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Nitroso-Dienophile Additions to Dendralenes: A Short Synthesis of Branched Aminosugars

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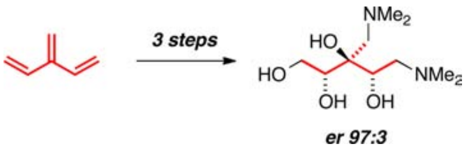
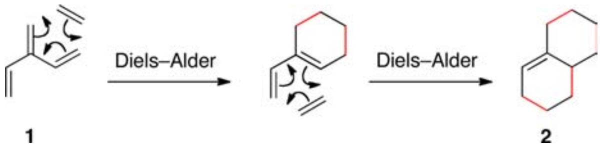
ABSTRACT



The first heteroatom-based dienophile cycloadditions to cross-conjugated alkenes ([*n*]dendralenes) are reported. Nitroso-dienophiles undergo smooth single and double Diels–Alder additions to the parent dendralenes with orientational regio- and stereoselectivity and, notably, with reactivity that depends upon the parity of the [*n*]dendralene. The first crystal structure of a cross-conjugated hexaene is reported. Vasella's nitroso-sugar reagent gives a highly enantiomerically enriched double cycloadduct with [3]dendralene. This bicyclic oxazine is successively dihydroxylated and then ring-opened to form a branched chain diamino tetrol.

Cross-conjugated trienes ([3]dendralenes)[1] have the unique ability to participate in diene-transmissive[2] Diels–Alder (DA) sequences.[3] Thus, in one synthetic operation, the triene **1** (Scheme 1) serves as a double diene, uniting with two dienophiles to form four new C–C bonds and a decalin framework **2** in a sequence of two concerted reactions, which can often be conducted in a "one pot" manner.[4] It is hard to conceive of a more step-efficient and atom-economical route to the decalin framework.

Scheme 1. Prototypical Diene-Transmissive Double Diels–Alder Sequence Involving [3]Dendralene



The higher dendralenes can also undergo sequences of DA reactions.[5,6] Despite their enormous potential in this regard, relatively little is known, since members of the [*n*]dendralene family higher than the tetraene (i.e., n = 5–8) were made available in useful amounts only in 2009.[7] In fact, the only reactions of the higher dendralenes reported so far involve the dienophile *N*-methyl maleimide (NMM).

Herein we report the first examples of DA reactions of dendralenes with heteroatom-containing dienophiles,

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(1) For a recent review of dendralenes, see: Hopf, H.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298–2338.

(2) This term was coined by Tsuge: Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett.* **1983**, *12*, 239–242.

(3) For a review of Diels–Alder sequences, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176.

(4) Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2010**, *75*, 491–494.

(5) For [4]dendralene, see: Payne, A. D.; Willis, A. C.; Sherburn, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12188–12189.

(6) For [5]dendralene, see: Bojase, G.; Payne, A. D.; Willis, A. C.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 910–912.

(7) Payne, A. D.; Bojase, G.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4836–4839.

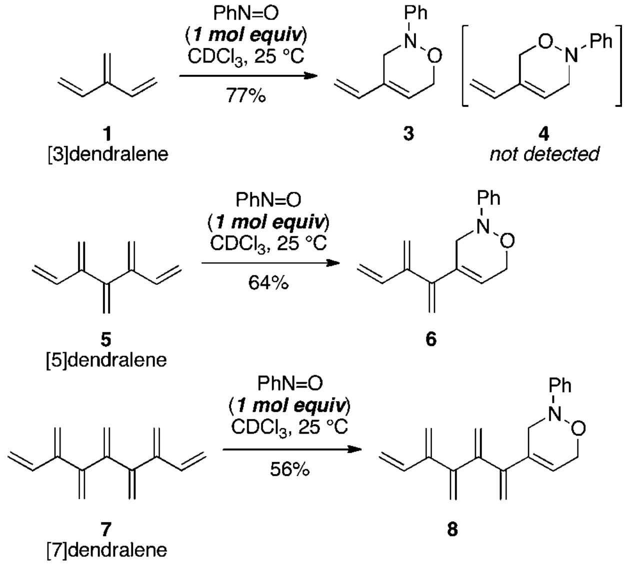
10.1021/ol302619r

namely nitroso-compounds.[8] We show that, in agreement with the aforementioned study involving the carbodienophile NMM,[7] the parent [*n*]dendralenes exhibit chemical reactivity that is dependent upon parity *n*, with odd and even [*n*]dendralenes displaying markedly differing behavior. As part of this study, we also report the first X-ray crystal structure analysis of a [6]dendralene,[9] the molecular structure from which displays a conformation that is consistent with our earlier theoretical predictions.[7] We also show that this chemistry allows the rapid synthesis of new variations on natural structures, specifically branched chain amino-sugars.

