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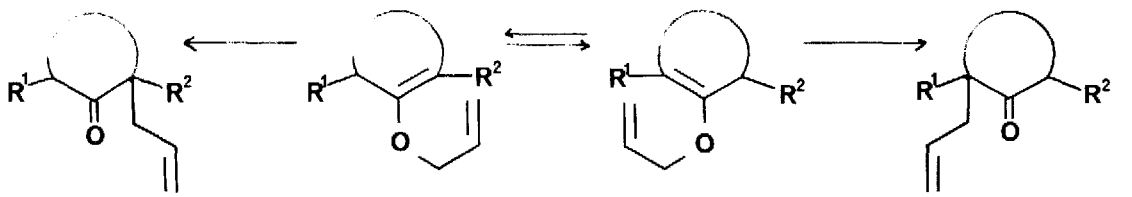
THE DIOSPHENOL CLAISEN REARRANGEMENT

A.A. Ponaras
Department of Chemistry
University of Maryland Baltimore County
Baltimore, MD 21228

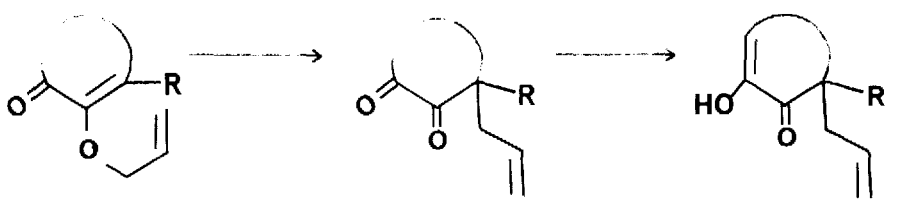
ABSTRACT: Thermal rearrangement of diosphenol allyl ethers provides a method for attachment of an allyl group to hindered carbon centers.

The development of new methods for the attachment of a functionalized carbon unit to a hindered carbon center in a cyclic structure is of current interest.[1] The Claisen rearrangement,[2] i.e. the thermal reorganization of allyl vinyl ethers, has been utilized for this purpose mainly in systems where the allyl double bond is contained in the ring. The alternative arrangement, where the vinyl double bond is contained in the ring, has been less-frequently employed, partly due to the difficulty of synthesizing the required enol ether 1 free of its regioisomer 2, and the possible isomerization 1→2 during the conduct of the rearrangement.



3 1 2 4

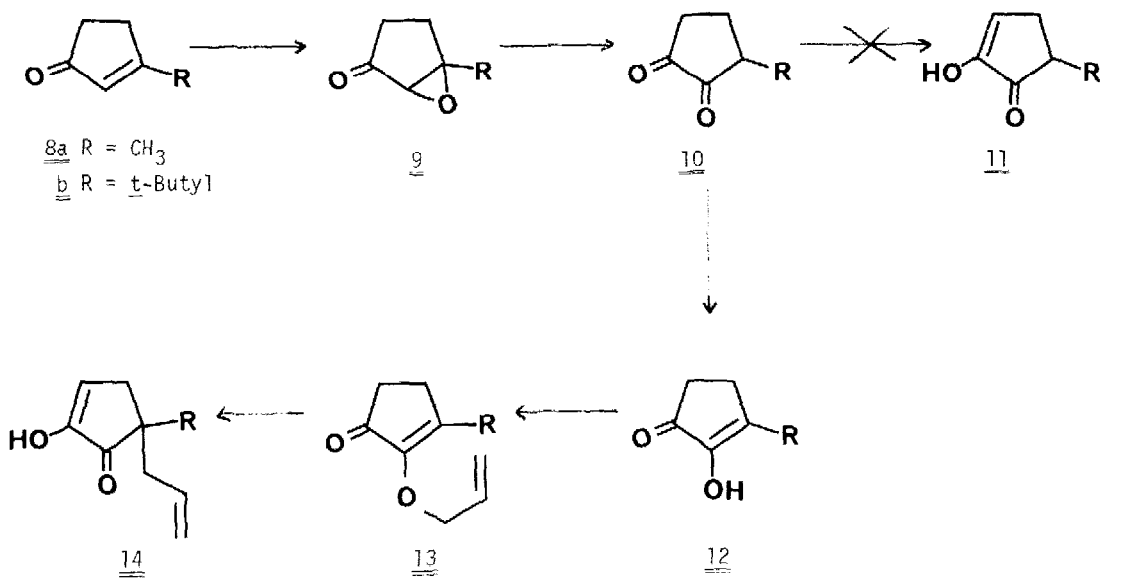
We have developed a new variant of this type of Claisen rearrangement that does not allow formation of regioisomers. Heating diosphenol allyl ethers 5 at about 200° produces α-diketones 6 which, if possible, tautomerize under the reaction conditions to the enolic form 7:



