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REGIOSPECIFIC MICHAEL REACTIONS TO AN ENEDIONE

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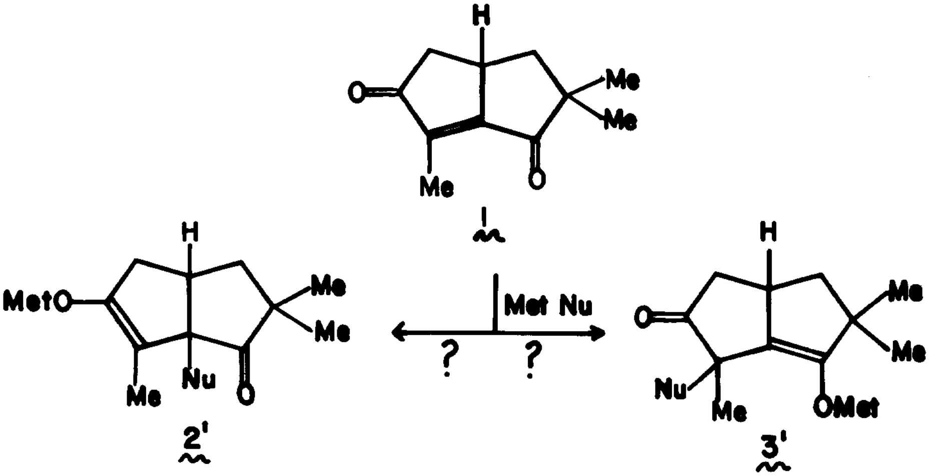
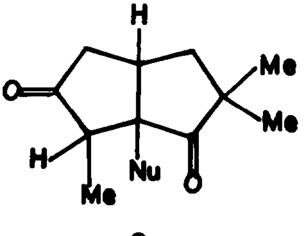
Summary: The directionality of Michael additions to unsymmetrical enedione 1 is governed by product development control in the emerging enolate intermediate.

Recently, we described the total syntheses of coriolin and coriolin B.[1-4] A key intermediate was enedione 1. An important subgoal in those syntheses was the conversion of compound 1 to a more advanced intermediate of the type 3 with the important proviso that "Nu" correspond to a potential acetonyl residue, and that this function be *cis* to the junction hydrogens. One possibility for achieving such a transformation would be by direct Michael addition of an organometallic specie to enedione, 1. In addition to the obvious stereochemical uncertainty, the regiochemical outcome of such a reaction was far from clear.

In this paper we describe the outcome of such experiments. In practice, we have found that these reactions afforded, uniformly, products of the structure 2. These results are described below.





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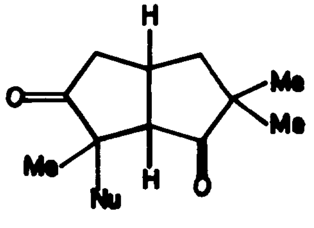

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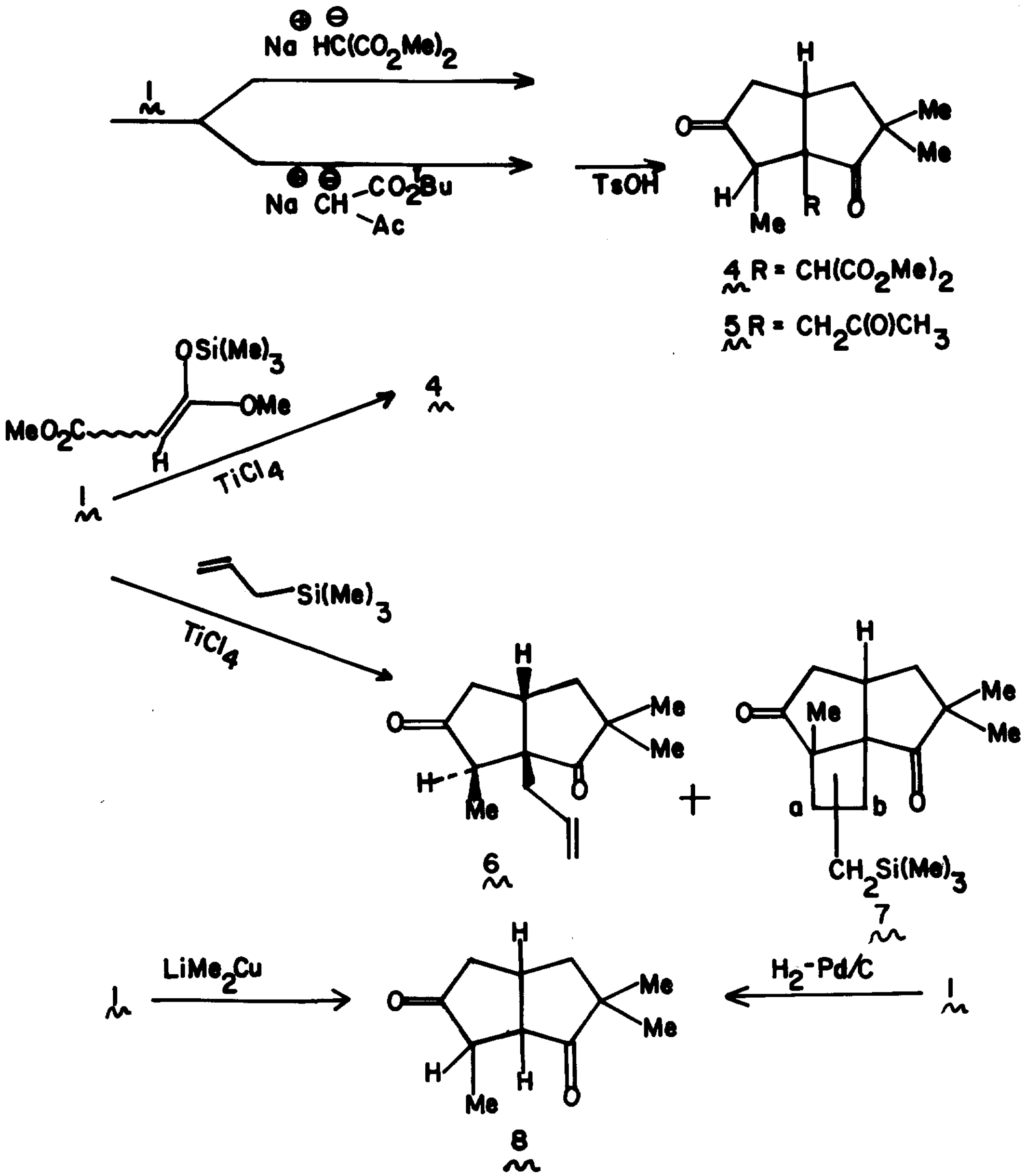
1
$Na^{\oplus}\ ^{\ominus}HC(CO_2Me)_2$
$Na^{\oplus}\ ^{\ominus}CH(CO_2{}^tBu)Ac$
TsOH
H
Me
Me
H
Me
R
O
O
4 R = CH(CO₂Me)₂
5 R = CH₂C(O)CH₃
OSi(Me)₃
OMe
MeO₂C
H
4
TiCl4
1
Si(Me)₃
TiCl₄
H
O
Me
Me
H
Me
O
6
+
H
O
Me
Me
Me
a
b
O
CH₂Si(Me)₃
7
1
LiMe₂Cu
H
O
Me
Me
H
Me
H
O
8
H₂-Pd/C
1

