Communications to the Editor

[Chem. Pharm. Bull. 32(1) 373—376 (1984)]

STEREOSELECTIVE ALDOL REACTION OF A LITHIUM α-VINYL ENOLATE TO α-ALKOXY ALDEHYDES

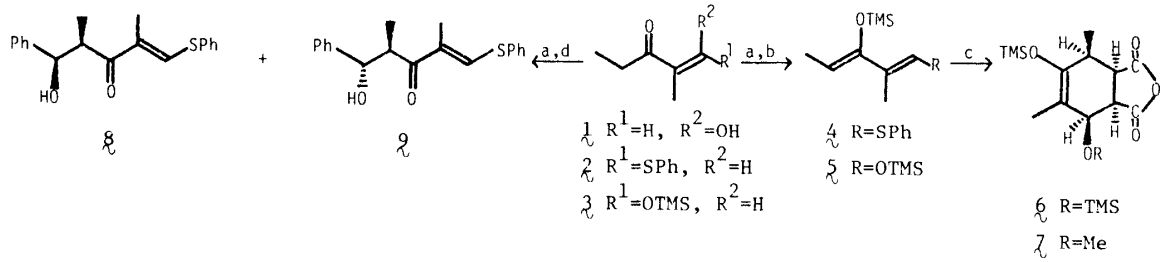
Masataka Ihara,[a] Masatoshi Chihiro,[a] Keiichiro Fukumoto,*,[a] and Tetsuji Kametani[b]
Pharmaceutical Institute, Tohoku University,[a] Aobayama, Sendai 980, Japan and
Institute of Medicinal Chemistry, Hoshi University[b]
Ebara, 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Stereoselective synthesis of the 4,5-syn, 5,6-anti adducts (14 and 16) on the aldol condensation of the Z(O)-lithium enolate, derived from the E-enone (2), to α-alkoxy aldehydes (12 and 13) was proved via the successive intramolecular Diels-Alder reaction.

KEYWORDS —— aldol reaction; lithium α-vinyl enolate; α-alkoxy aldehyde; intramolecular Diels-Alder reaction; benzocyclobutene; 4b, 5,6,7,8,8a,9,10-octahydrophenanthrene-8-one

Recently, there has been much investigation of the chemistry of the addition of enolates to aldehydes for the total synthesis of macrolide antibiotics and other polyoxygenated natural products.[1] However the aldol reaction of the enolates derived from enones has not been well examined. In the course of our synthetic study, finding the exclusive formation of the Z(O)-lithium α-vinyl enolate led us to investigate its addition to aldehydes and α-alkoxy aldehydes. Here we wish to report a high diastereoselectivity in the above reaction: the stereochemistry of the latter adducts was established via the successive intramolecular Diels-Alder reaction.

The hydroxy methylene (1)[2] was converted into the enones (2 and 3) as a single stereoisomer according to the usual method. Treatment of 2 and 3 with lithium hexamethyldisilazide at -78°C in tetrahydrofuran followed by trimethylsilyl chloride gave homogeneously the corresponding dienes (4 and 5)[3] (82 and 60%, respectively). The Diels-Alder reaction of 5 with maleic anhydride at room temperature produced the bicyclic compound (6)[3] (79%). Since the ^{1}H-NMR spectrum of 6 was similar to that of 7 as reported by Danishefsky,[4] the relative stereochemistry was assigned as formulated. Thus the geometry of 4 and 5 turned out to be E, Z.

