Tetrahedron Letters,Vol.24,No.13,pp 1353-1356,1983 0040-4039/83/131353-04$03.00/0
Printed in Great Britain

DIELS-ALDER REACTIONS OF 2-CARBOMETHOXY-4,4-DIMETHYLCYCLOPENTENONE[1]

Drury Caine, Charles R. Harrison, and Donald G. VanDerveer

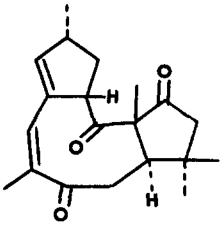
School of Chemistry

Georgia Institute of Technology

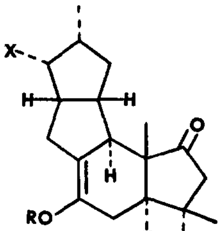
Atlanta, Georgia 30332

Abstract: 2-Carbomethoxy-4,4-dimethylcyclopentenone (9) was found to undergo cycloaddiiton to oxydiene 5b to give a 45:55 mixture of the exo and endo adducts 10 and 11 under thermal conditions and a 95:5 mixture of the respective adducts under Lewis acid-catalyzed conditions.

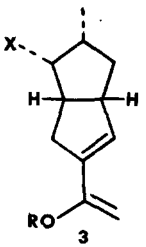
In connection with a possible synthetic approach to the antileukemic diterpene jatrophatrione (1),[2] we became interested in the construction of a 5/5/6/5-fused tetracyclic ring system (cf. 2) which after appropriate manipulation could be cleaved at the B/C ring junction to generate the 5/9/5-fused ring skeleton of the natural product. A possible approach to the desired tetracyclic intermediate involves a Diels-Alder reaction between an appropriate oxydiene, e.g. 3, and 2,4,4-trimethylcyclopentenone (4).



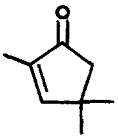
1



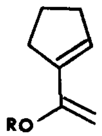
2



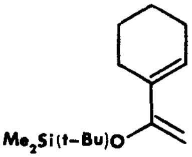
3



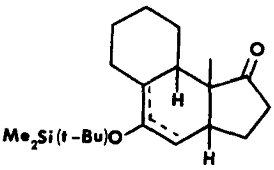
4



5 a. R = SiMe$_3$
b. R = Ac



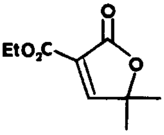
6



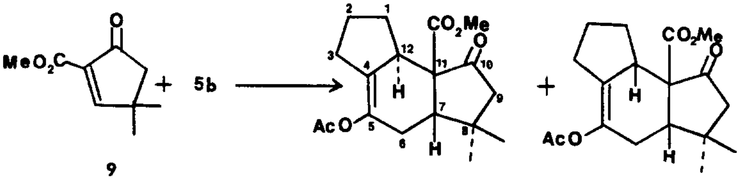
7

In view of the difficulties associated with Diels-Alder reactions of cyclopentenones,[3,4] we decided to investigate the reaction of 4 with oxydienes of the type 5[5] which we felt would be reasonable models for the more complex pentalene derivative 3. There is apparently no literature precedent for Diels-Alder reactions involving 4,4-disubstituted cyclopentenones. However, Ireland and coworkers[6] have reported that 2-methylcyclopentenone undergoes cycloaddition with the t-butyldimethylsilyloxy diene 6 to give the endo adduct 7, as a mixture of double bond isomers, in reasonable yield and with complete regioselectivity. Therefore, we felt that if a diene of the type 5 could be induced to react with enone 4, the same regioselectivity would be expected, but that because of the steric effect of the *gem*-dimethyl group the exo rather than the endo mode of addition would be observed.

However, we were disappointed to find that attempted reaction of dienes 5a and 5b with enone 4[7] under thermal conditions (neat or in xylene (trace hydroquinone), 120-180°, 18-32 h), or with a variety of Lewis acid catalysts ($AlCl_3(CH_2Cl_2)$, $SnCl_4$ (Et_2O), etc., -20° to 25°, 6-32 h), gave no trace of a Diels-Alder adduct.[8] Apparently, enone 4 is so sterically hindered that polymerization of the diene[9] occurred faster than cycloaddition under all the conditions investigated.



