Tetrahedron Letters,Vol.28,No.27,pp 3065-3068,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

DIASTEREOCONTROL OF THE CLAISEN REARRANGEMENT BY SUBSTITUENTS EXTERNAL TO THE PERICYCLIC ARRAY: SYNTHETIC STUDIES ON BETAENONE B AND STEMPHYLOXIN I

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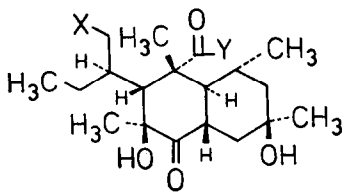
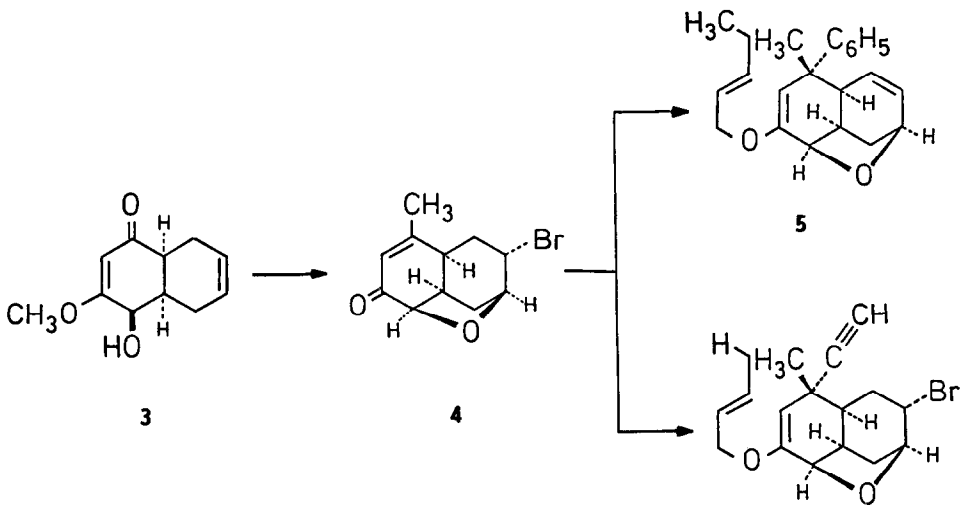
Summary: Thermal Claisen rearrangement of substrates **5** and **6**, each prepared in seven steps from the Diels-Alder adduct of methoxybenzoquinone and 1,3-butadiene, affords products **7** and **8**, respectively. These disparate results demonstrate that the stereochemical outcome of Claisen rearrangements of this type may be controlled by the spatial requirements of substituents external to the pericyclic array.

Despite years of extensive investigation,[2] there remain synthetically useful variations of the Claisen rearrangement which are little-studied.[3,4] One such variant is the attachment of an allylic appendage to derivatives of cyclohexanone. A previous study has indicated that in a suitably conformationally biased case, there exists a preference for the newly formed carbon-carbon bond to be axial.[4] This preference was, however, found to be slight, and would be expected to respond readily to external steric influence. We report in this letter an example of appendage attachment to a cyclohexanone via the Claisen rearrangement, in which the stereochemical outcome may be essentially quantitatively reversed by altering the spatial requirements of substituents external to the pericyclic array. The resulting products are of potential interest as intermediates in the synthesis of a family of phytotoxins of fungal origin, betaenone B (**1**)[5a] and stemphyloxin I (**2**).[5b,6]



	X	Y
1	-H	$-CH_2CH_2OH$
2	-OH	-CH=CHOH

The rearrangements of interest involve the tricyclic decalins **5** and **6**, which were prepared from the common intermediate, tricyclic enone **4**. The functionalized decalin **3**, prepared by sodium borohydride reduction[7,8] of the Diels-Alder adduct of methoxybenzoquinone and 1,3-butadiene,[8] was treated with 1.8 equiv N-bromosuccinimide in THF (25°, 1 h) to afford the corresponding tricyclic bromoether, which was in turn treated with 1.4 equiv methyllithium in THF (0°) followed by acidic work-up (PTSA•H_2O treatment of organic extract), providing the tricyclic enone **4** (m.p. 188-189°) in 62% overall yield from **3**.



