Tetrahedron Letters, Vol.22, No.35, pp 3381 - 3384, 1981
Printed in Great Britain

0040-4039/81/353381-04$02.00/0

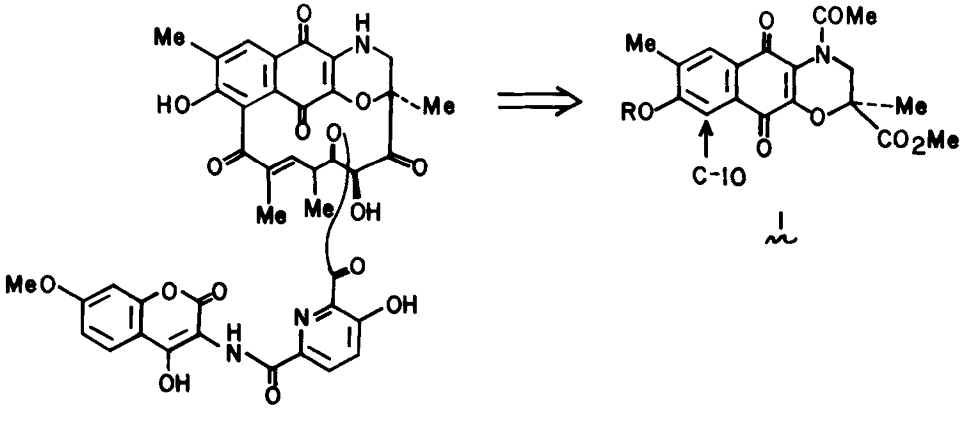
STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF THE RUBRADIRIN ANTIBIOTICS. 4. A NEW DIELS-ALDER—CLAISEN EFFECTIVE DIENE

Alan P. Kozikowski,* Kiyoshi Sugiyama and Edward Huie
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Summary: A new diene has been synthesized which effectively couples the Diels-Alder reaction with the Claisen rearrangement.

For some time we have been particularly intrigued with the notion of coupling the Diels-Alder process with other reaction processes through the use of appropriately substituted dienes. Such a strategy does have the ability to generate complex structures in a minimum of synthetic operations. One such example, and there are others, is Evans' use of a dienyl sulfoxide as an electron deficient Diels-Alder diene which after the (4+2) cycloaddition reaction produces an intermediate which is suitably poised for a [2,3] sigmatropic rearrangement.[1] Strategies such as this make available materials which may be otherwise extremely difficult to prepare by direct cycloaddition schemes.

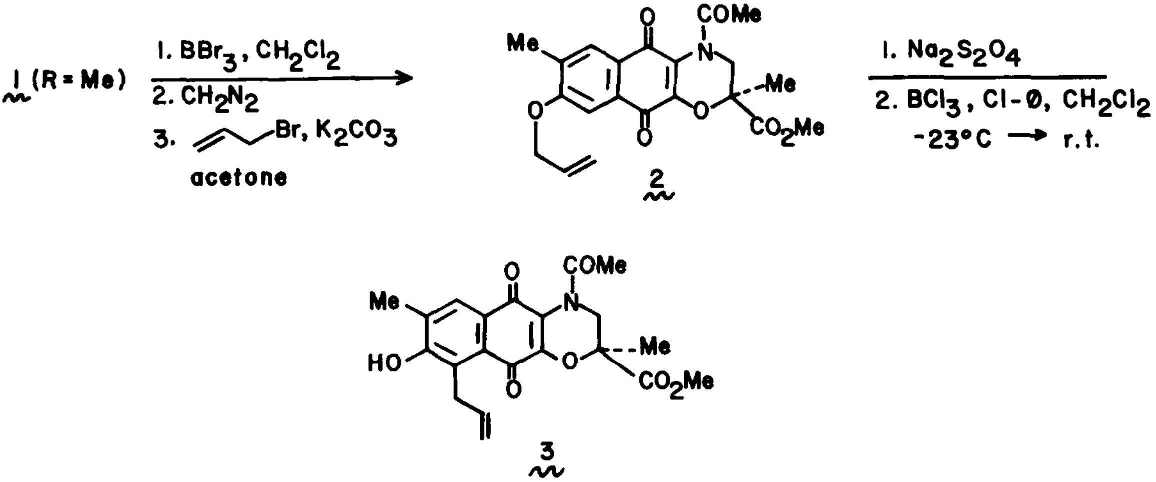
We now describe the preparation of yet another modified diene which makes possible a Diels-Alder-aromatization-Claisen sequence. The necessity for preparing this particular multi-operational diene emerged during our efforts to synthesize a special class of antibiotic