8



9

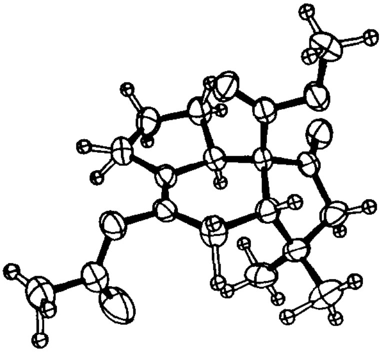
10

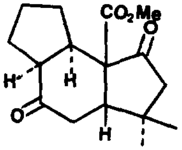
11

Recently it has been shown that the dienophilicity of cyclohexenones,[10] cyclohexadienones,[11,12] γ-butenolides,[13,14] and acyclic enones[14] is enhanced by the presence of carboalkoxy[10,11,13,14] or formyl[12] groups at the α-position. In fact, 2-carbomethoxy[11] and 2-formyl-4,4-dimethylcyclohexa-2,5-dienone[12] and the carboethoxy γ-butenolide (8)[13] were found to undergo cycloaddition readily even with a *gem*-dimethyl group present. These results prompted us to investigate the Diels-Alder reactions of 2-carbomethoxy-4,4-dimethylcyclopentenone (9)[15,16] with the dienes 5a and 5b. The Diels-Alder reaction between the diene 5b and the enone 9, conducted under the thermal conditions (sealed tube, neat, 135°, 18 h), gave a 67% yield of a *ca*. 45:55 mixture of the tricyclic adducts 10[16] and 11[16] resulting from the exo and endo modes of addition with respect of the cyclopentenone ring. When the cycloaddition reaction was conducted in the presence of a Lewis acid catalyst (1 eq. 9, 3 eq. 5b, 1.1 eq. $AlCl_3$, CH_2Cl_2, -78° 3 h, 25°, 3 h) adducts 10[16] and 11[16] were formed in a 19:1 ratio in 62% yield. The cycloadducts were separated by chromatography on florisil.

The structures of 10 and 11 were tentatively assigned on the basis of the positions of NMR (300 MHz) signals for the C-12 protons in the respective isomers. The C-12 proton in adduct 10 lies within the shielding cone of the carbonyl group of the cyclopentanone ring and was found at the relatively highfield position of δ 1.46, while the C-12 proton of 11, which is in an environment which causes it to be deshielded by the ester group, occurred at the relatively low-field location of δ 2.85. In order to confirm these structural assignments a single crystal xray analysis was performed on adduct 10.[17] An ORTEP drawing of the molecular structure of 10 is shown in Figure 1.

Figure 1





12

Apparently, in the thermal reaction of 5b and 9 secondary orbital overlap[18,19] which should favor endo addition is offset by the steric effect of the gem-dimethyl group which should favor exo addition and a ca. 1:1 mixture of adducts is obtained. The unusually large increase in the stereoselectivity of the cycloaddition of 5b and 9 in the presence of the Lewis acid catalyst is probably because the catalyst complexes more strongly with the ester than the enone carbonyl oxygen atom since the former is expected to be more basic.[19] This should increase the magnitude of the coefficient at the ester carbonyl carbon atom in the LUMO of the complex of 9 with aluminium chloride and make secondary orbital overlap of the approaching diene more favorable with the ester than the ketone carbonyl carbon atom.

Diene 5a was also found to react with enone 9 under thermal conditions, but the mixture of adducts produced was highly unstable and attempts to effect purification by chromatography on various adsorbants caused hydrolysis of the silyl enol ether function. The major product of the mixture of diketones which was produced was the only one which could be isolated reasonably pure. On the basis of its spectral properties this material was tentatively assigned the structure 12.[16]

In order for enone 9 to be a useful intermediate in the synthesis of jatrophatrione, the ester group would have to be converted to a methyl group at some point after the cycloaddition had been effected. Studies along this line are in progress.

