Tetrahedron Letters, Vol.31, No.17, pp 2407-2410, 1990
Printed in Great Britain

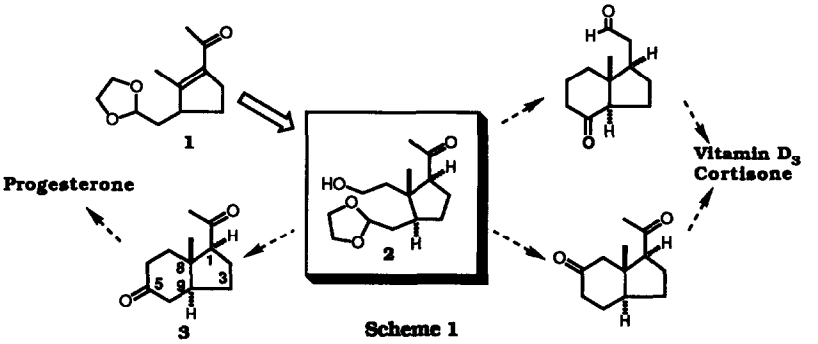
0040-4039/90 $3.00 + .00
Pergamon Press plc

NEW SYNTHETIC INTERMEDIATE FOR TRANS-8-METHYLHYDRINDANONES

Haruo YAMADA, Katsuya SHIMIZU, Mohammad NISAR, Takashi TAKAHASHI,* and Jiro TSUJI+
Tokyo Institute of Technology, Meguro, Tokyo 152, JAPAN

Summary: Synthesis of 1-acetyl-8-methylhydrindan-5-one (**3**) by the conjugate addition-enolate protonation of the 3-alkyl-2-methyl-1-acetylcyclopentene **1** followed by the cyclization of the cyanohydrin ether, and discussions for the diastereoselectivity in the enolate protonation based on MM2 calculations are presented.

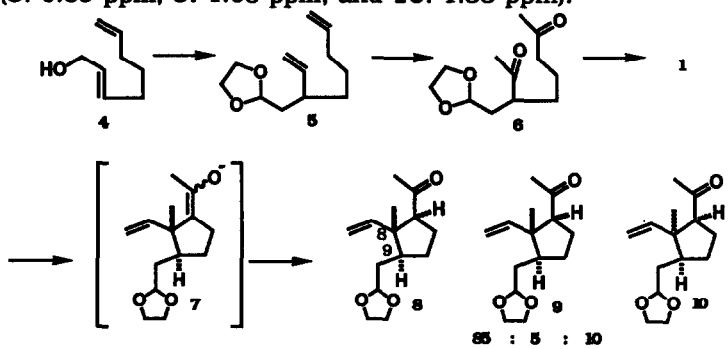
The stereodefined 1,2,2,3-tetrasubstituted cyclopentanes such as **2** would be an ideal precursor of trans-8-methylhydrindanones which are found naturally as C,D ring of steroids, cortisones and vitamin D3 (Scheme 1). We report here the stereoselective synthesis of the tetrasubstituted cyclopentane **2** as the new synthetic intermediate of steroid CD ring and its conversion to the trans-8-methylhydrindanone **3**. In our synthesis, the initial cuprate conjugate addition to the enone **1** proceeds from the less-hindered side to induce the trans stereochemistry[1] between C(8) methyl and C(9) hydrogen and the cyclization of the cyanohydrin ether[2] affords the C ring. However in this approach, the stereocontrolled protonation of the cuprate-generated enolate would be very difficult because of the quaternary carbon next to the reaction center. In this paper, we also discuss the computational transition models based on MM2[3] calculations for the analysis (or prediction) of the stereoselectivity in the enolate-protonation.



Scheme 1

The enone **1** was prepared in the following way (Scheme 2). Claisen rearrangement of the allyl alcohol **4**[4] (ethyl vinyl ether, Hg(OAc)2 then 160 °C) followed by ketalization of the resulting aldehyde (ethylene glycol, *p*-TsOH) gave the diene **5** in 70% overall yield. Oxidation of the terminal double bond in **5**

