Tetrahedron Letters Vol. 22, pp 489 - 492
©Pergamon Press Ltd. 1981. Printed in Great Britain

0040-4039/81/0201-0489$02.00/0

REGIOSPECIFICITY IN THE DIELS-ALDER REACTIONS OF AN ENEDIONE

Samuel Danishefsky and Michael Kahn
Department of Chemistry, Yale University, New Haven, Conn. 06511

Summary: The regiochemistry of cycloaddition of 1 with unsymmetrical dienes is explained by a preference for early rehybridization of the junction carbon.

During our syntheses of coriolin and coriolin B,[1-4] the conversion of enedione 1 to a more advanced intermediate with the regio and stereochemistry shown in 4 was an important subgoal. As noted in the previous communication,[5] this objective was not achieved by direct Michael addition to 1, since such reactions led to introduction of the substituent at the junction carbon.

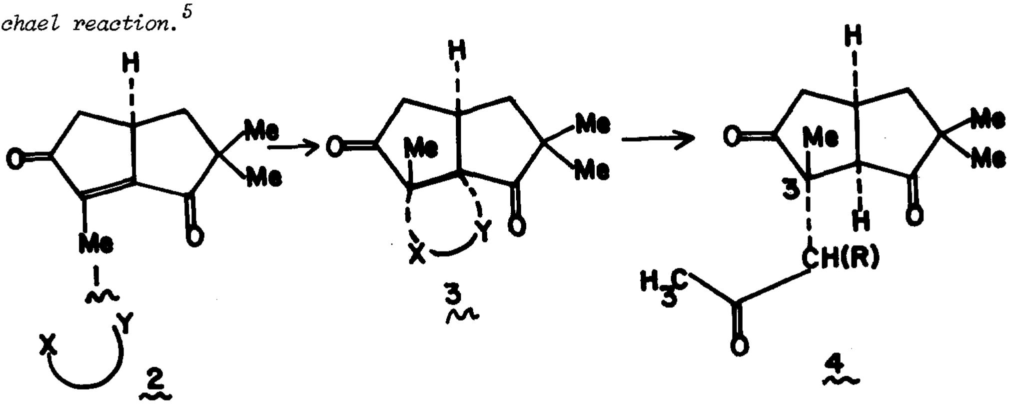
The strategy which eventually brought success is shown in the generalized cycloaddition-degradation sequence 1 → 3 → 4. This approach takes account of the stereochemical issue at C_3. Thus, reaction of 1 with 2 would be expected to occur syn to the junction hydrogen, since the alternative would result in a virtually prohibitive trans fusion of the two five membered rings.

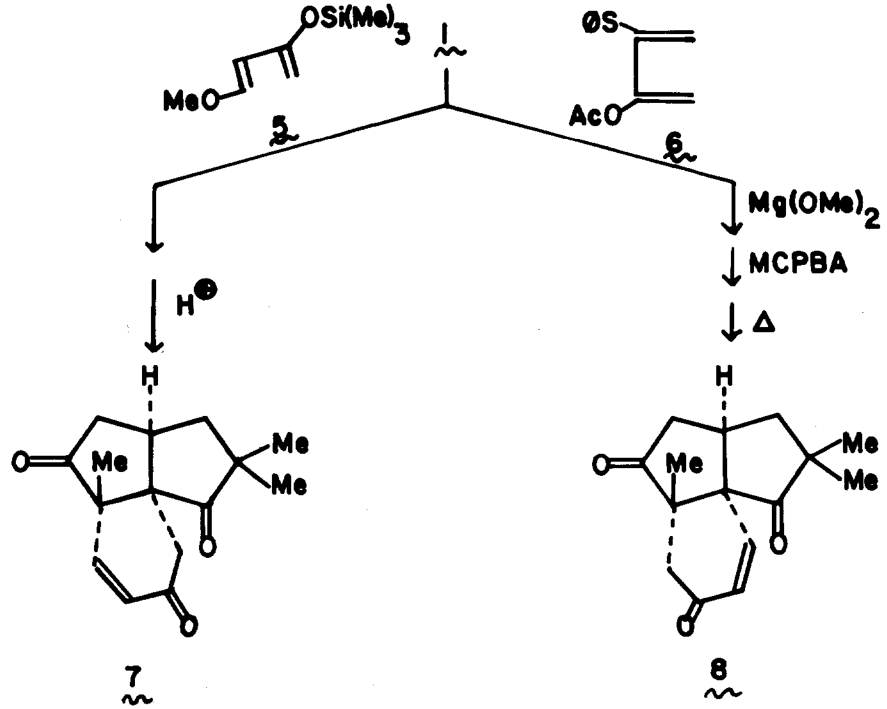
In this paper, we describe some Diels Alder reactions of compound 1. As will be seen, the remarkable regiospecificity of these reactions can be rationalized on the same basis as that which accounts for the unidirectionality of the Michael reactions.

