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INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS OF BIS-DIENE SUBSTRATES

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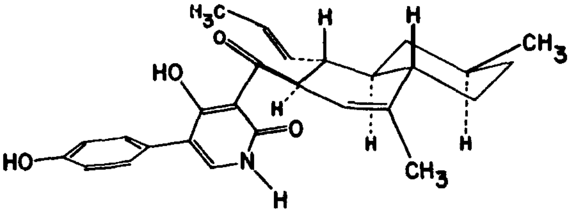
Summary: Unique internal competition in the intramolecular cycloaddition of bis-diene substrates occurs with high stereoselectivity. Aqueous reaction conditions promote coiling of the lipophilic chain which alters the observed regioselectivity.

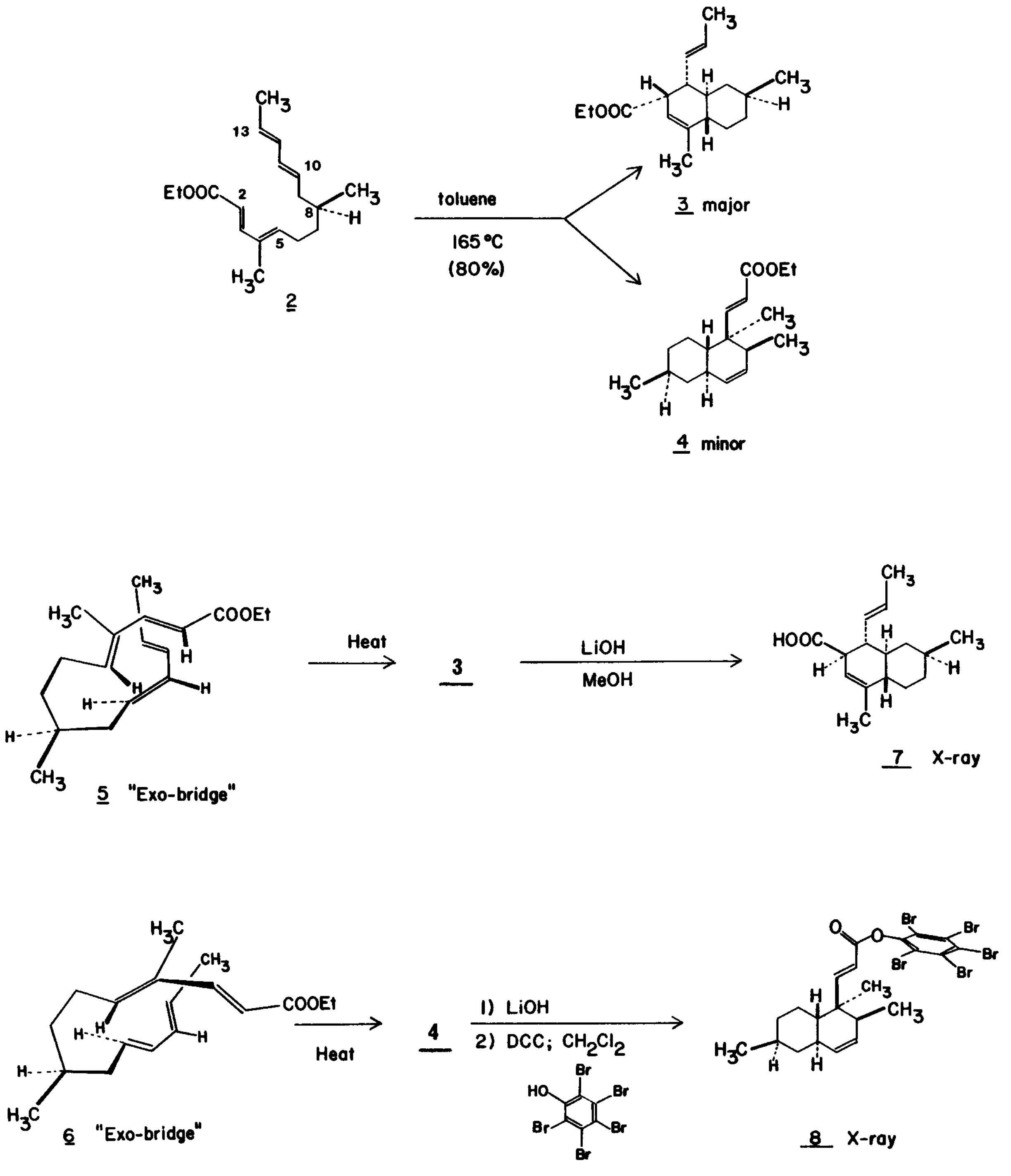
In the course of investigations toward the total synthesis of the antifungal antibiotic ilicicolin H (1), we have undertaken studies of the intramolecular Diels-Alder reaction as a strategy for formation of substituted *trans*-fused decalins. Our efforts are the first report of intramolecular cycloadditions in substrates bearing two dienic components, thus allowing for unique internal competition.[2]



Ilicicolin H 1

The unsaturated all *trans*-ethyl ester 2 has been prepared, and thermolysis results are displayed in Scheme I.[3] Heating in a resealable Carius tube at 165°C in toluene (18 hr) led to formation of two Diels-Alder products 3 and 4 in a 75:25 ratio. Isolated yields were generally about 80% and the products were separated by preparative tlc (silica gel, 1:1 CH_2Cl_2/Hex; 2 elutions). When reactions of 2 were conducted in distilled degassed water (under argon) at 100°C (48 hr) with rapid stirring, the same cycloaddition was observed.[4] However, product ratios were reversed affording 4 as the major component of the 40:60 mixture (60% yield). The corresponding free carboxylic acid and sodium carboxylate of 2 were also cyclized in water requiring similar reaction times and temperature, producing the carboxylic acids of 3 and 4 in approximately 1:8