Reaction of **1** with sodiodimethylmalonate in methanol at room temperature for 20 hr, affords an 88% yield of **4**[5]. There was no indication for the formation of any of the type **3** product. The stereochemistry at the secondary methyl center is not determined. The same compound was obtained (48%) from a Mukaiyama like reaction[6] of α-methoxy, β-trimethylsilyloxy acrylate[7] with **1**.

Similarly, reaction of **1** with sodio-tert-butyl acetoacetate (methanol/rt) gave an adduct which, after reaction with tosyl acid in benzene under reflux, afforded a 78% yield of **5**[5]. The stereochemistry at the secondary methyl center is undetermined. As before, there was no indication for the formation of type **3** product.

The reaction of **1** with allyltrimethylsilane (titatium tetrachloride-78°) was also studied. Two products, **6**[5] and **7**[5], were obtained in varying ratios. The only Sakurai type product[8] detected was 6 (12-31%). In this case the stereochemistry was determined to be that shown.[9] Whether this configuration arises from kinetic or thermodynamic control is not known.

The other product was the cyclobutane **7**.[10a,b] We have no evidence which rigorously defines the placement, or stereochemistry of the $CH_2Si(Me)_3$ group, though on the basis of the precedents above, and the mechanism advanced for the formation of such cycloadducts,[10a] one would favor its attachment at the "a" carbon.

The reaction of **1** with lithium dimethylcuprate (ether, 0°) gave no apparent addition product. Instead there was obtained, in 85% yield, the dihydro product **8**[5]. The ability of cuprates to serve as reducing agents is certainly well precedented.[11,12] Compound **8** was also obtained by the catalytic hydrogenation (H_2-Pd/C-EtOAc) of enedione **1**.

Presumably, the strain associated with the emergence of a bridgehead double bond (see structure **3**') discourages the formation of type **3** products. In contrast, attack of the nucleophile at the bridgehead carbon involves an energetically favorable rehybridization of this carbon from the sp^2 to the sp^3 level. Such an effect would tend to lower the activation energy of those processes leading to **2** by way of **2**'.

The energetic advantages of an early rehybridization of the bridgehead of **1** from sp^2 to sp^3 are also seen in its cycloaddition reactions.[13,14,15]

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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. The structure of this compound is in accord with its infrared, NMR and mass spectra.

6. K. Saigo, M. Osaki, T. Mukaiyama, Chem. Lett. 163 (1976).
7. S. Danishefsky, K. Vaughan, R.C. Gadwood, and K. Tsuzuki, Tetrahedron Lett., 2625 (1980).
8. A. Hosomi, and H. Sakurai, J. Am. Chem. Soc. **99**, 1673 (1977).
9. We thank Professor R. Adams of Yale University for his X-ray structure determination of compound **6**. The details for the determination will be disclosed elsewhere.
10. (a) R. Pardo, J. Zahra, and M. Santelli, Tetrahedron Lett., 4557 (1979); (b) A. Hosomi, H. Kobayashi, and H. Sakurai, Tetrahedron Lett., 955 (1980).
11. D.J. Hannah, and R.A.J. Smith, Tetrahedron Lett., 187 (1975).
12. R.A. Ruden, and W.E. Litterer, Tetrahedron Lett., 2043 (1975).
13. S. Danishefsky, and M. Kahn. See subsequent paper.
14. For a recent study of the reductive alkylation of enediones see: G. Stork, and E.W. Logusch, J. Am. Chem. Soc. 1218, 1219 (1980).
15. An alternative interpretation for the remarkable regiospecificity of both the Michael and cycloaddition reactions of enedione **1** has been rendered by a referee. It is argued that the π-orbitals of the olefin are more nearly parallel with the "s-trans" rather than the "s-cis" ketone. The relative effectiveness of the two carbonyl groups in overlapping with the olefin, would influence the polarization of the double bond, and, thereby, the directionality of nucleophilic attack. In our view the difference in the quality of overlap is very slight, but may be significant. Both explanations are fully consistent and cannot be distinguished with the available data.

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