We first examined the cycloaddition of 1 with diene 5.[6] The reaction was carried out in xylene at 130° for 12 hr. The crude adduct was hydrolyzed with 0.1NHCl in the usual way[6] to afford a 91% yield of an enone, which was contaminated with *ca.* 10% of a β-methoxyketone. Recrystallization from hexane-ethyl acetate gave a 60% yield of homogeneous enone, mp 75-76°. At this stage, we were unable to differentiate between 7 and 8 in assigning the structure of this enone but subsequent degradations showed it to be the former.

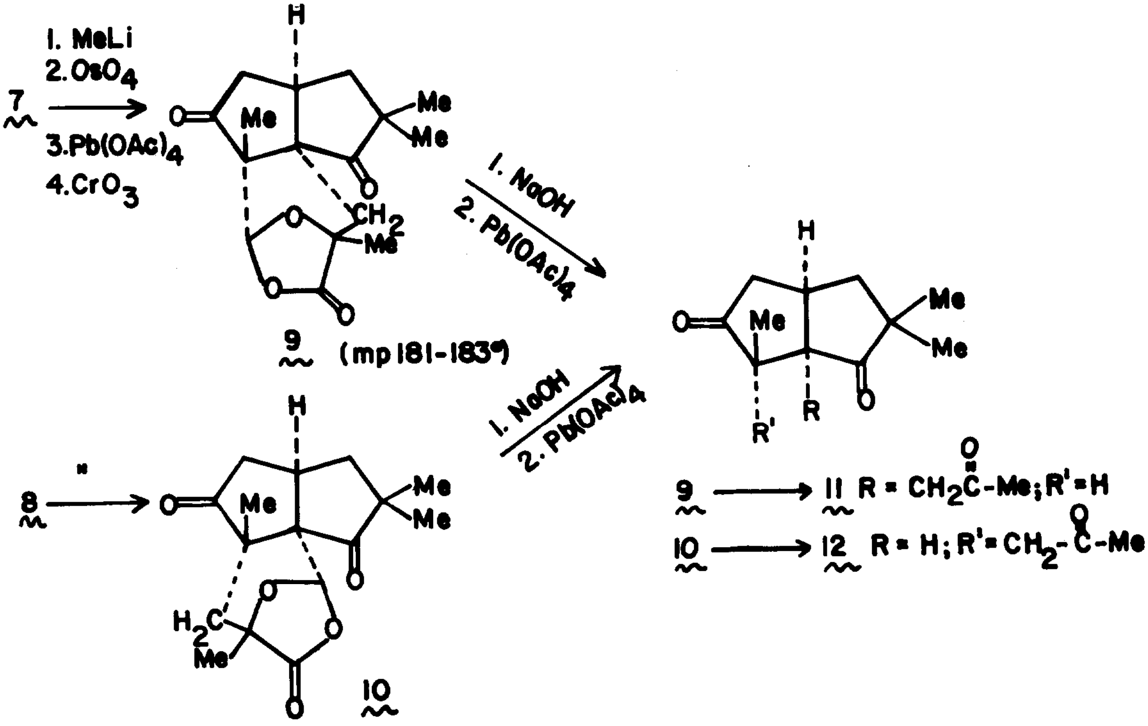
The isomeric enone, 8, was obtained (46%) yield by a sequence which started with the reaction of 1 with the Trost [7,8] type diene, 6 (excess) in the presence of the Kishi inhibitor[9] at 130° for 12 hr. Cleavage $(Mg(OMe)_2)$[7] of the enol acetate function was followed by oxidative de-sulfenylation.

