Tetrahedron Letters No. 51, pp 4899 - 4902.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/1215-4899$02.00/0

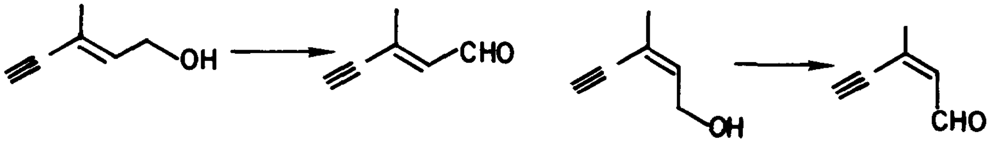
A VERSATILE SYNTHESIS OF RETINOIDS VIA CONDENSATION OF THE SIDE-CHAIN TO CYCLIC KETONES

Fadila Derguini, Valeria Balogh-Nair and Koji Nakanishi*
Department of Chemistry
Columbia University, New York, N. Y. 10027

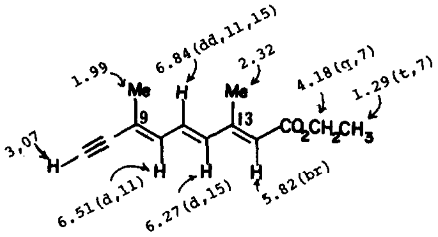
Summary. A simple synthesis of ethyl 3,7-dimethyl-2,4,6-nonatriene-8-ynoates and their corresponding alcohols is presented; condensation with various cyclic ketones can lead to retinoids having modified ring structures.

We have been interested in the synthesis of retinal analogues (retinoids) in connection with our studies on visual pigments[1]; in addition, retinoids have attracted interest in view of their properties to induce regression of precancerous cells[2]. We report in the following a simple synthesis of the side-chain which can then be condensed with various cyclic ketones as is exemplified with 2,2,6-trimethylcyclohexanone[3].

The published procedure[3] for preparing the C_{11} side-chain precursor of vitamin A, i.e., 9,13-dimethyl-9,11,13-nonatriene-7-yn-15-ol[4] 6a involves several steps of relatively low yields. The side-chains can now be prepared efficiently as follows. The commercially available C_6 enynols 1 and 3 are oxidized in quantitative yields[5] to the enynals 2 and 4 by treating with MnO_2[6,7] in CH_2Cl_2 for 3 hrs at room temperature. Emmons reaction of 2 with a 60/40 trans/cis mixture of phosphonosenecioates[8] $(EtO)_2POCH_2C(CH_3){=}CHCOOEt$ yielded esters 5 (60/40 trans/cis) in 81% yield.

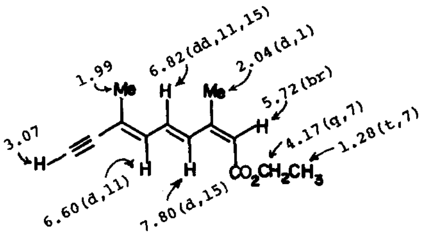


1 2 3 4



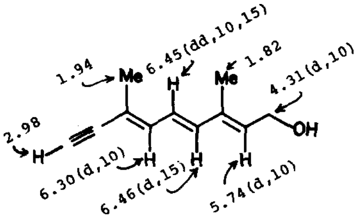
mp:38-40° UV: 319(45,000)

5a



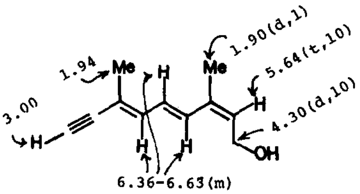
mp:73-74° UV: 322(40,000)

5b



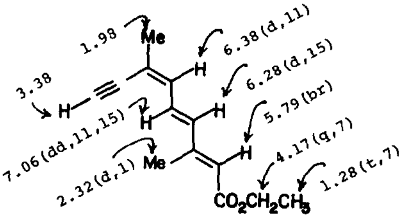
mp:53-54° UV: 285 sh(36,500)
295(51,000)
308(36,500)

6a



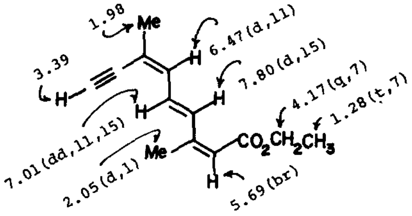
mp:38-42° UV: 287 sh(33,000)
297(43,800)
311(38,800)

6b



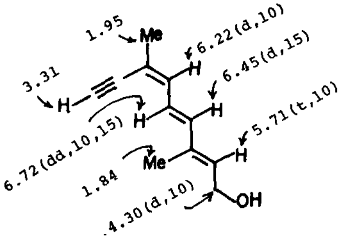
mp:51-53° UV: 317(41,500)

7a



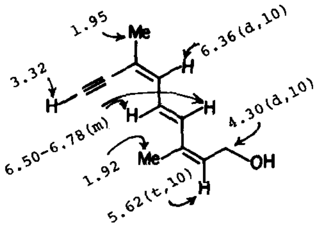
mp:25-26° UV: 318(38,000)

7b



mp:61-63° UV: 282 sh(34,000)
293(47,000)
307(40,000)

8a



mp:28-30° UV: 284(32,000)
296(43,000)
309(36,500)

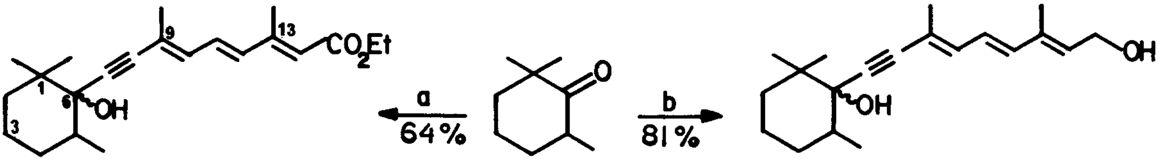
8b

Experimental.