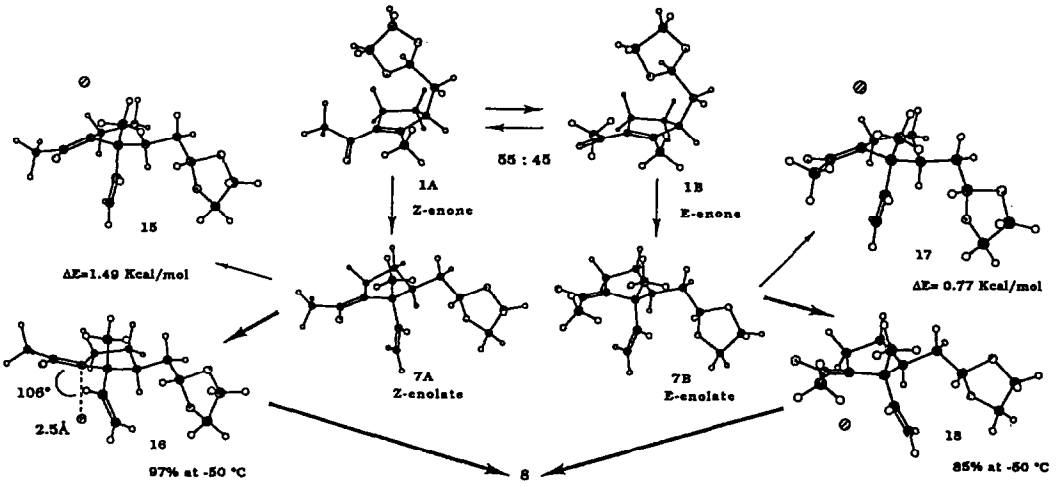
($PdCl_2/CuCl/O_2$;[5] 77%) and basic treatment (10% NaOH) of the diketone **6** gave the enone **1** in 78% yield. Then we examined the stereoselectivity in the conjugate addition-enolate protonation using the enone **1** and the higher ordered vinyl cuprate. Addition of **1** in ether to a mixture of 2 eq. of vinyllithium and 1 eq. of copper cyanide[6] in ether at -78 °C, followed by gradual warming to -50 °C, and workup (aq. NH_4Cl) gave the ketone **8** in 66% yield after chromatography. The HPLC analysis revealed that the conjugate addition of the vinyl group produced a 90 : 10 mixture of the trans adducts **8**, **9** (C(8) methyl/C(9) hydrogen) and the cis adduct **10**, and the protonation of the enolate resulted in a 85 : 5 ratio of the trans **8** (C(1) acetyl/C(8) methyl) to its cis isomer **9**. Stereochemical assignments of the successive chiral centers of the products **8**, **9**, and **10** were made by analyses of the ^1H NMR spectra of quaternary methyl groups[7] (**8**: 0.69 ppm, **9**: 1.05 ppm, and **10**: 1.33 ppm).



Scheme 2

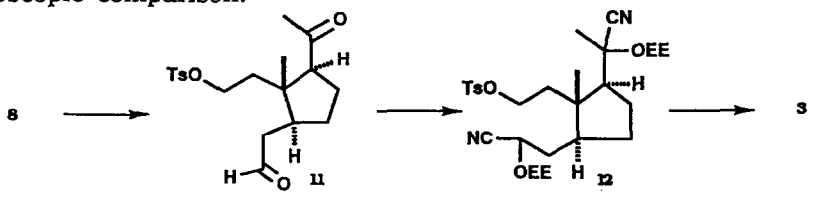
Previous studies of the kinetic enolate methylation[8] and protonation[9] seem best interpreted by assuming an early reactant-like transition state[10]. Thus, the conformational analyses of the enone **1** and its E,Z-enolate intermediates **7** were conducted.[11),12] MM2 calculations and Boltzmann distribution of the enone **1** showed that the s-cis- and s-trans enone conformations **1A** and **1B** were equilibrated at -78 °C in a ratio 55 : 45. Therefore the conjugate addition would lead a 1 : 1 mixture of the Z- and E-enolates **7A** and **7B**. The three and two lower energy enolate conformations were found for each Z and E enolate within 3 Kcal/mol above the lowest energy conformation. Then the transition state energies in the protonation of these enolates were calculated. In our computational model, the size of a chlorine atom was brought in toward the enolate as the proton donor and we constrained the distance (2.5 Å) and the attacking angle (106 °)[13] of the proton donor to the α-carbon and the atoms of enolate moiety. The geometry for the rest of system was fully optimized for the α- and β-attack of the proton. The energy difference (1.49 Kcal/mol) between the Z-transition state models **15** and **16** could rationalize the preferential α-protonation. Same result was also obtained from the energy difference (0.77 Kcal/mol) between the E-enolates **17** and **18**. Thus, the correspondence between experimental and calculated

product distribution is quite acceptable within the context of this crude transition state model.



