Tetrahedron Letters No. 4, pp 315 - 318, 1974. Pergamon Press. Printed in Great Britain.

THE STEREOCHEMISTRY OF THE PHOTOADDITION OF ALLENE TO CYCLOPENT-1-ENE-1-CARBOXALDEHYDES

Frederick E. Ziegler[1] and James A. Kloek[2]

Department of Chemistry, Yale University
New Haven, Connecticut, 06520, U.S.A.

(Received in USA 29 October 1973; received in UK for publication 10 December 1973)

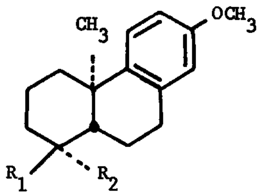
We have previously reported[3] a method for the synthesis of the 1-hydroxy-7-methylene-bicyclo[3.2.1]octane[4] ring system involving the photoaddition of allene to cyclopent-1-ene-1-carboxaldehyde. We wish to report the stereoselectivity of this reaction in a sequence leading to steviol methyl ester 6a and isosteviol methyl ester 6c.

Phenanthrone 1a[5] exists as a 2/1 mixture of cis/trans isomers, which upon exposure to methoxymethylene triphenylphosphorane (DMSO, room temperature, 3.5 hr.) cleanly provided an oily mixture of enol ethers 1b[6]. Hydrolysis of the isomers (aq. HCl/THF, room temperature, 18 hrs.) yielded a single aldehyde 1c as an oil from kinetic protonation[7] (δ 10.35, 1H, s). Exposure of 1c to tBuOH/t-BuOK caused epimerization to the thermodynamic aldehyde 1d (δ 9.70, 1H, d). Alkylation[8] of aldehyde 1c with t-BuOH/t-BuOK/CH_3I produced the crystalline aldehyde 1e, mp 84-86°, (δ 1.02(3H,s), 1.10(3H,s) and 9.96 (1H,s)) in 55% yield from phenanthrone 1a. Oxidation (Jones' reagent, 7°, 18 hrs.) of aldehyde 1e provided the known acid 1f, mp 192-193°, (lit.[4i] mp 193-194°), previously employed in a total synthesis of steviol.

Acid 1f was converted to enone 2a as previously described.[4i] Thioketalization of enone 2a produced thioketal 2b mp 243-245° (78% yield) which was reduced with lithium in liquid ammonia with subsequent treatment with diazomethane to provide olefinic ester 2c (δ 3.61 (3H,s) and 5.45(1H,s))(87% yield).

Ozonolysis (O_3, methanol-methylene chloride, -78°; Me_2S)[9] of 2c followed by hydrolysis of the intermediate acetal 3a (10% aq HCl/THF, room temperature, 90 min.) provided an oil to which was assigned the structure of keto-aldehyde 3b (δ 9.68, 1H, t). Cyclization to the unsaturated aldehyde 4, mp 114-116°, (1680 cm^{-1}, δ 9.83 (1H,s)) was effected in 29% yield by exposure of the ketoaldehyde 3b to pyrrolidine in refluxing benzene followed by hydrolysis with buffered aqueous acetic acid.

Irradiation (pyrex, 450W Hanovia lamp, -78°, N_2) of an ether solution of 4 in the



1a, $R_1,R_2{=}O$

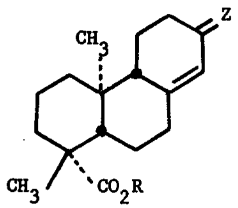
b, $R_1,R_2{=}\ {=}CHOCH_3$

c, $R_1{=}H, R_2{=}CHO$

d, $R_1{=}CHO, R_2{=}H$

e, $R_1{=}CH_3, R_2{=}CHO$

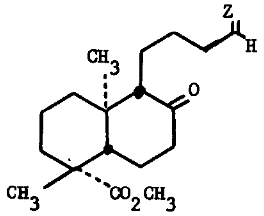
f, $R_1{=}CH_3, R_2{=}CO_2H$



2a, $R{=}H$ $Z{=}O$

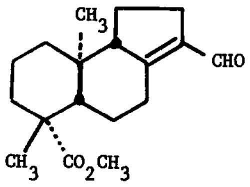
b, $R{=}H$ $Z{=}\text{-}(SCH_2)_2$

c, $R{=}CH_3$ $Z{=}H_2$

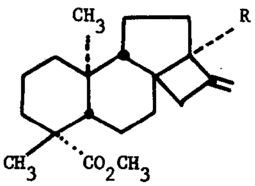


3a, $Z{=}OCH_3,OCH_3$

b, $Z{=}O$



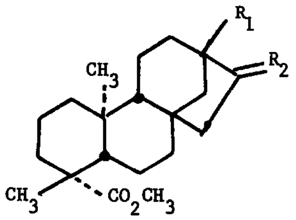
4



5a, $R{=}CHO$

b, $R{=}CH_2OH$

c, $R{=}CH_2OSO_2CH_3$



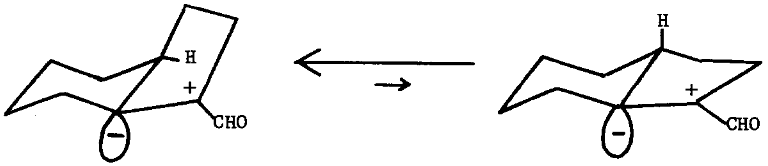
6a, $R_1{=}\alpha\text{-}OH, R_2{=}CH_2$