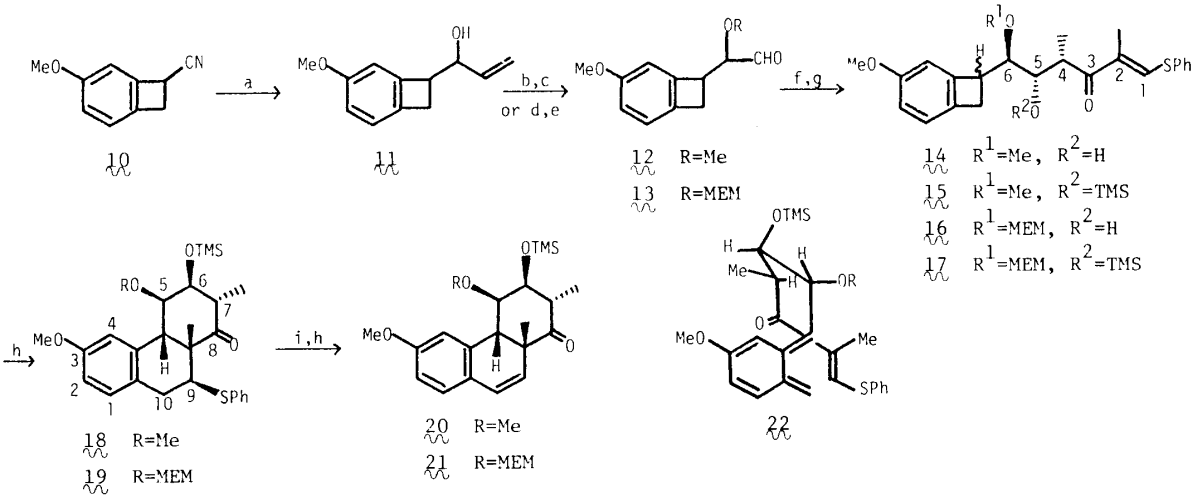


a: $(TMS)_2NLi$ b: TMSCl c: maleic anhydride d: benzaldehyde

The Z(O)-enolate formed under the same conditions as above was condensed with benzaldehyde for several seconds giving a mixture of 8[3] and 9[3] (93%) in the ratio of 8 : 1. Erythro and threo isomers were easily distinguished by ^{1}H-NMR spectral analysis.[5] The preferential formation of the former confirmed the above assignment of geometry.

Next we investigated the aldol reaction with α-alkoxy aldehyde and the determination of stereochemistry after conversion of the adducts into cyclic compounds via the intramolecular Diels-Alder reaction. The α-alkoxy aldehyde (12 and 13) were prepared as follows. Condensation of 1-cyanobenzocyclobutene (10)[6] with acrolein followed by decyanation furnished the allylic alcohol (11) (46%) as a mixture of diastereoisomers at the chiral center on the benzocyclobutene ring. The aldehyde (12) was synthesized by methylation followed by Lemieux oxidation, while 13 by methoxyethoxymethylation followed by ozonolysis.

The enolate was condensed with 12 at -78°C to afford a mixture of adducts (66%), separable into two components (14A and 14B), which seem to be mainly two diastereoisomers at the C_1 position of benzocyclobutene, since intramolecular Diels-Alder reaction of both compounds gave the same octahydrophenanthrene. Therefore the above mixture was converted into the hexahydrophenanthrene (20). Namely after protection as trimethylsilyl ether (65%), heating 15 at 230°C for 45 min in o-dichlorobenzene in a sealed tube produced 18[3] (50%) as a single stereoisomer. Oxidation of 18 with m-chloroperbenzoic acid followed by syn-elimination formed 20.[3] The cis-ring juncture of 20 was determined on the basis of the long range coupling (J = 1 Hz) between C_{4b} and C_9-hydrogens. This result is reflected in the favored conformation of one endo-modes (22). The exo-modes would not be favored, because of serious interaction between the aromatic ring and the C_2-methyl. The relative



10 11 12 R=Me 13 R=MEM

14 R^1=Me, R^2=H
15 R^1=Me, R^2=TMS
16 R^1=MEM, R^2=H
17 R^1=MEM, R^2=TMS

18 R=Me 19 R=MEM 20 R=Me 21 R=MEM 22

a: $NaNH_2$, liq. NH_3, acrolein then Na b: KOH, MeI c: OsO_4, $NaIO_4$
d: MEMCl, $^iPr_2NEt$ e: O_3, Me_2S f: 2, $(TMS)_2NLi$ g: TMSCl, Et_3N
h: Δ i: MCPBA

configuration on ring C was determined by the coupling constants in the ^{1}H-NMR spectrum. Furthermore, the α-orientation of the C_7-methyl was confirmed by NOE with the C_9-hydrogen.[7] Therefore the stereochemistry of the above aldol product (14) proved to be the 4,5-syn, 5,6-anti.[8,9]

Addition of 2 to 13 (76%), followed by silylation of 16[3] afforded 17 (78%). Successive cyclization of 17 furnished 19[3] (87%), which was transformed into 21[3] having the same configuration as above. Thus it was made clear that aldehydes (12 and 13) possessing different types of alkoxy groups produced diastereoselectively the products of the anti-Cram's cyclic (coordination) model.[9,10]

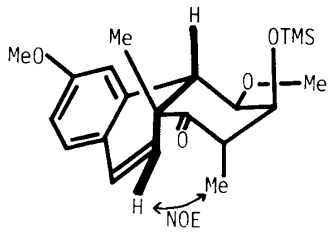
REFERENCES AND NOTES

1) a) T. Mukaiyama, "Organic Reactions," Wiley, New York, 1982, Vol.28, pp.203 - 331; b) S. Kiyooka and C. H. Heathcock, Tetrahedron Lett., 24, 4765 (1983); c) S. Masamune, J. W. Ellingboe, and W. Choy, J. Am. Chem. Soc., 104, 5526 (1982); d) D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, J. Am. Chem. Soc., 103, 3099 (1981).

2) S. Sugasawa, S. Yamada, and M. Narahashi, Yakugaku Zasshi, 71, 1345 (1951).

