Tetrahedron Letters,Vol.24,No.1,pp 3-6,1983
Printed in Great Britain

0040-4039/83/010003-04$03.(

AXIAL ALLYLATION ON THE DIOSPHENOL CLAISEN REARRANGEMENT

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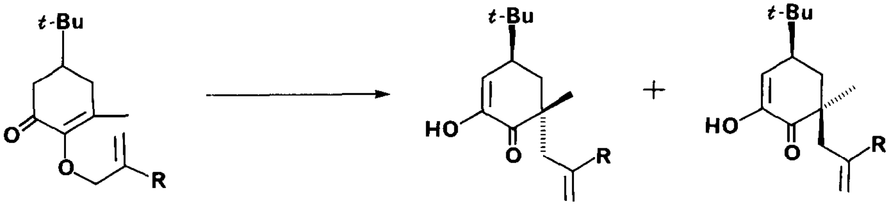
ABSTRACT: A 5:1 preference for axial <u>vs</u>. equatorial allylation is shown in the Claisen rearrangement of the conformationally-rigid diosphenol allyl ether **1**.

Most applications of the Claisen rearrangement[1] in stereoselective synthesis are based on the stereochemical consequences of a chair transition state[2] or on chirality transfer from a C-O bond to a C-C bond.[3] Another potential source of stereocontrol, namely a preference for axial bond formation in rearrangement of allyl-vinyl ethers contained within conformationally-rigid cyclohexane systems, has received little attention.[4] Since diosphenol allyl ethers are readily accessible substrates for cycloalkenyl-allyl ether Claisen rearrangements[5] we have investigated this stereochemical question in the system **1**:



1a R=H
1b $R=CH_3$

2

3

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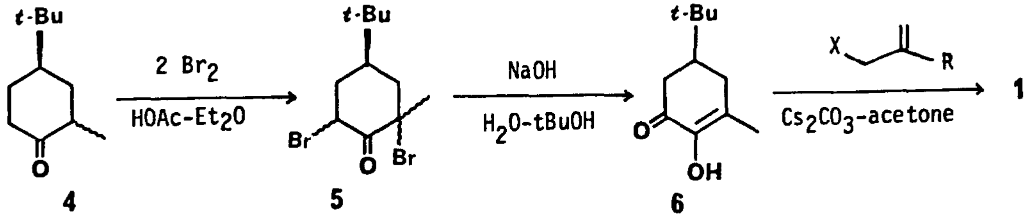
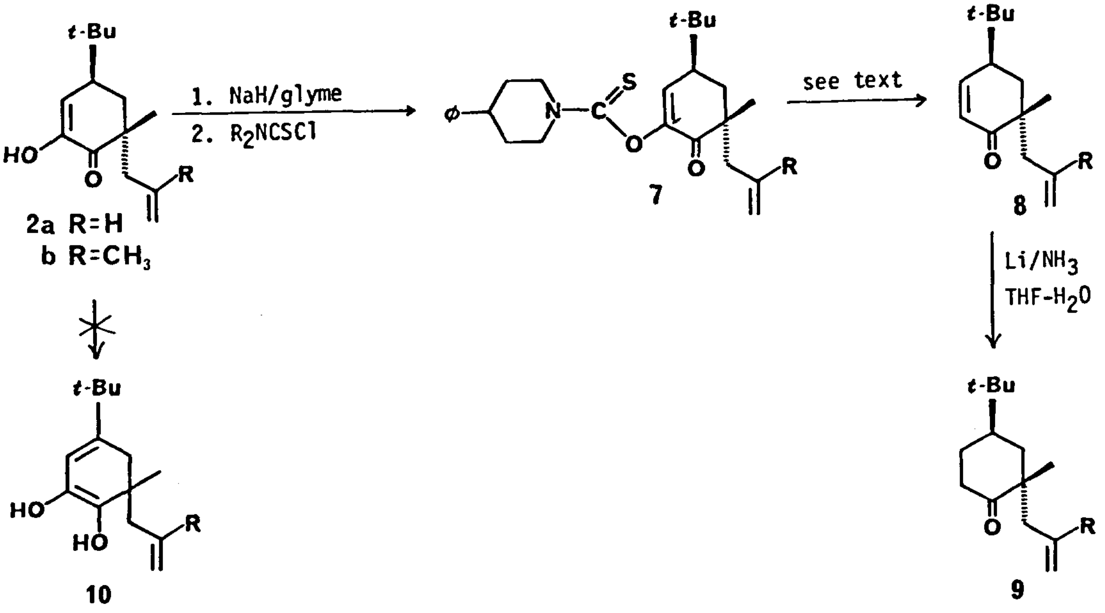
1a[6] and 1b[6] were prepared from diosphenol 6[6], m.p. 81.5-83.5°, synthesized in 65% yield by the method of Wallach[7] from 4-t-butyl-2-methylcyclohexanone 4:



Heating a 1 M solution of 1a in pyridine at reflux (117°) for twelve hours produced, in 89% isolated yield, an 84:16 mixture of two diosphenols having essentially identical NMR spectra in $CDCl_3$. They were tentatively assigned the structures 2a[6] and 3a[6] on the basis of the benzene solvent shifts[8] of their methyl groups (Δ = +0.06 and +0.22, resp.). This assignment was confirmed as follows.