5 6 7

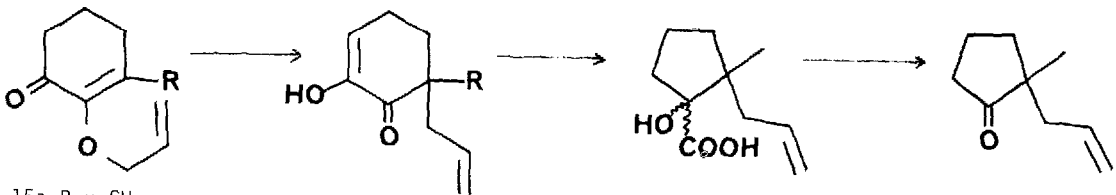
These C-allylated diosphenols 7 are versatile synthetic intermediates: The allyl group may be transformed into a variety of functionalized units and the diosphenol array provides excellent functionality for further synthetic elaboration of the ring.[3] In this Letter the sensitivity of the rearrangement to steric hindrance is defined for a series of monocyclic diosphenol allyl ethers with increasing steric bulk at the migration terminus; in future publications the use of this reaction to deliver an allyl group to a ring junction in hydrindane[4a] and decalin[4b] systems will be demonstrated.

α,β-Unsaturated ketones may be used as precursors of the required diosphenol allyl ethers For example, epoxidation[5] of 3-methyl-2-cyclopentenone 8a followed by acid-catalyzed isomerization[5,6] gave, in 62% overall yield, the well-known[7] diosphenol 12a which exists almost exclusively as the more-highly substituted enol. Alkylation with allyl bromide and potassium carbonate in refluxing acetone afforded the corresponding enol ether 13a in 95% yield.[8] Heating 13a at 200° for 30 minutes followed by evaporative distillation gave diosphenol 14a in 93% yield (NMR in $CDCl_3$: 1.11, s, 3H; 1.9-2.8, m. 4H; 4.8-6.1, m, 3H; 6.52, t, J=3 Hz., 1H; 7.18, s, 1H. IR: 3360, 1695, 1645 cm^{-1}). For the purpose of additional characterization, 14a was converted to its oily quinoxaline derivative and to its brosylate, m.p. 63-64°.



A t-butyl group at the β-carbon sharply diminished the rate of the rearrangement and the yield of product: 13b (prepared as above in 35% overall yield from 8b) gave a 45% yield of 14b after heating at 230° for one hour.[9]

3-Methyl-2-cyclohexenone was similarly converted to 15a which upon heating at 200° for one hour rearranged to 16a in 88% yield. Treatment of 16a with boiling 10% aqueous sodium hydroxide solution gave the hydroxy acids 17 which upon oxidative fission with lead tetraacetate in methanol gave 2-allyl-2-methylcyclopentanone 18:[10]

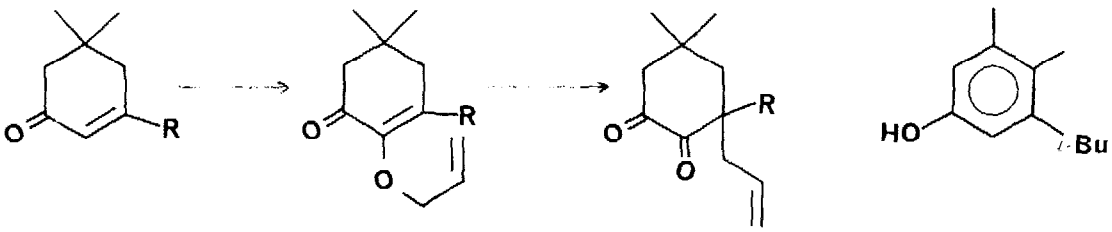


15a R = CH_3
b R = t-butyl

16 17 18

In the cyclohexenone series a β-t-butyl group similarly diminishes the yield of product from the Claisen rearrangement: 15b, when heated at 240° for one hour, gave a 40% yield of 16b.