References and Notes

1. This investigation was supported by Grant No. CA 28355 awarded by the National Cancer Institute DHHS.
2. Torrance, S. J.; Wiedhopt, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Beavers, W. A.; Culter, R. S. J. Org. Chem. 1976, 41, 1855.
3. (a) Dane, E.; Eder, K. Ann. Chem. 1939, 539, 207; (b) Granger, R.; Nau, P. F. G.; Francois, C. Bull. Soc. Chem. Fr. 1962, 1902; (c) Ichihara, A.; Kimura, R.; Moriyasu, K.; Sakamura, S. Tetrahedron Lett. 1977, 4331; (d) Improvements in the yields of Diels-Alder adducts of cyclopentenones have been reported when aluminium chloride is used as a catalyst, see Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. Synth. Commun. 1979, 9, 391.
4. For the use of an α-phenylthio group for the activation of cyclopentenones toward cycloaddition reactions, see (a) Knapp, S.; Lis, R.; Micha, P. J. Org. Chem. 1981, 46, 624; (b)

Lee, T. V.; Toczek, J. J. Chem. Soc. Chem. Commun. 1982, 968.

5. Dienes 5a and 5b were prepared by treatment of acetylcyclopentene with LDA in THF at -78° followed by trapping of the kinetic dienolate with chlorotrimethylsilane or acetic anhydride, respectively.
6. Ireland, R. E.; Thompson, W. J.; Mandel, N. S.; Mandel, G. S. J. Org. Chem. 1979, 44, 3583.
7. Wakui, T.; Ostuji, Y.; Imoto, E. Bull. Soc. Chem. Jp 1974, 47, 2967.
8. Attempted cycloadditions of 4 with cyclopentadiene, 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefshy, S.; Kitahara, T. J. Am. Chem. Soc. 1974, 96, 7807) and 2-trimethylsilyloxy-1,3-butadiene (June, M. E.; McCombs, C. A. Tetrahedron Lett. 1976, 2935; Org. Syn. 1978, 58, 163) under the conditions described in the text for diene 5a also were unsuccessful.
9. Belanger, J.; Landry, N. L.; Paré, J. R. J.; Jankowski, K. J. Org. Chem. 1982, 47, 3649.
10. Liu, H. J.; Ngooi, T. K. Synth. Commun. 1982, 12, 715.
11. (a) Liu, H. J.; Browne, E. N. C. Tetrahedron Lett. 1977, 2919; (b) Liu, H. J.; Browne, E. N. C. Can. J. Chem. 1979, 57, 377; 1981, 59, 601.
12. Liotta, D., Saindane, M.; Barnum, C. J. Am. Chem. Soc. 1981, 103, 3225.
13. Liu, H.-J.; Browne, E. N. C.; Pednekar, P. R. Can. J. Chem. 1982, 60, 921.
14. Hoye, T. R.; Caruso, A. J.; Magee, A. S. J. Org. Chem. 1982, 47, 4152.
15. The α-carbomethoxycyclopentenone 9 was prepared in low yield by alkylation of the potassium enolate of isobutyraldehyde (Groenewegen, P.; Kallenberg, H.; van der Gen, A. Tetrahedron Lett. 1978, 491) with methyl γ-bromo-β-methoxycrotonate (Weinreb, S. M.; Auerback, J. J. Am. Chem. Soc. 1975, 97, 2503) followed by hydrolysis of the enol ether and intramolecular aldol cyclization of the intermediate aldehydo β-keto ester.
16. The NMR and IR spectral properties of all new compounds were consistent with the assigned structures. Correct elemental analyses and/or parent ion exact mass spectral data were also obtained for all new compounds.
17. The crystals of 10 are monoclinic, space group $P2_1/C$, $a = 6.214(2)$Å, $b = 30.197(7)$Å, $c = 9.008(3)$Å; $\beta = 98.07(2)$Å, $V = 1673.4(8)$Å; $\rho_c = 1.27$g cm^{-3} for 4 formula units per cell. A total of 2966 reflections were collected from which 1891 were accepted as statistically above background on the basis that F was greater than 3 T (F). The structure was determined by routine multisolution direct methods (Programs utilized were Sheldrich's SHEL X-76 program and Johnson's ORTEP program, MULTAN-78, P. Main, Univ. of York, York, England) and refined to a current residual of R = .071.
18. See, Stephenson, L. M.; Smith, D. E.; Current, S. P. J. Org. Chem. 1982, 47, 4171, and references cited therein.
19. MINDO calculations of the charge densities and molecular orbital coefficients for a model compound, 3-carboxy-3-buten-2-one, performed by Prof. Dennis Liotta and Ms. Judy Grossman, support these suggestions. We are grateful to Prof. Liotta for making these results available to us.

(Received in USA 10 January 1983)