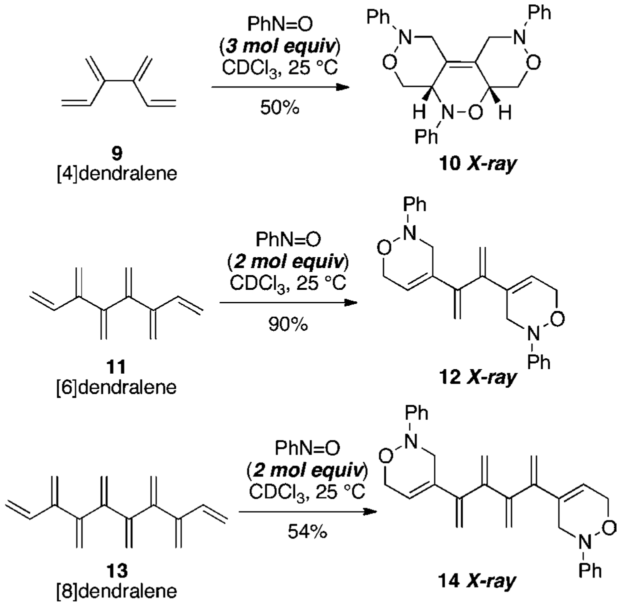
The results of nitrosobenzene dienophile cycloadditions to the [*n*]dendralene family are depicted in Schemes 2 and 3. The odd [*n*]dendralenes, namely [3]dendralene **1**, [5]dendralene **5**, and [7]dendralene **7**, undergo selective single cycloadditions at the terminal diene site to form the corresponding mono-oxazines **3**, **6**, and **8**, respectively, in good yields. The mass balance from these reactions is unreacted starting dendralene and multiple adducts. It is noteworthy that the orientational regioisomer (i.e., **4**) is not observed in these reactions.

In contrast, the even [*n*]dendralenes gave monocycloadducts as minor products on exposure to 1 mol equiv of nitrosobenzene. With 2 mol equiv of dienophile, however, [6]dendralene **11** and [8]dendralene **13** underwent smooth transformations into terminal-terminal double adducts **12** and **14**, respectively (Scheme 3). [4]Dendralene **9** behaves in the same way but also participates in a third cycloaddition at the "transmitted" diene, resulting in mixtures of double and triple products. The use of 3 mol equiv of nitrosobenzene, however, gives a reasonable isolated yield of triple adduct **10**. Minor products resulting from additions to internal dienes and orientational regioisomers were also observed in these reactions.

Scheme 2. Selective Single Cycloadditions of Odd [*n*]Dendralenes with Nitrosobenzene as Dienophile



Scheme 3. Selective Double/Triple Cycloadditions of Even [*n*]Dendralenes with Nitrosobenzene as Dienophile



Leach and Houk reviewed the available experimental data and performed DFT calculations on nitroso-dienophile additions to substituted 1,3-butadienes.[10] In both experiment and calculations, reactions of 2-substituted 1,3-butadienes give moderate to poor orientational regioselectivity. Our reactions of dendralenes (Schemes 2 and 3) contrast with these previous studies since they exhibit high orientational regioselectivities, and our calculations agree with these findings, with a predicted kinetic product ratio of 99.8%:0.2% for **3**:**4** (only **3** is detected experimentally). The calculated transition structures leading to these two products (**3-TS** and **4-TS**) are depicted in Figure 1.

As can be seen from inspection of **3-TS** and **4-TS** (Figure 1), the cycloaddition of nitrosobenzene and [3]dendralene proceeds through highly asynchronous TSs. These TSs have biradicaloid character and can be approximated to biradicals **3-*birad*** and **4-*birad***, in which the shorter developing bond in the TS is fully formed.[11] The TS leading to the major orientational regioisomer, namely

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(8) Reviews: (a) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087–3128. (b) Waldmann, H. *Synthesis* **1994**, 535–551. (c) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107–1117. (d) Streith, J.; Defoin, A. *Synlett* **1996**, 189–200. (e) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348. (f) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031–2043. (g) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595–607.

