Diels–Alder reactions of nitroalkenes for the stereocontrolled synthesis of *trans*-decalin ring systems¹

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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. A 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**.

Keywords

intramolecular Diels–Alder reaction; 1-nitro-deca-1,3,7,9-tetraenes; 1-nitro-deca-1,7,9-trienes; *trans*-decalins; asynchronous transition states

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 towards 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

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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 result 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 asynchronicity¹⁰ as a relevant concept leading to internal compression of the reacting C₂ and C₇ 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 $[4\pi + 2\pi]$ cycloaddition of the 1-nitro-deca-1,3,6,8-tetraene system **8** (Scheme 1).¹¹

Investigations of IMDA reactions of related tetraenes have not been previously explored. However, the incorporation of the (*Z*)-C₃–C₄ double bond in **8** was expected to provide an important element of conformational constraint which, in addition to the presence of the fully substituted C₆ 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 hours. 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 C₁ 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 this IMDA reaction. However, geometrical constraints imposed by the additional C=C benefit the asynchronous, *endo*-transition state affording higher *trans*-selectivity as compared with corresponding *exo* transition states leading to *cis*-decalins as seen in Table 1.

The observed stereochemical preference favoring the production of *trans*-fused decalins provided encouragement for studies of increasing structural complexity within the tethering chain as a prelude for efforts toward biologically significant natural products. In this regard, Scheme 2 illustrates a pathway of general utility which has led to the Diels–Alder nitroalkene precursors **14** and **15**. The optically active (*Z*)-allylic alcohol **16** affords nearly quantitative esterification with (+)-3-methylnonanoic acid (**17**) to yield **18** as a single, nonracemic diastereomer.¹⁴

A Claisen rearrangement protocol, featuring the slow addition of **18** into a THF solution of LDA and freshly distilled TMS-Cl, provides for conversion to an intermediate (*E*)-silylketene acetal which is heated to reflux in toluene (12 h). The methyl ester **19** is obtained in 86% yield following an aqueous workup and esterification. Subsequent cleavage of the silyl ether gave a primary alcohol and mesylation provided an unstable homoallylic mesylate for elimination, yielding the desired diene **19** (91% yield; 3 steps). Elongation of the carbon chain via an aldol condensation of the enolate of *tert*-butylacetate with aldehyde **20** leads to **21** (dr approximately 1:1) in excellent overall yield. However, further manipulations incorporating the (*E*)-nitroalkene dienophile required a selection of conditions to avoid β -elimination of the C-4 MOM ethers. This is accomplished by DIBAL reduction of **21** at -78°C and buffered Dess–Martin oxidation of the resulting primary alcohols to give the aldehydes **22**. Finally, Henry reactions¹⁵ with nitromethane are effectively achieved using KF in isopropanol at 22°C (98% yields) and resulted in the isolation of the diastereomeric β -hydroxynitroalkane adducts. Subsequently, mild dehydrations are accomplished with methanesulfonyl chloride and Et_3N to produce the triene precursors **14** and **15**, respectively, as unstable species which readily undergo the IMDA reaction.

Based upon our mechanistic analysis of these IMDA cyclizations, we anticipated a transition state B-ring anchored by the branched alkyl group at C₅ as an equatorial substituent of a preferred chair arrangement. The protected hydroxyl functionality was viewed as less significant although there were initial concerns about the propensity for elimination reactions under the thermal conditions. These fears proved to be unwarranted since the IMDA reaction of triene **23**, as described in our previous efforts toward norzoanthamine, proceeded at 80°C in refluxing benzene over 65 hours to yield **24** and **25** in 92% yield [dr 91:9].⁵ On the other hand, we were surprised to observe a remarkable rate enhancement in studies of the trienes **14** and **15** which resulted in production of small amounts of cyclization products at room temperature during silica gel chromatography of the IMDA precursors. Upon heating to reflux in benzene (containing BHT), the triene **14** was completely converted to **26** (85% yield) and **27** (4% yield) within 4 hours.¹⁶ Under identical conditions, the C-4 diastereomer **15** yielded three cyclization products (dr 25:55:20). The more polar, minor component was readily separated by flash chromatography and identified as *cis*-fused **29**.¹⁷ Preparative HPLC led to the separation and purification of the *trans*-fused decalin **28** as the major product,¹⁷ and an additional isomer, which is assumed to be the alternative *trans*-fused system based on previous trends. Unfortunately, an unambiguous assignment of

this third diastereomer was not feasible because key ^1H signals were overlapping and insufficiently resolved for correlations in 2D-COSY and 2D-NOESY spectra.

The presence of the branched C-5 alkyl substituent in trienes **14** and **15** leads to a substantial IMDA rate acceleration as a consequence of a Thorpe–Ingold effect from which steric repulsions of C-5 and C-6 substituents result in the compression of internal C-2 and C-7 loci in the Diels–Alder *endo*-transition states. The presentation of an axial OMOM substituent in the transition state from **15** destabilizes the B-ring chair arrangement owing to the 1,3-diaxial interaction with the C-6 methyl group and diminishes *trans*-selectivity in this IMDA example.

In conclusion, investigations of IMDA reactions using nitroalkene dienophiles have demonstrated the production of *trans*-fused decalin systems with high stereoselectivity. Our mechanistic rationale considers the benefits of geometrical constraints and steric repulsions within the tethering carbon chain which facilitate asynchronous, *endo*-transition states. Applications for the synthesis of natural products are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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13. Colorless monoclinic crystals of **12** (space group $P2_1$) were submitted for X-ray diffraction and the structure **12** was solved using SIR-2004 and refined with SHELLXL-97. The final full matrix least squares refinement converged to $R1 = 0.0225$ and $wR2 = 0.0560$ (F^2 , all data). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (No CCDC-796539) and can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax (+44) 1223-336-033; deposit@ccdc.cam.ac.uk).
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16. Key observed NOESY cross peaks for **26** and **27** from 2D NMR are summarized below:

17. Key NOESY cross peaks observed in the 2D NMR spectra of **28** and **29** are shown below:

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

Scheme 1.
Studies of tetraene **8**

Scheme 2.
Preparation of trienes **14** and **15**

Scheme 3.
IMDA cyclization of **23**

Scheme 4.
IMDA cyclizations of trienes **14** and **15**

Table 1A 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 ₂ AlCl (1.4 eq) -30 °C/CH ₂ Cl ₂	88 (97:3)	Ref. 9