Tetrahedron Letters 52 (2011) 2120-2123

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet



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

David R. Williams*, J. Cullen Klein, Nicholas S. C. Chow

Department of Chemistry, Indiana University, Bloomington, IN 47405, United States

ARTICLE INFO

Article history: Available online 11 November 2010

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

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

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 stereo-controlled formation of *trans*-fused **26**.

© 2010 Elsevier Ltd. All rights reserved.

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 stereoselec-

tivity 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 transfused 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 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



^{*} Corresponding author. Tel.: +1 812 855 6629; fax: +1 812 855 8300. *E-mail address:* williamd@indiana.edu (D.R. Williams).

^{0040-4039/\$ -} see front matter \odot 2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2010.11.012

 Table 1

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

	EWG 9	$\xrightarrow{2}_{7} \xrightarrow{4}_{6}^{R} \xrightarrow{EWG}_{H}$	+ H H H	
		1 2	3	
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	$1e EWG = O \bigvee_{Bn} V f^{s}; R = H$	$Me_2AlCl (1.4 equiv) -30 \circ C/CH_2Cl_2$	88 (97:3)	Ref. 9
	EWG	H H H H H H H H H H H H H H H H H H H		
	biene Flip Flip			
	EWG	H H H H H H H H H H H H H H H H H H H		
		6	7	

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 $(Z) \rightarrow (E)$ 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



Scheme 1. Studies of tetraene 8.

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



Figure 1. Key NOESY correlations for 9 and 10.

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*)-silvlketene 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 silvl ether gave a primary alcohol and mesylation provided an unstable homoallylic mesylate for elimination, yielding the desired diene 19 (91% yield; three-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*-hydroxy-nitroalkane adducts. Subsequently, mild dehydrations are accomplished with methanesulfonyl chloride and Et₃N 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 C_5 as an equatorial substituent of a pre-

17 OPMB HC H ОН OPMB H₁₀C EDCI: DMAP RC RO CH₂ CH₂Cl₂ (98%) **16** (R = Si^tBuPh₂) 18 (R = Si^tBuPh₂) CH₃ L i⁺ -0 1) LDA; THF TMSCI ^tBuO C₆H₁₃ THF; -78 °C then: toluene; Δ OPMB ĒН₃ then: MOM-Cl 2) CN₂N₂ DMAP (83%; 2 steps) 1) LAH CH₂Cl₂ 3) TBAF 19 R = OMe ether (90%) 4) Ms₂O; pyr -20 °C 20 B = H DMP then: K+-OtBu 2) NaHCO₃ (91%; 3 steps) (91%) MOMC CH₃ C_eH₁₃ OPMB H₃CNO₂ 1) ĊΗ₃ KF; i-PrOH O₂N C₆H₁₃ (98%) 14 OPMB 10 ĊH₃ 2) MsCl; Et₃N CH₃ момо н CH₂Cl₂ at 0 °C C₆H₁₃ 1) DIBAL R = O^tBu 21 –78 °C OPMB DMP 2) ĊH₃ 22 R = H NaHCO₃ (85%; 2 steps) 15

Scheme 2. Preparation of trienes 14 and 15.

ferred 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 h to yield 24 and 25 in 92% yield [dr 91:9] (Scheme 3).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 the 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 h (Scheme 4).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







Scheme 4. IMDA cyclizations of trienes 14 and 15

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.

Acknowledgments

We thank Indiana University, Faculty Research Support Program, and the National Institutes of Health (GM041560) for partial support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.012.

References and notes

- 1. For a review: Takao, K.-i.; Munakata, R.; Tadano, K.-i. Chem. Rev. 2005, 105, 4779-4807
- 2 For a tutorial review: Juhl, M.; Tanner, D. Chem. Soc. Rev. 2009, 38, 2983-2992. (a) Kurth, M. J.; O'Brien, M. J.; Hope, H.; Yanuck, M. J. Org. Chem. 1985, 50, 2626-3.
- 2632; (b) Retherford, C.; Knochel, P. Tetrahedron Lett. 1991, 32, 441-444. 4. Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. Tetrahedron 1998, 54,
- 1773-1782.
- Williams, D. R.; Brugel, T. A. Org. Lett. 2000, 2, 1023-1026. 5
- For a leading publication in this area, see: (a) Denmark, S. E.; Seierstad, M. J. 6. Org. Chem. 1999, 64, 1610-1619; For a review of tandem [4+2]/[3+2] cycloaddition reactions of nitroalkenes, see: (b) Denmark, S. E.; Thorarensen, A. Chem. Rev. 1996, 96, 137-166.
- Lin, Y.-T.; Houk, K. N. Tetrahedron Lett. 1985, 26, 2269-2272.
- 8. Roush, W. R.; Hall, S. E. J. Am. Chem. Soc. 1981, 103, 5200-5211.
- 9. Evans, D. A.; Chapman, K. T.; Bisaha, J. Tetrahedron Lett. 1984, 25, 4071-4074.
- Brown, F. K.; Houk, K. N. Tetrahedron Lett. 1985, 26, 2297-2300. 10. 11.
- Synthesis of optically active tetraene 8 utilized the terminal alkyne i which was prepared by sequential execution of an Eschenmoser-Claisen rearrangement, DIBAL reduction and Seyferth-Gilbert homologation beginning with the enantiomeric allyl alcohol of 16. Acylation followed by the syn-addition of dimethylcuprate produced the Z-unsaturated ester ii for the subsequent Henry reaction of iii and dehydration. A full description will be incorporated in the complete account of these studies.



- 12. Felzmann, W.; Arion, V. B.; Mieusset, J.-L.; Mulzer, J. Org. Lett. 2006, 8, 3849-3851
- Colorless monoclinic crystals of **12** (space group P2₁) were submitted for X-ray 13 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; e-mail: deposit@ccdc.cam.ac.uk).
- 14. Preparation of (+)-3-methylnonanoic acid (17) is accomplished via an asymmetric conjugate addition using N-acyloxazolidinone iv and subsequent hydrolysis of v. For a general reaction protocol and examples: Williams, D. R.; Kissel, W. S.; Li, J. Tetrahedron Lett. 1998, 39, 8593-8596; The chiral acid 17 has been previously described: Meyers, A. I.; Kamata, K. J. Am. Chem. Soc. 1976, 98, 2290-2294



15. For a review of the Henry reaction: Luzzio, F. A. Tetrahedron **2001**, 57, 915–945. 16. Key observed NOESY cross peaks for 26 and 27 from 2D NMR are summarized



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

PMB

NO,