b, $R_1{=}\alpha\text{-}OSO_2CH_3,$ $R_2{=}CH_2$

c, $R_1{=}\beta\text{-}CH_3, R_2{=}O$

presence of allene[10] provided upon chromatography 42% of a photoaldehyde 5a (δ 4.72(1H,m), 4.85(1H,m) and 9.60(1H,s)), mp 113-116°. A second product (3%) could be isolated and was presumed to be a photoisomer of 5a on the basis of mass spectral and nmr data. Reduction ($NaBH_4$, ethanol, 0°) provided the alcohol 5b which was converted to the mesylate 5c (CH_3SO_2Cl, pyr., 0°)(δ 3.13(3H,s)). Solvolysis[11] (50% aq. acetone, 2,6 lutidine, reflux) provided among several products, (±) steviol methyl ester (3%) identical by nmr spectroscopy and multiple elution tlc with a sample of optically active steviol methyl ester prepared by esterification of steviol[12] derived from natural stevioside.[13] A second oily product (21%) was assigned the structure of the internal return mesylate 6b (δ 3.10(3H,s)) on the basis of the similarity of its nmr spectrum to that of steviol methyl ester. Confirmation of the structural assignment was secured when the mesylate was converted to isosteviol methyl ester 6c[14] upon treatment with 20% hydrochloric acid.[13]

The chemical transformation of photoaldehyde 5a to steviol methyl ester and isosteviol methyl ester secures the stereochemistry of the photoaldehyde. This result is in accord with the theory of Wiesner[15] which postulates that the ground state of allene reacts with the more stable configuration (7a) of the excited state of the conjugated carbonyl compound, having the negative charge localized at the β-carbon and the positive charge at the α-carbon. Thus, hydrindenals provide cis-ring fusions while 2-octalones provide trans-ring fusions.[10,16]



7a 7b

REFERENCES

1. National Institutes of Health Career Development Awardee, 1973-1978.

2. National Institutes of Health Predoctoral Fellow, 1969-1972. Taken in part from the Ph.D. thesis of J.A.K., Yale University, 1972.

3. F.E. Ziegler and J.A. Kloek, Tetrahedron Lett., 2201 (1971).

4. For other methods for the construction of this ring system, see: (a) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, J. Amer. Chem. Soc., 87, 1148 (1965);(b)R.A. Bell, R.E. Ireland, and L.N. Manders, J. Org. Chem., 31, 2536 (1966);(c)E.J. Corey, M. Narisada, T. Hiroaka, and R.A. Ellison, J. Amer. Chem. Soc., 92, 396 (1970); (d) K. Mori, M. Matsui, and Y. Sumiki, Tetrahedron Lett., 429 (1970); (e) K. Mori, Y. Nakahara, and M. Matsui, ibid., 2411 (1970); (f) I.F. Cook and J.R. Knox, ibid., 4091 (1970); (g) F.E. Ziegler and M.E. Condon, J. Org. Chem., 36, 3707 (1971); (h) E.J. Corey and R.L. Carney, J. Amer. Chem. Soc., 36, 7318 (1971); (i) Y. Nakahara, K. Mori, and M. Matsui, Agr. Biol. Chem. (Tokyo), 35, 918 (1971); and (j) H.O. House and D.G. Melillo, J. Org. Chem., 38, 1398 (1973) and earlier papers in this series.

5. G. Stork and A. Burgstahler, J. Amer. Chem. Soc., 73, 3544 (1951).

6. Epimerizations under these conditions have been reported: J.A. Marshall, M.T. Pike, and R.D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); C.H. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, **93**, 1746 (1971); J.W. Huffman, *J. Org. Chem.*, **37**, 13 (1972); J.A. Marshall, W.F. Huffman, and J.A. Ruth, *J. Amer. Chem. Soc.*, **94**, 4691 (1972) and Y. Nakahara, K. Mori, and M. Matsui, *Agr. Biol. Chem. (Tokyo)*, **35**, 918 (1971).

7. W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89** , 1483 (1967).

8. R.E. Ireland and L.N. Mander, *J. Org. Chem.*, **34**, 142 (1969).

9. J.J. Pappas, W.P. McKeaveney, E. Gaucher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

10. (a) P.E. Eaton, *Tetrahedron Lett.*, 3695 (1964); (b) E.J. Corey, J.D. Bass, R. LeMahieu, and R.B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (c) R.W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 2945 (1965); (d) R.W. Guthrie, Z. Valenta, and K. Wiesner, *ibid.*, 4645 (1966); (e) K. Wiesner, I. Jirovsky, M. Fishman, and C.A.J. Williams, *ibid.*, 1523 (1967); (f) D. Sunder-Plassman, P.H. Nelson, P.H. Boyle, A. Cruz, J. Iriante, P. Crabbé, J.A. Zderic, J.A. Edwards, and J. Fried, *J. Org. Chem.*, **34**, 3779 (1969); (g) R.B. Kelley and J. Zamecnik, *Chem. Commun.*, 1102 (1970); and K. Wiesner, I. Jirovsky, M. Fishman, and C.A.J. Williams, *Tetrahedron Lett.*, 1523 (1967).

11. G.N. Taylor, Ph.D. thesis, Yale University, 1968. W.G. Dauben and J.A. Chitwood, *J. Amer. Chem. Soc.*, **92**, 1624 (1970), and ref. cited therein.

12. We are grateful to Professor A.I. Scott for a sample of optically active steviol.

13. E. Mosettig, V. Beglinger, F. Dolden, H. Lichti, P. Quitt, and J.A. Wates, *J. Amer. Chem. Soc.*, **85**, 2305 (1963).

14. We are indebted to Professor R.M. Coates for a sample of isosteviol methyl ester.

15. K. Wiesner, L. Poon, I. Jirkovsky, and M. Fishman, *Can. J. Chem.*, **47**, 433 (1969).

16. We are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society (5854-AC1), the National Science Foundation (GP-30960X), and the National Institutes of Health (CA-08869) for generous, partial support of this work.