In order to examine the effect of a developing 1,3-diaxial methyl-alkyl interaction[11] on the yield in this rearrangement, allyl ethers 20a-f were prepared from the corresponding ketones 19a-f.[12] Yields of rearranged α-diketones 21a-e (as their enols) were quite satisfactory (temperature, time and isolated yields are given in parenthesis next to the structure number). For the highly-hindered 20f no allyl diosphenol 21f could be detected after heating at 230° for one hour. Upon prolonged heating at 260° phenol 22 was the major reaction product, along with several non-polar products which were not identified.



19a R = H
b R = CH_3
c R = allyl
d R = iso-propyl
e R = phenyl
f R = t-butyl

20

21a (200°, 60 min., 88%)
b (230°, 25 min., 90%)
c (230°, 30 min., 70%)
d (215°, 60 min., 90%)
e (200°, 60 min., 80%)
f (230°, 60 min., <5%)

22

It is interesting to note that this intramolecular delivery of allyl to the β-carbon of an α,β-unsaturated ketone system succeeds where existing methods for intermolecular delivery fail: lithium diallyl cuprate[13] and allyltrimethylsilane[14] give negligible conjugate addition to 19d, and the latter reagent apparently does not react with β-substituted cyclopentenones in general.[15] Thus, for example, 8a does not react with allyltrimethylsilane under the recommended[14] conditions ($TiCl_4$/methylene chloride) or with other Lewis acids we have tried.[16]

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[2]For reviews of the Claisen rearrangement see
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b. Bennett, G.B., Synthesis, 1977, 589.

[3]We shall show in a future publication that, among other selective transformations, either of the two carbonyl groups of 6 may be reduced to methylene.

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[5]House, H.O. and Wasson, R.L., J. Amer. Chem. Soc., 1957, 79, 1488.

[6]a. Langin-Lanteri, M.T. and Huet, J., Synthesis, 1976, 541.
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d. Camerino, B., Patelli, B. and Vercellone, A., J. Amer. Chem. Soc., 1956, 78, 3540.

[7]Inter alia, Sato, K., Kojima, Y. and Sato, H., J. Org. Chem., 1970, 35, 2374.

[8]All new compounds gave satisfactory NMR, IR and mass spectra; crystalline compounds gave satisfactory elemental analyses.

[9]The base-solubility of diosphenols greatly aids their isolation and purification.

[10]Asselin, A.A., Humber, L.G., Dobson, T.A., Komlossy, J. and Martel, R.R., J. Med. Chem., 1976, 19, 787.

[11]A fully-developed such interaction is worth about 3.7 kcal/mole: Allinger, N.L. and Miller, M.A., J. Amer. Chem. Soc., 1961, 83, 2145.

[12]Ketone 19a was prepared by reduction of dimedone ethyl ether with lithium aluminum hydride. Ketone 19b is commercially-available isophorone. Ketones 19c-f were prepared from dimedone ethyl ether and the corresponding alkyl lithium. The epoxidation-rearrangement-alkylation sequence (cf. 8→13) was used to prepare 20b-e. Substrates 20a and 20f, on the other hand, were prepared by brominating 19a and 19f at the γ-carbon (0.95 eq. NBS in refluxing CCl_4) followed by treatment with sodium allyloxide/allyl alcohol - cf. Verhe, R., Schamp, N., DeBuyck, L. and Vanloocke, R., Bull. Soc. Chim. Belg., 1975, 84, 371, 381.

[13]For pertinent references see House, H.O. and Wilkins, J.M., J. Org. Chem., 1978, 43, 2443.

[14]Hosomi, A. and Sakurai, H., J. Amer. Chem. Soc., 1977, 99, 1673.

[15]Allyltrimethylsilane has been added to 2-cyclopentenone (Becker, K.B. and Pfluger, R.W., Tetra. Lett., 1979, 3713) and to 1-acetyl-2-methylcyclopentene (Pardo, R., Zahra, J.P. and Santelli, M., Tetra. Lett., 1979, 4557).

[16]$AlCl_3$, $SnCl_4$ or $BF_3{\cdot}Et_2O$, 1.1 equiv; allyltrimethylsilane, 1.1 equiv; 3-methyl-2-cyclopentenone, 1 equiv; 2 mL CH_2Cl_2 per mmole of ketone; -78° one hour, warm to room temp. over 20 minutes, stir at room temp. one hour. In most runs about 60% of the starting material could be recovered.

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