(9) Structures of substituted [3]- and [4]dendralenes have been previously reported. For X-ray crystal structures of [4]dendralenes, see: (a) Katoh, T.; Ogawa, K.; Inagaki, Y.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1109–1114. (b) Reference 6. (c) Kanibolotsky, A. L.; Forgie, J. C.; McEntee, G. J.; Talpur, M. M. A.; Skabara, P. J.; Westgate, T. D. J.; McDouall, J. J. W.; Auinger, M.; Coles, S. J.; Hursthouse, M. B. *Chem.—Eur. J* **2009**, *15*, 11581–11593.

(10) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192–5200.

(11) (a) Paddon-Row, M. N.; Sherburn, M. S. *Chem. Commun.* **2012**, *48*, 832–834. (b) Toombs-Ruane, H.; Pearson, E. L.; Paddon-Row, M. N.; Sherburn, M. S. *Chem. Commun.* **2012**, *48*, 6639–6641.

3-TS, enjoys stabilization through pentadienyl radical-like delocalization. The TS leading to the minor regioisomer has only allyl radical-like character. A pentadienyl radical is calculated to be 22.6 kJ/mol more stable than an allyl radical,[12] hence explaining the strong preference for regioisomer **3** over **4**.[13]

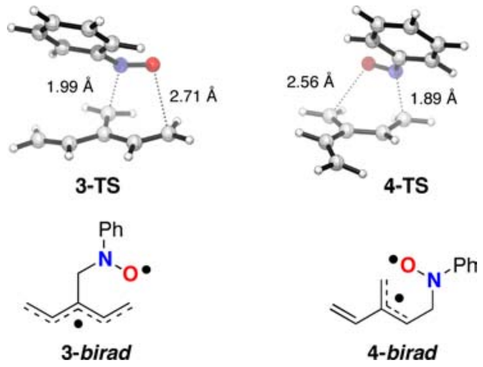


Figure 1. B3LYP/6-31G(d) transition structures for reaction of [3]dendralene and PhN=O leading to regioisomers **3** and **4**.

Single crystal X-ray analyses were conducted on samples of the three products depicted in Scheme 3,[14] which secured the assignment of orientational regioselectivity of the cycloadditions and also gave insights into the preferred conformations of cross-conjugated polyenes more generally. The molecular structures obtained from analyses of tetraene **12** and hexaene **14** are shown in Figure 2. These substituted [4]- and [6]dendralene structures comprise two and three *s-trans*-1,3-butadienes, respectively, in which adjacent butadiene units are arranged in an approximately orthogonal manner. To our knowledge, no X-ray crystal structure of a cross-conjugated polyene higher than a [4]dendralene has been previously reported.[15] These experimental structures closely match the calculated lowest energy conformations for the parent even [*n*]dendralenes.[7]

Odd dendralenes are by no means limited to single additions (Scheme 4). Thus, [3]dendralene **1** undergoes a diene-transmissive double cycloaddition with nitrosobenzene to give fused bicyclic oxazine **16** as the major product. As is the case with many such nitroso-Diels–Alder reactions,[10] the orientational regioselectivity of the second cycloaddition is poor and isomer **15** is also formed in sizable amounts. [5]Dendralene **5** undergoes a related diene-transmissive triple DA sequence to form tricyclic adduct **17** as the major product.

