Tetrahedron Letters,Vol.24,No.5,pp 465-468,1983 0040-4039/83/050465-04$03.00/0
Printed in Great Britain

STEREOCHEMICAL CONTROL IN THE CONSTRUCTION OF VICINALLY SUBSTITUTED CYCLOPENTANES AND CYCLOHEXANES. INTRAMOLECULAR CONJUGATE ADDITION OF β-KETOESTER ANIONS.

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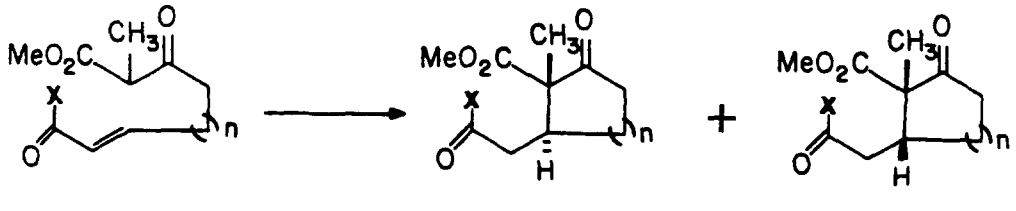
Abstract: The intramolecular addition of β-ketoesters to unsaturated enones and esters produces vicinally substituted carbocycles with high stereoselectivity.

We have recently reported that the intramolecular addition of an aldehyde to a conjugated enone can be controlled by the proper choice of reaction conditions to give vicinally substituted cyclopentanes with high stereoselectivity.[1] The very small number of highly stereoselective methods which can serve this purpose prompts us to report further results on the scope of this reaction.

Systems in which a β-ketoester undergoes intramolecular addition to an unsaturated system appeared particularly suitable for this study for several reasons. The starting materials are very readily prepared, the stereochemistry of the products is easily ascertained, and the two ester groups of cyclized products such as 5 can be selectively hydrolyzed. Most important to our mechanistic concerns, we expected that the enolates of β-ketoesters would have a much more easily controlled geometry than the aldehydes that were the object of our original studies.

Cyclization of 1 was found to be quite non-selective in polar media leading to 2 and 3 in which the cis to trans ratio varies from ca. 1:1 (potassium t-butoxide in t-butanol) to ca. 3:1 (sodium methoxide in methanol) in favor of cis-3.[2] Similarly, compounds 4 and 7 also produced ca. 1:1 mixtures of cyclopentanones (5 and 6)[3] and cyclohexanones (8 and 9),[4] respectively (potassium t-butoxide in t-butanol).[5]

Scheme I



1: n=1, X=Me
4: n=1, X=OMe
7: n=2, X=OMe

2: n=1, X=Me
5: n=1, X=OMe
8: n=2, X=OMe

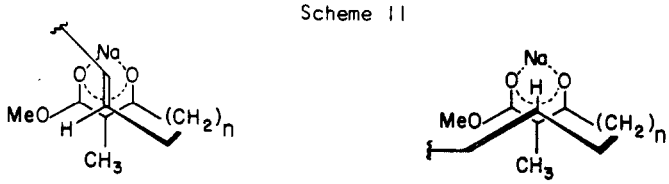
3: n=1, X=Me
6: n=1, X=OMe
9: n=2, X=OMe

In very sharp contrast to this rather uninteresting result, we have found that the cyclic metal chelate of 1 (catalytic sodium hydride in benzene, 15 minutes at room temperature) gives a

90% yield of trans-2. None of the cis isomer 3 could be detected. Reaction of 4 under the same conditions produced a 22:1 ratio of 5 to its cis isomer 6 (isolated yield of 5, 85%). Similarly, the cyclization of 7 resulted in a 30:1 ratio of 8 to its cis isomer 9 (isolated yield of 8, 88%).

We believe that the high stereoselectivity of the reaction is the result of the orientation of the acceptor chain away from the chelate ring, stabilizing transition state B leading to 2, 5, and 8, respectively.[6]

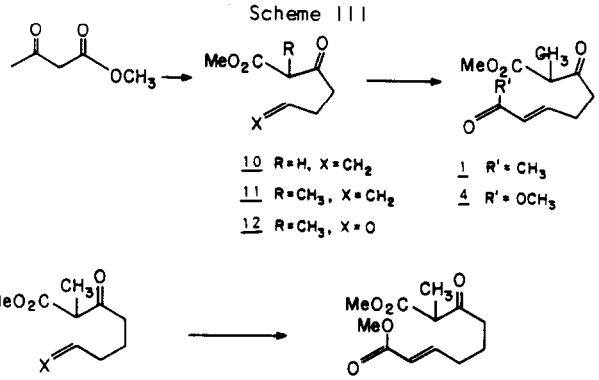
Scheme II



A B

The syntheses of the cyclization substrates 1, 4, and 7 are outlined below (Scheme III). Alkylation of the dianion of methyl acetoacetate[7] with 3-bromopropene (tetrahydrofuran, 0°C) afforded ketoester 10, which was methylated (K_2CO_3, MeI, acetone) to furnish ketoester 11 in