Rubradirin B

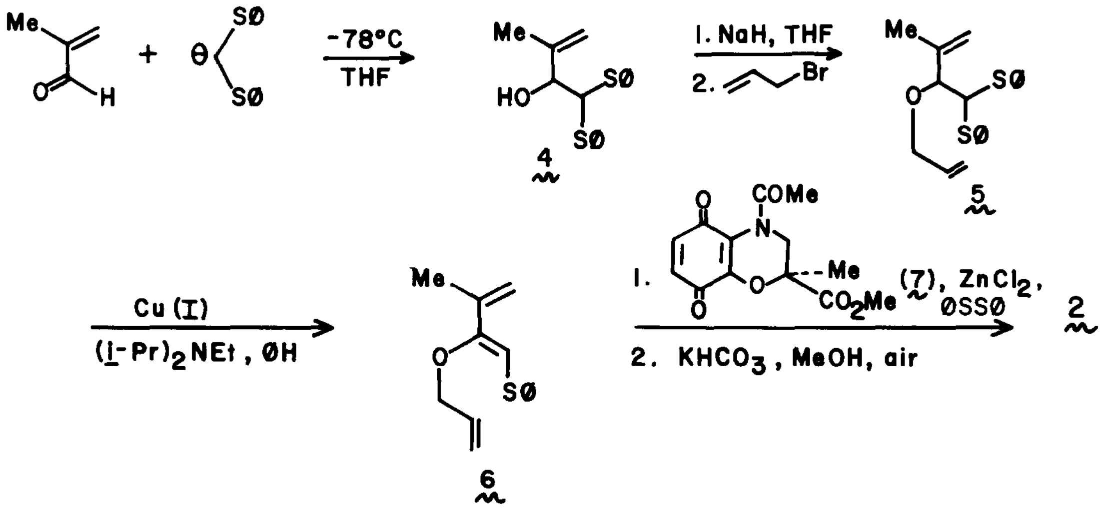
1

substances, the rubradirins.[2] In studying the further elaboration of the aromatic/heterocyclic component 1, whose preparation has been reported earlier,[3] to the target substances, we required an efficient method for functionalizing the C-10 position (rubradirin numbering). Attempts to effect the introduction of an acyl appendage by the Friedel-Crafts reaction or its variants on the hydroxyl protected hydroquinone form of 1 resulted in very poor yields of the desired material. It thus became necessary to investigate C-10 functionalization by means of a [3,3] sigmatropic rearrangement process instead. Accordingly, the methyl ether of 1 was cleaved by the action of boron tribromide. Since concomitant demethylation of the ester also occurred under these conditions, the crude product was reesterified with diazomethane. The free hydroxyl group was then converted to the O-allyl derivative by the action of allyl bromide and potassium carbonate. The quinone was reduced to hydroquinone and the thermal rearrangement of this intermediate investigated. At the temperatures generally required to effect the aromatic Claisen rearrangement, extensive decomposition of the allyl aryl ether took place. Only a small amount of the deallylated quinone could be recovered. Fortunately, the rearrangement reaction was subject to Lewis acid catalysis.[4] When the hydroquinone of 2 was exposed to six equivalents of boron trichloride, over a temperature range of from -23°C to room temperature, the desired C-10 allylated product could be isolated in 95% yield (reoxidation to quinone occurred on workup)

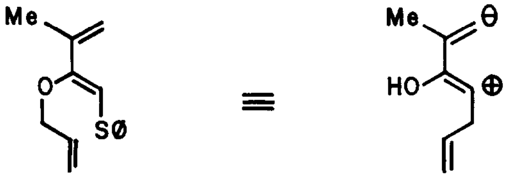


Since a number of steps are required to generate the pre-Claisen compound 2, we felt that it would be advantageous to prepare an "operationally" defined diene which could lead directly to 2 from the dienophile 7. In analogy to an existing method,[5] the anion of bis(phenylthio)-