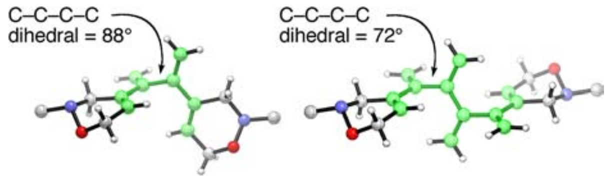
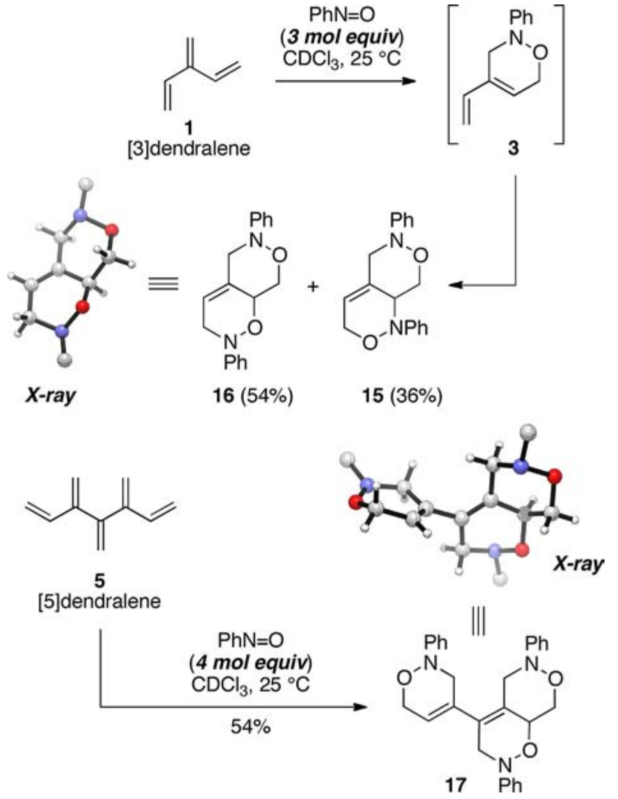


Figure 2. Molecular structures of dendralenes **12** and **14** from single crystal X-ray analyses. Polyene groups are highlighted in green, and phenyl groups are omitted for clarity.

Scheme 4. Diene-Transmissive Two- and Threefold Cycloadditions of Nitrosobenzene to [3]- and [5]Dendralenes[a]



[a] Phenyl groups are omitted from the X-ray structures for clarity.

These reactions appear to be quite general for nitroso dienophiles and, moreover, display significant synthetic potential. As shown in Scheme 5, [3]dendralene **1** undergoes selective single and double cycloadditions with the nitrosocarbonyl dienophile[16] prepared in situ from periodate oxidation of CbzNH–OH [*N*-(benzyloxycarbonyl)-hydroxylamine, **18**]. Interestingly, the orientational regioselectivity of the second cycloaddition is much higher in this

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(12) See the Supporting Information for details.

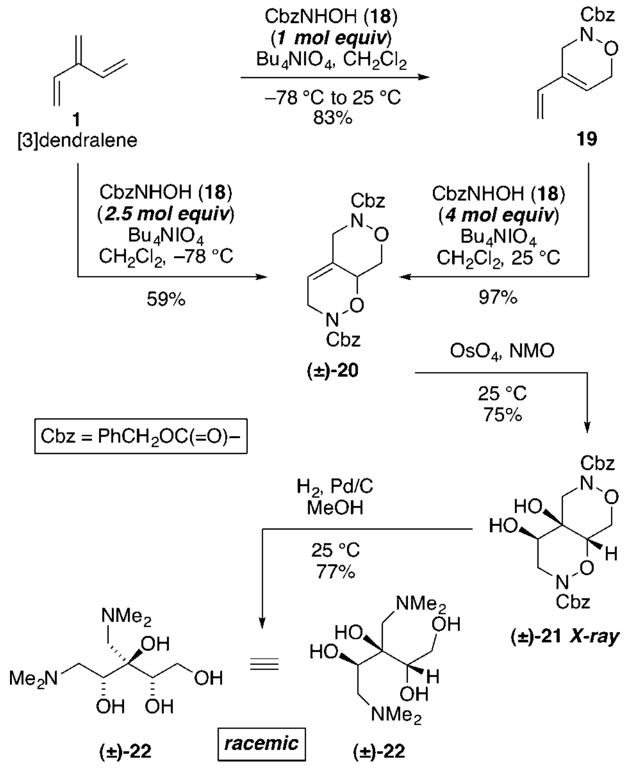
(13) Experiments on PhNHOH have shown that the O–H bond dissociation energy (BDE) is 42 kJ mol^{-1} weaker than the N–H BDE: Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 8777–8781. Our preliminary B3LYP/6-31G(d) calculations are consistent with these findings and predict that the PhNH–O• nitroxide radical is 25 kJ mol^{-1} more stable than the PhN•(OH) oxyaminyl radical.

(14) CCDC 892226–892232 contain the crystallographic data for compounds **10**, **12**, **14**, **16**, **17**, **21**, and **24**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Search conducted on the Cambridge Crystallographic Database, June 2012.

(16) For a recent review, see: Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630–5647.