Scheme III



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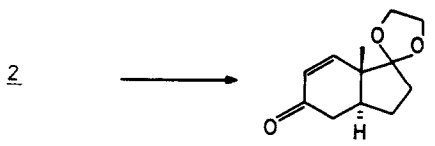
68% overall yield. Ozonolysis of 11 (CH_2Cl_2, -78°C) followed by treatment with 1-triphenylphosphoranylidene-2-propanone or methyl 2-(triphenylphosphoranylidene)acetate (benzene, room temp.) yielded substrates 1(68%) and 4(81%), respectively. Compound 7 was similarly prepared in 35% overall yield from methyl acetoacetate and 4-bromobutene. It is interesting to note that the mono-substituted β-ketoester is compatible with both the ozonolysis and the Wittig reaction.

The stereochemistry of 2 was established by conversion to the trans-fused hydrindenone 13[8] (Scheme IV), identical with an authentic sample of 13 prepared by another route.[1] The configurations of compounds 5, 6, 8, and 9 were also shown to be as depicted in Scheme I by conversion to known compounds[9], identical to authentic samples prepared by independent routes.[10]

Scheme IV



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Finally, we draw attention to an important distinction between two classes of intramolecular addition of an anion to a Michael acceptor: In one class, the electrophilic unsaturation is in a ring; in the other it is not.[11] The first class normally leads to cis-fused bicyclic systems. By contrast, we have shown that trans-fused bicyclic systems are the eventual result of this second new class of these intramolecular conjugate additions.

Acknowledgement. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

References

1. G. Stork, C. Shiner, J. Winkler, J. Am. Chem. Soc. 104, 310 (1982); G. Stork, J. Winkler, C. Shiner, J. Am. Chem. Soc. 104, 3767 (1982).

2. Ratios of products were determined by glass capillary VPC chromatography (SE-30 or 3%FFAP). 2: ^{1}H NMR (80 MHz, $CDCl_3$) δ1.13 s (3H), 2.15 s (3H), 2.0-2.7 m (7H), 3.73 s (3H); IR ($CDCl_3$): 1765, 1730 cm^{-1}; MS (Cl-Me) M+1 213. 3: ^{1}H NMR (80 MHz, $CDCl_3$) 1.26 s (3H), 2.17 s (3H), 2.0-2.8 (7H), 3.69; IR ($CHCl_3$): 1750, 1720 cm^{-1}; MS (Cl-Me) M+1 213.

3. 5: ^{1}H NMR (80 MHz, $CDCl_3$) 1.18 s (3H), 1.1-1.9 m (2H), 2.1-2.7 m (4H), 3.0-3.4 m (1H), 3.67 s (3H), 3.73 s (3H); IR (neat): 1760, 1740, 1730, 1715 cm^{-1}; MS (Cl-NH_3) M+1 229. 6: ^{1}H NMR (80 MHz, $CDCl_3$) 1.31 s (3H), 2.0-2.8 m (7H), 3.69 s (3H), 3.71 s (3H); IR (neat): 1770-1700 cm^{-1}; MS (Cl-NH_3) M=1 229.

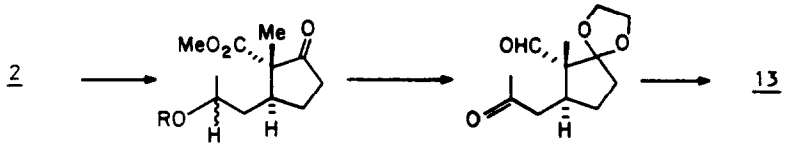
4. 8: ^{1}H NMR (80 MHz, $CDCl_3$) 1.29 s (3H), 1.5-2.6 m (8H), 2.8-3.2 m (1H), 3.68 s (3H), 3.75 s (3H); IR (neat): 1760, 1701 cm^{-1}; MS (Cl-NH_3) M+1 243. 9: ^{1}H NMR ($CDCl_3$, 80 MHz) 1.34 s (3H), 1.6-2.7 m (9H), 3.69 bs (6H); IR (neat): 1750-1710 cm^{-1}; MS (Cl-NH_3) M+1 243.