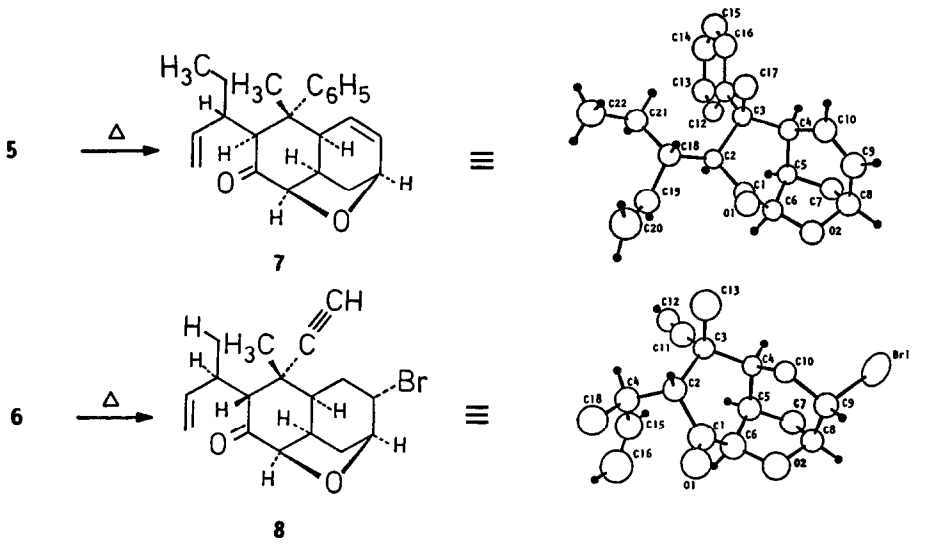
3 4 5 6

The enone **4** was converted to Claisen rearrangement substrate **5** by the three-step sequence: 1) 1.3 equiv $(C_6H_5)_2CuLi$, THF/Et_2O, -40° (60%); 2) excess trans-2-penten-1-ol, $PTSA{\bullet}H_2O$, C_6H_6, reflux, Dean-Stark trap; 3) neat DBU, 105° (58%, two steps). Substrate **6** was prepared from enone **4** by the analogous sequence: 1) 2 equiv n-$C_5H_{11}C{\equiv}CCuCH{=}CHSn(n\text{-}C_4H_9)_3Li$, 5 equiv $(C_6H_5)_3P$, THF, -78°→ -40°; 2) excess $Pb(OAc)_4$, CH_3CN, 25° (71%, two steps)[9]; 3) excess trans-2-buten-1-ol, $PTSA{\bullet}H_2O$, C_6H_5, reflux, Dean-Stark trap (50%).

Thermolysis of **5** [96:4(v/v) n-$C_{10}H_{22}$:N,N-dimethylaniline, 210°] afforded a single product (^1H NMR analysis) which crystallized directly from the reaction mixture on cooling to 25° in 86% yield. A single crystal X-ray analysis of this product unequivocally established it to be ketone **7**,[10] the product of concave face appendage attachment via a chair-type pericyclic transition state.

The latter result is interesting with regard to both the mechanism of the Claisen rearrangement and the synthesis of stemphyloxin I. The rearrangement of **5** to **7** formally follows the rule of axial appendage delivery,[4] despite this requiring carbon-carbon bond formation on the crowded *concave* face of the tricyclic system. We believe that this reflects not an inherent preference for axial bond formation, but rather the severe steric congestion present on the *convex* face of the molecule. Specifically, inspection of CPK models clearly suggests that in the ground state conformation of **5**, one of the ortho-hydrogens of the phenyl ring blocks convex face carbon-carbon bond formation. This orientation of the phenyl ring (the result of avoiding steric contact with the hydrogen atoms at the ring fusion of **5**) is also observed in the X-ray structure of ketone **7**. Support for this explanation is found in the outcome of thermolysis of **6** (see below). The ketone **7** is of synthetic interest as a stemphyloxin I (**2**) precursor: Epimerization of the newly attached pentenyl appendage from its pseudoaxial to an equatorial position would potentially establish several key stereorelationships in **2**.[5b]

Thermolysis of Claisen substrate **6** [99:1 (v/v) n-$C_{10}H_{22}$:N,N-dimethylaniline, 160°] cleanly afforded a single rearrangement product (^1H NMR analysis), **8**, in 70% yield. Single crystal X-ray analysis revealed the structure of **8** to be as shown,[10] the product of convex face carbon-carbon bond formation.