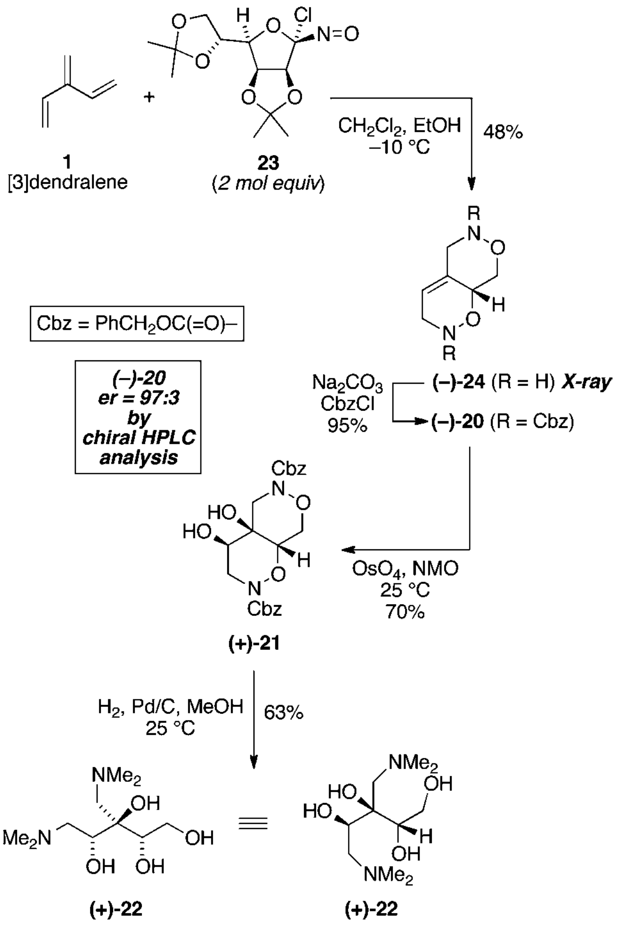
Scheme 5. Three-Step Synthesis of Branched Chain Diamino-Tetrol **22** in Racemic Form



series than with nitrosobenzene (cf. **3** → **15** + **16**, Scheme 4). Presumably, this outcome is brought about by the significant steric requirements of the Cbz group. The trisubstituted alkene of bicyclic oxazine **20** was dihydroxylated to give a single diastereomer of diol **21**. Simultaneous Cbz-deprotection, ring-opening, and N-methylation[17] afforded racemic diamino-tetrol (±)-**22**. In this short sequence, a heteroatom has been added to each of the six carbons of [3]dendralene to generate a highly functionalized chiral product with (within the limits of detection) complete control of diastereoselectivity.

Evidently, an enantioselective version of this transformation would be more attractive. The successful realization of this goal is depicted in Scheme 6. Thus, Vasella's nitroso-sugar **23**[18] brings about a highly (*er* = 97:3) enantioselective *second* cycloaddition reaction to give bicyclic oxazine **24**. Protection, diastereoselective dihydroxylation, and deprotection/ring-opening/N-methylation furnish the enantioenriched branched diamino-tetrol (+)-**22**. The easy access to this new compound, combined with its structural similarity to natural aminosugars, will stimulate further synthetic and biological investigations into dendralene-derived branched chain sugars.

Scheme 6. Enantioselective Synthesis of Branched Chain Diamino-Tetrol (+)-**22**



In conclusion, this project has shed new light on the physical and chemical behavior of the fundamental class of hydrocarbon structures known as dendralenes. Moreover, the first hetero-Diels–Alder reactions on the dendralene family have underscored the immense synthetic potential of this fascinating and neglected group of compounds.

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Supporting Information Available. Experimental procedures and characterization data; cifs and atomic displacement ellipsoid plots for compounds **10**, **12**, **14**, **16**, **17**, **21**, and **24**; computational details; ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(17) Xu, C.-P.; Xiao, Z.-H.; Zhuo, B.-Q.; Wang, Y.-H.; Huang, P.-Q. *Chem. Commun.* **2010**, *46*, 7834–7836.

(18) (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273–1295. (b) Aebischer, B. M.; Hanssen, H. W.; Vasella, A. T.; Schweizer, W. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2139–2147. (c) Felber, H.; Kresze, G.; Prewo, R.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 1137–1146. (d) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103–6106.