3) Spectral data: 4 ^{1}H-NMR (CCl_4) δ:0.15 (9H, s, TMS), 1.63 (3H, d, J = 7 Hz, 4-Me), 1.88 (3H, s, 2-Me), 4.90 (1H, q, J = 7 Hz, 4-H), 6.40 (1H, br s, 1-H), 7.22 (5H, br s, Ph); ^{13}C-NMR ($CDCl_3$) δ: 0.7, 12.0, 15.3, 104.9, 120.7, 126.4, 129.0, 129.2, 133.5, 136.4, 150.5. 5 ^{1}H-NMR (CCl_4) δ: 0.20 (18H, s, 2 × TMS), 1.55 (3H, d, J = 7 Hz, 4-Me), 1.62 (3H, s, 2-Me), 4.58 (1H, q, J = 7 Hz, 4-H), 6.42 (1H, br s, 1-H). 6 ^{1}H-NMR (CCl_4) δ: 0.12 and 0.13 (each 9H, each s, 2 × TMS), 1.40 (3H, d, J = 7 Hz, 4-Me), 1.70 (3H, s, 2-Me), 2.62 (1H, dq, J = 10, 7 Hz, 4-H), 3.10 (1H, dd, J = 4, 10 Hz, 1a-H), 3.47 (1H, t, J = 10 Hz, 4a-H), 4.50 (1H, d, J = 4 Hz, 1-H). 8 ^{1}H-NMR (CCl_4) δ: 1.03 (3H, d, J = 7 Hz, 4-Me), 4.85 (1H, d, J = 4 Hz, 5-H). 9 ^{1}H-NMR (CCl_4) δ: 0.93 (3H, d, J = 7 Hz, 4-Me), 4.63 (1H, d, J = 8 Hz, 5-H). 14A ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J = 7 Hz, 4-Me), 1.92 (3H, d, J = 1 Hz, 2-Me), 3.22 (3H, s, OMe), 3.74 (3H, s, OMe), 7.60 (1H, q, J = 1 Hz, 1-H). 14B ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J = 7 Hz, 4-Me), 1.94 (3H, d, J = 1 Hz, 2-Me), 3.42 (3H, s, OMe), 3.74 (3H, s, OMe), 7.59 (1H, q, J = 1 Hz, 1-H). 16 ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J = 7 Hz, 4-Me), 1.93 (3H, s, 2-Me), 7.66 (1H, s, 1-H). 18 IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (C=O); ^{1}H-NMR (CCl_4) δ: 0.03 (9H, s, TMS), 1.08 (3H, d, J = 6 Hz, 7-Me), 1.63 (3H, s, 8a-Me), 3.70 (3H, s, 5-OMe), 3.83 (3H, s, 3-OMe). 19 IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 0.10 (9H, s, TMS), 1.13 (3H, d, J = 6 Hz, 7-Me), 1.68 (3H, s, 8a-Me). 20 ^{1}H-NMR (CCl_4) δ: 0.10 (9H, s, TMS), 1.07 (3H, s, 8a-Me), 1.23 (3H, d, J = 8 Hz, 7-Me), 2.67 (1H, dq, J = 4, 8 Hz, 7-H), 2.98 (3H, s, 5-OMe), 3.18 (1H, dd, J = 1, 10 Hz, 4b-H), 3.42 (1H, dd, J = 2, 10 Hz, 5-H), 3.80 (3H, s, 3-OMe), 3.95 (1H, dd, J = 2, 4 Hz, 6-H), 5.28 (1H, dd, J = 1, 10 Hz, 9-H), 6.35 (1H, d, J = 10 Hz, 10-H). 21 ^{1}H-NMR ($CDCl_3$) δ: 0.18 (9H, s, TMS), 1.07 (3H, s, 8a-Me), 1.27 (3H, d, J = 8 Hz, 7-Me), 2.47 ∿ 2.73 (1H, m, 7-H), 3.27 (3H, s, OMe), 3.80 (3H, s, 3-OMe), 5.32 (1H, dd, J = 1, 9 Hz, 9-H), 6.37 (1H, d, J = 9 Hz, 10-H).

4) S. Danishefsky, C.-F. Yan, R. K. Singh, R. B. Gammill, P. M. McCurry, Jr., N. Fritsch, and J. Clardy, J. Am. Chem. Soc., 101, 7001 (1979).
5) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).
6) T. Kametani, M. Kajiwara, and K. Fukumoto, Tetrahedron, 30, 1053 (1974).
7) The molecular model of 20 is described as below.



8) S. Masamune, T. Kaiho, and D. S. Garvey, J. Am. Chem. Soc., 104, 5521 (1982).
9) This result is consistent with the observation by Heathcock and associates; C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, J. Org. Chem., 45, 3846 (1980).
10) W. C. Still and J. H. McDonald, III, Tetrahedron Lett., 21, 1031 (1980).

(Received November 16, 1983)