methane was treated with methacrolein at -78°C in tetrahydrofuran. The crude alcohol **4** isolated in 98% yield was reacted sequentially with sodium hydride and allyl bromide to afford the corresponding ether **5** (isolated in 95% yield after purification on silica gel with 2% ethyl acetate-hexane as eluent). Copper (I) promoted elimination of thiophenol from **5** gave **6** as the sole isomer in 46% isolated yield [purification can be effected either by bulb-to-bulb distillation (90°C oven temperature, 0.015 mm) or by chromatography on neutral silica gel with 20% benzene-hexane as eluent].[6] The new diene is stable for months if stored with some 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide in a refrigerator.[7] Zinc chloride catalyzed cycloaddition of the new diene with quinone **7**[3] took place at room temperature in methylene chloride *in the presence of diphenyl disulfide*[8] to give a crude cycloadduct which when treated with potassium bicarbonate followed by air oxidation generated the requisite pre-Claisen material **2** in 75% isolated yield. Claisen rearrangement of the hydroquinone as detailed above completed this operationally simpler strategy for generation of the crucial rubradirin precursor **3**.



The new diene **6** behaves as a functional equivalent of the diene zwitterion **8** in its (4+2) cycloaddition reactions with quinones. The successful employment of this diene in the context of a total synthesis suggests that the design of other multi-operational dienes does constitute a worthwhile objective.



6

8

References and Notes

1. D. A. Evans, C. A. Bryan and C. L. Sims, *J. Am. Chem. Soc.*, **94**, 2891 (1972). For an example of a diene which produces on cycloaddition an allylsilane system capable of reacting with electrophiles, see: S. R. Wilson, L. R. Phillips, and K. J. Natalie, *J. Am. Chem. Soc.*, **101**, 3340 (1979).

2. S. A. Mizsak, H. Hoeksema and L. M. Pschigoda, *J. Antibiotics*, **32**, 771 (1979) and references cited therein.

3. For Part 2 in this series, see: A. P. Kozikowski and K. Sugiyama, *J. Org. Chem.*, **46**, 2426 (1981). Part 3: *idem*, *Tetrahedron Lett.*, **21**, 4597 (1980).

4. J. Borgulya, R. Madeja, P. Fahrni, H-J. Hansen, H. Schmid, and R. Barner, *Helv. Chim. Acta*, **56**, 14 (1973).

5. T. Cohen and Z. Kosarych, *Tetrahedron Lett.*, **21**, 3955 (1980).

6. The spectral data for compounds **4**, **5** and **6** are:

   4: IR (thin film) 3480, 1650, 1585, 1575 cm^{-1}; NMR (CCl$_4$) δ 7.30 (m, 10 H), 5.12 (br s, 1 H) 4.96 (br s, 1 H), 4.44 (d, 1 H, *J* = 5.5 Hz), 4.15 (d of d, 1 H, *J* = 3.4, 5.5 Hz), 3.02 (d 1 H; *J* = 3.4 Hz), 1.72 (br s, 3 H); mass spectrum, m/e calcd 302.0799, obsd 302.0807.

   5: IR (thin film) 3070, 3050, 1705, 1580, 1570, 1060 cm^{-1}; NMR (CCl$_4$) δ 7.30 (m, 10 H), 5.70 6.20 (m, 1 H), 5.00-5.40 (m, 2 H), 5.10 (sharp m, 2 H), 4.44 (d, 1 H, *J* = 7 Hz), 3.94 (d, 1 H, *J* = 7 Hz), 3.75-4.20 (m, 2 H), 1.78 (br s, 3 H); mass spectrum, m/e calcd 342.1112, obsd 342.1111.

   6: IR (thin film) 3080, 3020, 1650, 1615, 1585, 1570, 1095 cm^{-1}; NMR (CCl$_4$) δ 7.30 (m, 5 H), 5.85-6.28 (m, 1 H), 5.92 (s, 1 H), 5.10-5.55 (m, 2 H), 5.30 (sharp m, 1 H), 4.95 (sharp m 1 H), 4.34 (m, 2 H), 1.90 (br s, 3 H); mass spectrum, m/e calcd 232.0922, obsd 232.0924.

7. M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis"; Wiley-Interscience: New York, 1974; Vol. 4, p. 503.

8. The omission of diphenyl disulfide from the reaction leads to the generation of **2** in only 40% yield. The disulfide may thus either ameliorate the Lewis acidity of the zinc chloride or else, more importantly, it may function as a radical scavenger.

9. This work was supported by Merck Sharp & Dohme and by the Sloan Foundation.

(Received in USA 5 May 1981)