A suspension of NaH (768 mg 50% NaH, 16 mmol) in 20 ml dry THF was treated at 0° with a solution of the senecioate (4.22 g, 16 mmol) in 20 ml THF. After stirring for 30 min at 25°, the mixture was cooled to -10°, treated with crude aldehyde 2 (1.5 g, 16 mmol) in 10 ml THF, warmed to room temperature and stirred for 3 hrs. After dilution with an equal amount of ether, the mixture was poured into ice water and the organic layer separated. The aqueous layer was extracted with ether after saturation with NaCl, the organic layers were combined, dried and evaporated. Filtration of the oil through a silica gel column (hexane/ether, 80:20) gave pure esters 5, 2.6 g.

Separation of pure isomers 5a and 5b was achieved either with a "Chromatotron"[9] (0.5 g quantities) or by prep-liquid chromatography[9] (ca. 3g quantities). Reduction of esters 5a and 5b with diisobutylaluminum hydride in ether, -78°, 5 min., gave the respective alcohols 6a and 6b in quantitative yield. Similarly the cis aldehyde 4 afforded esters 7a/7b (60/40) in 90% yield, which after separation were converted into the 9-cis side-chains 8a and 8b, ca. 100%. The physical constants of these side-chain precursors are given in the Figure; these values may be useful for identification of the side-chain in other syntheses of retinoids. UV and PMR spectra were measured in MeOH and $CDCl_3$, respectively. All compounds gave satisfactory M+1 peaks in CI-MS(CH_4 carrier gas).

Condensation of trans ester 5a with 2,2,6-trimethylcyclohexanone gave a 1:2 mixture of diastereomers 9[10] which were separated by tlc. Similarly the trans alcohol 6a gave a 1:2 diastereomeric mixture of diols 10[10] which, if necessary, could be separated by hplc, μ-Porasil (semiprep), EtOAc/hexane (1:1).



9

10

a: $LiNH_2$, 5a, Et_2O, r.t., 6 hrs. b: EtMgBr, 6a, THF, reflux, 5 hrs.

Reduction of the triple bond in mixture 9 or 10 with LAH gave the tetraene diols (50-60%), which were converted into the 15-acetates[6] and dehydrated with aqueous HBr[11] to give vitamin A acetate (ca. 20% from tetraene diols).

Condensations of key intermediates 5-8 with various cyclic ketones are in progress.

Acknowledgements This work was supported by NIH Grant EY 01253.

References and Notes

1. a) M.A. Gawinowicz, V. Balogh-Nair, J.S. Sabol, and K. Nakanishi, *J. Amer. Chem. Soc.*, *99*, 7720 (1977); b) M. Arnaboldi, M. Motto, K. Tsujimoto, V. Balogh-Nair and K. Nakanishi, *J. Amer. Chem. Soc.*, in press
2. M.B. Sporn, N.M. Dunlop, D.L. Newton, W.R. Henderson, *Nature*, *263*, 110 (1976); M.B. Sporn, R.A. Squire, C.C. Brown, J.M. Smith, M.L. Wenk, S. Springer, *Science*, *195*, 487 (1977); H. Mayer, W. Bollag, R. Hänni and R. Rüegg, *Experiencia*, *34*, 1105 (1978).
3. E.R.H. Jones, R.M. Evans, *British Patent*, 696,235 (1953).
4. The retinoid numbering system is employed for the side-chain for the sake of convenience.
5. The yield varied from 85-100% depending on conditions of solvent removal; quantitative yields were obtained by removing CH_2Cl_2 at 0°.
6. J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).
7. This oxidation and all subsequent reactions were carried out under an argon atmosphere in dim red light.
8. G. Pattenden and B.C.L. Weedon, *J. Chem. Soc. (C)*, 1984 (1968).
9. Chromatotron Model 7824, Harrison Research, 840 Moana Court, Palo Alto, Calif. 94306: centrifugal TLC plate, 1 mm SiO_2, hexane/ether (99:1), argon carrier gas, 100 mg quantities applied continuously. Prep-LC, Waters Prep LC 500, hexane/ether (99:1). Recovery of pure esters 5a/5b and 7a/7b from the chromatotron was 90% and from the prep-LC, 80%.
10. G.L. Olson, H.-C. Cheung, K.D. Morgan, R. Borer, G. Saucy, *Helv.*, *59*, 567 (1976).
11. U. Schwieter, G. Saucy, M. Montavon, C.v. Planta, R. Rüegg, O. Isler, *Helv.*, *45*, 517 (1962).

(Received in USA 20 September 1979)