5. All cyclizations were performed at room temperature overnight. Ratios of products were obtained by integration of the 80 MHz ^{1}H NMR.

6. The deformation required to achieve the type of transition state we are suggesting, a "5-endo-trig" closure [Cf. J. Baldwin, J. Chem. Soc., Chem. Comm. 734 (1976); J. Baldwin, L. Kruse, J. Chem Soc., Chem. Comm. 233 (1977)] is decreased by the fact that, in the case of the β-ketoester enolate system, it is only a partial double bond which is internal to the incipient 5-membered ring.

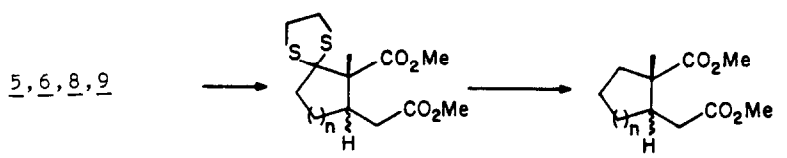
7. S. Huckin, L. Weiler, J. Am. Chem. Soc. 96, 1082 (1974).

8. Selective reduction of 2 (Dibal-H, THF, 0°C, 71% yield) followed by acetylation (Ac_2O, pyridine, 97% yield) gave i (R=Ac), which was ketalized with ethylene glycol (p-TSA, benzene, 63% yield), followed by LAH reduction (60% yield) and oxidation (73% yield) with Collins reagent [J. Collins, W. Hess, F. Frank, Tetrahedron Letters 3363 (1968); R. Ratcliffe, R. Rodehorst, J. Org. Chem. 1970, 35, 4000] to provide ii. Cyclization of ii with sodium methoxide in benzene gave trans-fused 13 in 90% yield.



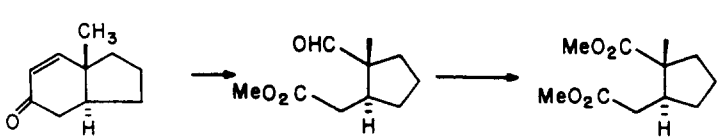
i ii

9. Thioketalization of 5, 6, 8, and 9 (CH_2Cl_2, ethanedithiol, $BF_3 \cdot Et_2O$) gave the corresponding thioketals, which were desulfurized (Raney Ni, ethanol, room temp.) and hydrogenated (Pd/C, H_2, methanol) to give compounds 14-17, respectively. Overall yields for the transformations were 5--14, 23%; 6--15, 28%; 7--16, 32%; 8--17, 33%.



14: n=1, trans
15: n=1, cis
16: n=2, trans
17: n=2, cis

10. Authentic samples of 14-17 were prepared in the following manner: 14 was prepared by ozonolysis of trans-hydrindenone 18[11] (ethyl acetate, -40°C) followed by oxidative work-up (H_2O_2 HOAc) and treatment with diazomethane to yield aldehyde iii (30%). Jones oxidation of iii followed by diazomethane furnished the trans-diester 14 (45%); 15 was prepared by treatment of cis-2-methyl-2-cyclopentane-1-acetic acid [H. Conroy, J. Am. Chem. Soc. 74, 3046 (1952)] with diazomethane (diethyl ether, 0°C, 87%); 16 was prepared by treatment of trans-2-methyl-2-carboxy-cyclohexane-1-acetic acid [R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. McLamore, J. Am. Chem. Soc. 74, 4223 (1952)] with diazomethane (diethyl ether, 0°C, 90%); 17 was prepared by treatment of cis-2-methyl-2-carboxy-cyclohexane-1-acetic acid [Cf. R. Linstead, A. Millidge, A. Walpole, J. Chem. Soc. 1140 (1937); W. Bachmann, S. Kushner, J. Am. Chem. Soc. 65, 1963 (1943)] with diazomethane (diethyl ether, 0°C, 98%).



18 iii 14

11. For examples of stereocontrol of the intramolecular Michael reaction of β-ketoester nucleophiles in the synthesis of cyclohexanes, see D. Taber, Ph. D. Thesis, Columbia University, New York, New York, 1974; Diss. Abstr. Int. B. 35, 4399 (1975); L. Lombardo, L. Mander, S. Pyne, J. Am. Chem. Soc. 101, 3378 (1979). See also D. Brattesani, C. Heathcock, J. Org. Chem. 40, 2165 (1975).

(Received in USA 20 September 1982)