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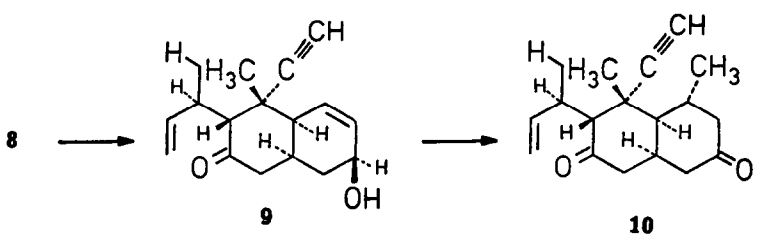
8

The conversion of **6** to **8** is again of interest both mechanistically and synthetically. Apparently, the diminished spatial requirements of the acetylene substituent of **6** (relative to the phenyl group of **5**) permit convex face carbon-carbon bond formation, avoiding reaction at the sterically congested concave face.[11,12] The energetic advantage of avoiding concave-face bond formation is qualitatively reflected in the significantly diminished temperature at which **6**→**8** (160°) relative to **5**→**7** (210°). This example is a clear illustration of the potentially dominant role of steric effects in determining the stereochemical outcome of Claisen rearrangements which append an allylic unit to a cyclohexanone.

Ketone **8** is of synthetic interest as a precursor to betaenone B (**1**), and has been carried several steps toward this end. Treatment of **8** with excess neat DBU (90°),[13] followed by reduction with 1.5 equiv samarium(II)iodide[14] in THF (-78°) afforded allylic alcohol **9**. Oxidation of **9** (PCC, 50% from **8**), followed by treatment of the resulting enone with lithium dimethylcuprate (Et_2O, -78°) afforded a 4:1 mixture of diastereoisomers, the major isomer of which is believed to be **10** (delivery of methyl from the less hindered convex face). Intermediate **10** is a promising intermediate for betaenone B (**1**) synthesis, since it possesses all of the stereochemistry and functionality required for construction of the northern periphery, as well as sufficient functionality to allow elaboration of the southern periphery.[15]



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References and Endnotes

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6. For the synthesis of a less substituted member of this family, see: Ichihara, A.; Kawagishi, H.; Tokugawa, N.; Sakamura, S. *Tetrahedron Lett.* **1986**, *27*, 1347.

7. Satisfactory ^{1}H NMR, IR, and MS were obtained for all of the compounds described herein.

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10. Tables of final atomic coordinates, bond lengths and angles along with a computer generated plot with atomic labels are available as supplementary data. See Announcement to Authors *Tetrahedron Lett.* **1983**, *24*, 5154. Discussion of the conformational details of **7** and **8** is deferred to a later publication, but we note that both structures possess a twist boat cyclohexanone.

11. We cannot at this time rule out the unlikely possibility that the product **8** results from initial concave face (axial) appendage attachment via a boat-type transition state followed by epimerization adjacent to the ketone.

12. While it is also true that the concave face of **6** is more congested than the concave face of **5**, this effect alone cannot be responsible for the observed results, since the immediate synthetic precursor of **5** also appears (2D NOESY and COSY ^{1}H NMR) to undergo Claisen rearrangement with concave face carbon-carbon bond formation.

13. The possibility of side chain epimerization during the DBU-promoted HBr elimination is argued against by the observation that treatment of **8** with i) $NaBH_4$; ii) DBU; iii) PCC also affords the same product.

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15. This work was supported by the Dreyfus Foundation, Research Corporation, and the Petroleum Research Fund Administered by the American Chemical Society. We thank Professor Gary Drobny for assistance in 2D NMR measurements, Mr. Jeff Bryan and Dr. Bernard Santarsiero for determining the X-ray structure of **8**, and Mr. Regan Shea for assistance in the preparation of the figures.

(Received in USA 18 February 1987)