Since the orientational characteristics of both 5[6] and 6[7] are by now well recognized, it is clear that the dienophile 1 was reacting such that initial bonding was occurring at the junction carbon. Thus, the Diels Alder regiochemistry is subject to the same kind of influences which governed the Michael reaction.[5]





The structures of 7 and 8 were established through the degradations shown below. The C-methyl region of the nmr spectra of 11 and 12 clearly allowed for their differentiation. The stereochemistry of the secondary methyl group of 11 is unassigned.

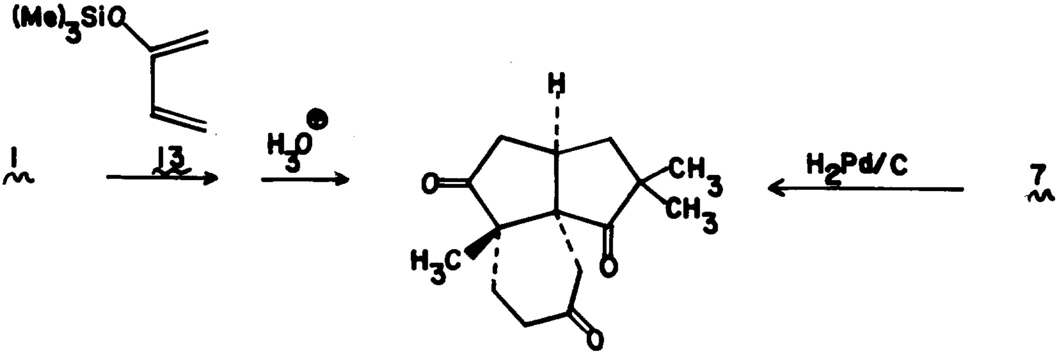


Cycloaddition of enedione 1 with 13[10a,b] followed the same pattern as was observed in its reactions with 5 and 6 (xylene, 135°, 8 hr). Hydrolysis of the adduct afforded trione 14, mp 142-143°, in 79% yield. As before, we did not observe the formation of any isomeric adduct, though we cannot rule out its formation to a slight extent. Compound 14 was also obtained by the catalytic hydrogenation of 7.

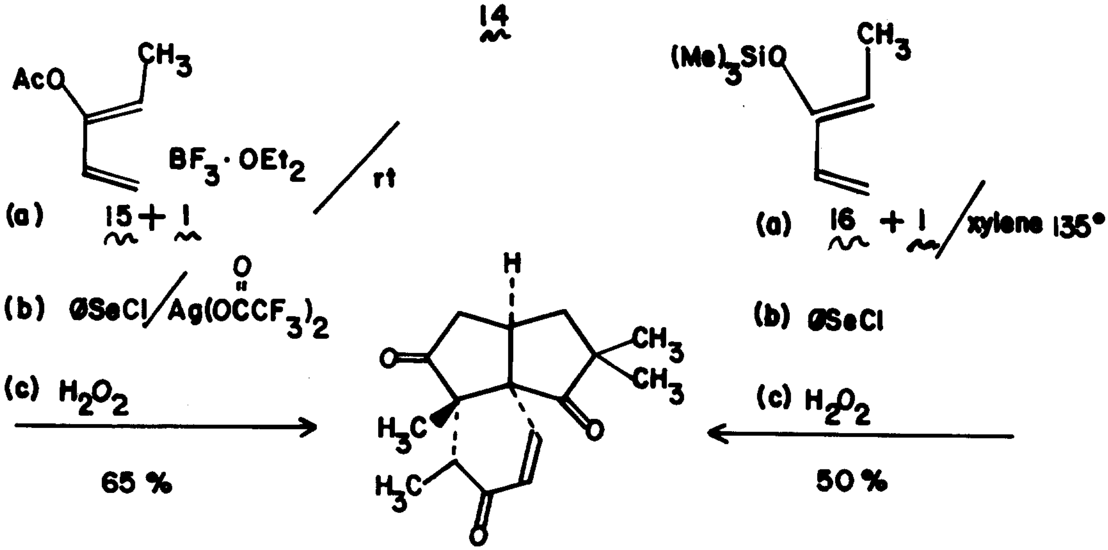
It was of interest to study the regiochemical outcome of the reactions of 1 with the 1,2-disubstituted dienes 15[11] and 16[12,13] There is a considerable body of evidence to indicate that in Diels Alder reactions, the directing effects of a 1-alkyl group of a 1,3-butadiene may predominate over those of a 2-hetero substituent.[14,15]