Scheme 3

Synthesis of the hydrindanone **3** was carried out as shown in Scheme 4. Protection of the ketone **8** (Me3SiCN/KCN/18-crown-6-complex: 93% yield) and hydroboration of the terminal olefin with 9-BBN followed by basic treatment (10% NaOH, 30% H_2O_2) gave the alcohol **2** in 60% yield. Tosylation of the alcohol (*p*-TsCl/pyridine) and hydrolysis of the acetal group (3N HCl/THF) gave the aldehyde **11** in 90% overall yield. Protected cyanohydrin formation[14] of the resulting keto aldehyde **11** in three steps (Me3SiCN/KCN/18-crown-6, 1N HCl/THF, ethyl vinyl ether/*p*-TsOH) gave **12** in 86% overall yield. Cyclization of **12** with NaN(TMS)2 in THF at 60 °C, and acid treatment (3N HCl/THF) of the cyclized product followed by basic treatment (2% aq. NaOH) of the cyanohydrin gave the hydrindanone **3** in 58% overall yield from **12**. Thus obtained hydrindanone **3**[15] was identical with authentic sample[16] by its spectroscopic comparison.



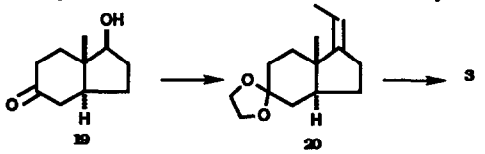
Scheme 4

References and Notes

+ Present address; Okayama University of Science, Ridai-cho 1-1, Okayama-shi, Okayama 700, Japan.

1) P. R. Bernstein and G. Stork, *Tetrahedron Lett.*, **1979**, 1967.

2) T. Takahashi, H. Yamada, and J. Tsuji, *J. Am. Chem. Soc.*, 1981, **103**, 5259.
3) N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.
4) The starting material was easily available in high yield by palladium catalyzed telomerization of butadiene. J. Tsuji, 'Organic Synthesis with Palladium Compounds.' Springer-Verlag, Berlin Heidelberg New York, 1980.
5) J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, **1976**, 2975.
6) B. H. Lipshutz, R. S. Wilhelm, and J. Kozlowski, *Tetrahedron Lett.*, 1982, **23**, 3755.
7) In related systems, the quaternary methyl groups absorb 0.72 ppm, 1.07 ppm, 1.33 ppm for trans-trans, cis-trans, and cis-cis isomers, respectively (see ref 1)).
8) a) W. C. Still and I. Galynker, *Tetrahedron*, 1981, **37**, 3981; b) W. C. Still, L. J. MacPherson, T. Harada, J. F. Callahan, and A. L. Rheingold, *Tetrahedron*, 1984, **40**, 2275; c) T. Takahashi, K. Shimizu, T. Doi, J. Tsuji, and K. Yamamoto, *Tetrahedron Lett.*, 1989, **30**, 4999; d) T. Takahashi, Y. Yamashita, T. Doi, and J. Tsuji, *J. Org. Chem.*, 1989, **54**, 4273.
9) H. E. Zimmerman and L. W. Linder, *J. Org. Chem.*, 1985, **50**, 1637.
10) H. O. House, W. V. Phillips, and D. VanDerveer, *ibid.*, 1979, **44**, 2400.
11) The Program MacroModel was employed for these calculations. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, and W. C. Still, MacroModel V2.0 Department of Chemistry, Columbia University, New York, NY 10027.
12) Recent X-ray and NMR studies of lithium enolates show the oligomeric structure of the enolates, lithium counterion, and solvent. Force field parameters which implicitly incorporated their effect were applied for MM2 calculations of enolates. G. W. Spears, C. E. Caufield, and W. C. Still, *J. Org. Chem.*, 1987, **52**, 1226.
13) K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, and R. J. Loncharich, *Science*, 1986, **231**, 1108.
14) G. Stork, J. C. Depezay, and J. d'Angelo, *Tetrahedron Lett.*, **1975**, 389.
15) Trans-hydrindanone **3** : ^{1}H-NMR ($CDCl_3$): 0.89 (s, 3H), 2.16 (s, 3H), 2.18-2.72 (m, 5H); IR(neat) cm^{-1}: 2950, 1700, 1360.
16) The authentic sample **3** was obtained in high yield from the keto-alcohol **19** in the following manner. Protection of the carbonyl group in **19** (ethylene glycol, *p*-TsOH), oxidation of the alcohol (CrO_3, Pyridine) and Wittig reaction of the resulting ketone gave the Z-ethylidene hydrindane **20**. The hydroboration of **20** with diborane proceeded exclusively from α-face with the desired configuration at C(1) hydrogen. Hydrolysis of the acetal (3N HCl), followed by Collins oxidation of the alcohol gave the trans-hydrindanone **3** in 53% overall yield from **19**.



(Received in Japan 11 December 1989)