Scheme I


CH3
13
10
EtOOC
2
CH3
8
H
5
H3C
2
toluene
165 °C
(80%)
CH3
H
H
CH3
EtOOC
H
H3C
H
3 major
COOEt
H
CH3
CH3
H3C
H
H
4 minor
CH3
H3C
COOEt
H
H
H
H
CH3
5 "Exo-bridge"
Heat
3
LiOH
MeOH
CH3
HOOC
H
CH3
H
H
H3C
H
7 X-ray
H3C
CH3
COOEt
H
H
H
H
H3C
6 "Exo-bridge"
Heat
4
1) LiOH
2) DCC; CH2Cl2
HO
Br
Br
Br
Br
Br
O
O
Br
Br
Br
Br
Br
H
CH3
CH3
H3C
H
H
8 X-ray

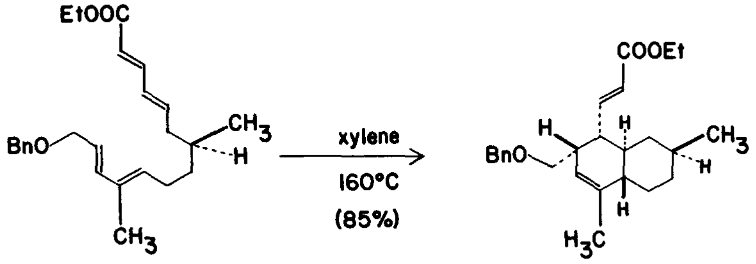
ratio, respectively.

The regioselectivity and stereospecificity of these reactions are especially noteworthy. Thus, the *trans*-fused decalin **3** may be rationalized from the *exo*-bridged transition state as available from **5**. In this case, the *trans*-disubstituted olefin (C10-C11) of the 1,4-dialkyl butadiene segment has functioned as a dienophile for an electron deficient diene (C2-C5). Likewise, formation of **4** is apparent from conformer **6** proceeding through an *exo*-bridged transition state in which a hindered trisubstituted olefin (C4-C5) participates as the dienophilic partner. This mode of cycloaddition is surprising in light of steric interactions leading to a product having two tertiary cyclohexyl carbons on either side of a fully substituted center. Note that a classical Diels-Alder reaction with the dienophilic α,β-unsaturated ester and the C10-C13 butadiene portion would result in an eight-membered ring containing the *E*-(*trans*) olefin (C4-C5).

The preference for *exo*-bridged transition states, affording *trans*-fused decalins, versus the corresponding *endo*-bridged situations would be anticipated as a result of steric considerations and secondary orbital interactions. In a simpler system, Wilson and coworkers have previously demonstrated the overwhelming preference for *trans*-ring fusions for dienes containing the vinylic methyl as seen at C-4 leading to **3**.[5] This is a result of unfavorable steric congestion between the methyl and C-9 methylene in the alternative *endo*-bridged transition state. More recently, Roush and Hall have reported a general tendency for *cis*-fused decalins, which is independent of dienophile stereochemistry, clearly indicating the modest contributions of secondary orbital interactions.[6]

Our examples also feature complete selectivity between two possible diastereotopic *exo*-bridged transition states on route to product **3** as well as **4**. Thus, the dienophile may approach the diene in an *exo*-bridging manner as visualized from beneath or above the plane of the diene. Products **3** and **4** feature only direct formation of a chair conformer in the cyclohexane ring with the C-8 methyl substituent disposed in a pseudoequatorial orientation.[7] The individual cyclized products were resubjected to the Diels-Alder conditions, and were recovered unchanged. Thus, interconversions of **3** and **4** appear unlikely. Our results may suggest a late or "product-like" transition state.

The structural assignments of **3** and **4** were unambiguously confirmed by X-ray diffraction studies of the carboxylic acid 7 and the phenolic ester 8 as shown in Scheme I.[8] Similarly, intramolecular cycloaddition of the related ethyl ester 9 (all E-stereochemistry) gave decalin 10 as its sole reaction product.[9]



9 10

Further studies and efforts toward ilicicolin H are underway.

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References:

1. Alfred P. Sloan Foundation Fellow (1983-1986).
2. For a review of intramolecular Diels-Alder reactions: G. Brieger and J.N. Bennett, Chem. Rev., 80, 63 (1980).
3. A description of the stereoselective preparation of tetraene 2 will be provided in the full account of this work. Purified samples were characterized by infrared, ^{1}H and ^{13}C nuclear magnetic resonance and mass spectral data.
4. Aqueous intermolecular Diels-Alder reactions have been observed with remarkably enhanced rates: P.A. Grieco, K. Yoshida, and P. Garner, J. Org. Chem., 26, 3137 (1983), and references therein.
5. S.R. Wilson and D.T. Mao, J. Am. Chem. Soc., 100, 6289 (1978).
6. S.E. Hall and W.R. Roush, J. Am. Chem. Soc., 103, 5200 (1981).
7. The influence of asymmetry in the bridging chain has been reported for cases in which alkoxy or alkyl substituents are located directly adjacent (α) to the diene moiety. Very few examples are known with asymmetry elsewhere on a flexible carbon bridge: D.F. Taber, "Intramolecular Diels-Alder and Alder Ene Reactions", Springer-Verlag, New York, (1984) pages 50-57, and S.W. Remiszewski, R.R. Whittle and S.M. Weinreb, J. Org. Chem., 49, 3243 (1984).
8. Complete X-ray crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 83071 for carboxylic acid 7 and Report 84053 for phenolic ester 8.
9. Stereochemical assignments of 10 are based on the observed similarities of ^{1}H-NMR (360 MHz) chemical shifts and coupling constants with 3, and comparisons with the corresponding alcohols available by carbonyl reduction.

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