This trend was evident in the reactions shown below. In each case, the Diels Alder adduct was directly selenenylated[13], as shown. Oxidative de-selenenylation afforded enetrione 17. Degradation of this compound afforded compound 4, R = Me, which became our key intermediate to reach the coriolins.[1,3]

In summary, all of the known chemistry of enedione 1 is interpretable in terms of a driving force for removal of unsaturation from the junction.



14



17

Acknowledgments: This research was supported by PHS Grant CA12107-15&16. The NMR measurements at 270 MHz were obtained from the Northeast Regional N.S.F./N.M.R. Facility at Yale University supported by the N.S.F. Chemistry Division on Grant CHE7916210. The authors wish to thank Professor Barry Trost for providing a preprint of the manuscript on the preparation and use of compound 6, and Professor Theodore Cohen and Mr. Daniel Ouellette for a generous gift of tetrathiophenylbutane used in the preparation of this diene.

References:

1. S. Danishefsky, R. Zamboni, M. Kahn, and S.J. Etheredge, J. Am. Chem. Soc. 102, 2097 (1980).
2. S. Danishefsky, and R. Zamboni, Tetrahedron Lett., 3439 (1980).
3. S. Danishefsky, R. Zamboni, M. Kahn, and S.J. Etheredge, J. Am. Chem. Soc. in press.
4. For some alternate syntheses in the coriolin area see: (a) K. Tatsuta, K. Akimoto, and M. Kinoshita, J. Antibiotics, 33, 100 (1980); (b) M. Shibasaki, K. Iseki, and S. Ikegami, Tetrahedron Lett., 3587 (1980).
5. S. Danishefsky, and M. Kahn, see preceeding paper.
6. S. Danishefsky, T. Kitahara, C.F. Yan, and J. Morris, J. Am. Chem. Soc., 101, 6996 (1979).
7. B.M. Trost, W.C. Vladuchick, and A. Bridges, J. Am. Chem. Soc., 102, 3548, 3554 (1980).
8. T. Cohen, D. Ouellette, and W.M. Daniewski, Tetrahedron Lett., 5063 (1978).
9. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, Chem. Commun., 64 (1972).
10. (a) C. Girard, P. Amice, J.P. Barnier, and J.M. Conia, Tetrahedron Lett., 3329 (1974); (b) M.E. Jung, and C.A. McCombs, Tetrahedron Lett., 2935 (1976).
11. F. Bohlmann, H.J. Foerster, and H.C. Fisher, Justus Liebigs Ann. Chem., 1487 (1976).
12. G.A. Mock, A.B. Holmes, and R.A. Raphael, Tetrahedron Lett., 4539 (1979).
13. S. Danishefsky, C.F. Yan, Synth. Commun., 8, 211 (1978).
14. In support of this trend *cf.* inter alia (a) see reference II; (b) C. Schmidt, S.D. Sabnis, E. Schmidt, and D.K. Taylor, Can. J. Chem., 49, 371 (1971); (c) K. Yamakama, and T. Satah, Chem. Pharm. Bull., 27, 1747 (1979); (d) K. Yamakama, T. Satah, N. Ohba, and R. Sakaguchi, Chem. Lett., 763 (1979); (c) L.E. Overman, Acc. Chem. Res., 13, 218 (1980). (f) R.A. Dickinson, R. Kubela, G.A. MacAlpine, Z. Stojnac, and Z. Valenta, Can. J. Chem., 50, 2377 (1972).
15. For some other cases bearing on this question see: (a) reference 12; (b) R.E. Beyer, and L.H. Sarett, J. Am. Chem. Soc. 74, 1397 (1952) and (c) U.R. Chatak, and P.C. Chakraborti, J. Org. Chem., 45, 4562 (1979); (d) C.D. Perchonock, and J.A. Finkelstein, Tetrahedron Lett. 3323 (1980).

(Received in USA 9 October 1980)