The major diosphenol 2a was converted to 7a[6], m.p. 121-124°, which was treated with three equivalents each of lithium iodide and lithium acetate in boiling acetic acid for fifteen minutes producing, in 70% yield from 2a, the deoxygenated product 8a.[6,9] Selective reduction of the conjugated double bond produced the known[10] 9a (oxime m.p. 144-148°, reported[10a] m.p. 142°).



Rearrangement of **1b** was slower than that of **1a** but after forty-five hours reflux in pyridine an 85% isolated yield of diosphenols **2b**[6] and **3b**[6] in the ratio of 83:17 was produced. The major isomer **2b**, m.p. 42-47°, was converted to **7b**[6], m.p. 135.5-138.5°, and then, *via* **8b**,[6] to **9b**[10] (oxime m.p. 150-151°, reported[10a] m.p. 150-151°).

Heating **2b** in pyridine for sixty hours produced no detectable **3b** (VPC analysis can detect <1%), thus demonstrating once again[5b] that the diosphenol Claisen rearrangement is irreversible and, furthermore, that enolization to **10** does not occur under the reaction conditions. Additionally, analysis of the rearrangement products at low conversion showed **2** and **3** in the ratio of 5:1, and thus this is the true kinetic ratio.

It is noteworthy that this Claisen rearrangement shows a greater preference for axial attachment of allyl or methallyl than does alkylation of **4** with alkyl halide/ sodium *t*-amylate/benzene whereby a 4:3 ratio of **9** and its epimer are produced.[10a] We are presently exploiting this enhanced stereoselectivity in sesquiterpene synthesis.

ACKNOWLEDGEMENT: I thank the National Institutes of Health for support of this work.

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[4] Almost all examples of Claisen rearrangement involving 1-substituted cyclohexenes have steric bias or are enmeshed in conformationally-mobile frameworks. *In situ* formation and cracking of 4-*t*-butylcyclohexanone allyl ketals gives, initially, a preference for axial allylation, but product equilibration under the reaction conditions has prevented an accurate measurement of the stereoselectivity:

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[6] All new compounds gave satisfactory NMR, IR and mass spectra as well as the correct exact mass. The 90 MHz NMR spectra ($CDCl_3$) are summarized below.

1a: 0.92, s, 9H; 1.7, m, 1H; 1.91, s, 3H; 2.0-2.8, m, 4H; 4.32, d, J=6, 2H; 4.9-5.5, m, 2H; 5.5-6.3, m, 1H.

1b: 0.92, s, 9H; 1.7, m, 1H; 1.80, s, 3H; 1.93, s, 3H; 2.0-2.8, m, 4H; 4.16, s, 2H; 4.89, "d", J=5, 2H.

2a: 0.94, s, 9H; 1.13, s, 3H; 1.3-2.0, m, 2H; 2.23, d, J=7, 2H; 2.4, m, 1H; 5.00, m, 1H; 5.18, s, 1H; 5.5-6.0, m, 1H; 6.18, t, J=2, 1H.

2b: 0.90, s, 9H; 1.16, s, 3H; 1.3-2.0, m, 2H; 1.71, narr m, 1H; 2.20, s, 2H; 2.41, ddd, J=2,2,9, 1H; 4.66, br. s, 1H; 4.88, narr m, 1H; 6.07, t, J=2, 1H.

3a: same as **2a**.

3b: same as **2b**.

6: 0.88, s, 9H; 1.84, s, 3H; 1.8-2.7, m, 5H; 5.96, s, 1H.

7a: 0.98, s, 9H; 1.11, s, 3H; 1.4-2.1, m, 6H; 2.1-3.4, m, 6H; 4.6-5.4, m, 4H; 5.4-6.1, m, 1H; 6.48, s, 1H; 7.23, s, 5H.

7b: 1.00, s, 9H; 1.13, s, 3H; 1.3-3.5, m, 12H; 1.80, s, 3H; 4.6-5.4, m, 4H; 6.51, s, 1H; 7.22, s, 5H.

8a: 0.96, s, 9H; 1.08, s, 3H; 1.2-1.9, m, 3H; 2.18, d, J=7, 2H; 4.93, m, 1H; 5.15, s, 1H; 5.4-6.1, m, 1H; 5.90, dd, J=3,10, 1H; 6.89, ddd, J=2,2,10, 1H.

8b: 0.96, s, 9H; 1.10, s, 3H; 1.2-1.9, m, 3H; 1.71, s, 3H; 2.20, s, 2H; 4.68, s, 1H; 4.88, narr m, 1H; 5.96, dd, J=3,10, 1H; 6.90, ddd, J=2,2,10, 1H.

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[9] Treatment of dialkyl thiocarbamates of diosphenols with iodide ion is a general method for replacement of the enolic hydroxyl by hydrogen. We will report the details of this reaction in a future publication. 4-Phenyl-1-piperidinecarbothioyl chloride, m.p. 90-91.5°, (prepared from commercially-available 4-phenylpiperidine and thiophosgene) was chosen as the dialkylthiocarbamyl reagent to ensure highly crystalline derivatives.

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(Received in USA 13 September 1982)