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Short Synthetic Route to Retinoids Through Dialkylation of 3- Methyl -3-Sulfolene

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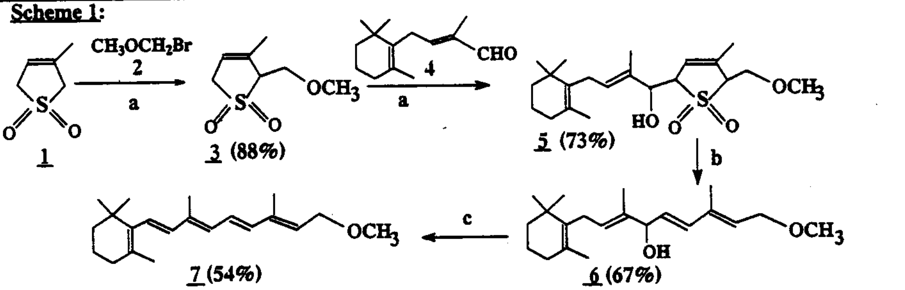
Abstract:- The C_{20}-retinoid carbon skeleton has been synthesised through sequential alkylations of 3-methyl-3-sulfolene with bromomethyl methyl ether followed by C_{14}-aldehyde to give dialkyl sulfolene which on further desulfonylation and dehydration yielded retinol methyl ether.

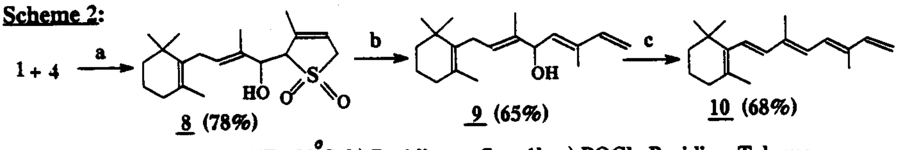
Vitamin A and its derivatives continue to recieve considerable attention both from a synthetic and a pharmacolgical point of views. Retinoids are capable of mediating a wide variety of biological processes, including vision, cellular proliferation, differentiation, anticancer activity etc.[1] Consequently many synthetic routes towards retinal and its analogues have been developed since the subject was comprehensively reviewed in 1984 reflecting the substantial increased interest in the field.[2] Some of the prominent synthetic methods involve condensations with Wittig,[3]palladium[4] and sulfoxide or sulfone reagents.[5] The reaction of 3-sulfolene anion with alkyl halides followed by thermal extrusion of sulfur dioxide provides a facile stereoselective method for synthesis of (E), (EZ) and (EE) conjugated dienes.[6,7,8]

We wish to report herein a new strategy in the construction of the C_{20}-carbon skeleton through dialkylation of 3- methyl 3- sulfolene followed by desulfonylation, dehydration with rearrangement by treatment with $POCl_3$ /pyridine in toluene at 50 °C to yield retinol methyl ether. (Scheme 1).

Scheme 1:



Scheme 2:



Reagents: a) LiHMDS, THF, -90°C b) Pyridine, reflux, 1h c) $POCl_3$ Pyridine, Toluene

The alkylation of 3-methyl 3-sulfolene (1) with bromomethyl methyl ether (2) at -90°C yielded the adduct 3. The adduct 3 was condensed with C_{14}-aldehyde (4) to yield compound 5. The desulfonylation of adduct 5 in refluxing pyridine gave tetraene 6. The hydroxy tetraene 6 on treatment with $POCl_3$ /pyridine in toluene at 50 °C gave Vitaminol methyl ether (7).[9] Similarly C_{14}-aldehyde was condensed with 3-methyl-3-sulfolene to yield adduct 8. The desulfonylation of the latter in refluxing pyridine gave hydroxytetraene 9 which on treatment with $POCl_3$ /pyridine in toluene at 50°C yielded pentaene 10 . (Scheme 2).

Thus we have established a novel as well as a short route to retinoids. The studies on synthesis of more anologues and its biological activities are in progress.

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References and Notes.

1. Sporn, M. B.,Roberts, A.B. and Goodman D.S. *The retinoids: Biology, Chemistry and Medicine*, 2nd Edition ; Raven Press: New York **1994**, pp 319-387.
2. a) Liu, R.S.H.and Asato, A.F.,*Tetrahedron.*,**1984**, 40,1931.b) Akimori,W.,Chisato,T.,Saeko,H.,Yukiko, T.,Tomoko,O. and Masayoshi,T., *Synthesis*.,**1995**,1107. c) Ivanova, D, I., Eremin, S.V. and Shivets, V.I. *Tetrahedron*., **1996**, 52, 9581.
3. a) Pommer, H. *Angew Chem*., **1960**, 72, 811, b) Mukaiyama, J. and Ishida, I., *Chem.Lett*.,**1975**,1201
4. Manchand, P.S.,Wong, H.S and Bout, J.F. *J.Org.Chem*.,**1978**, 43, 4769
5. a) Julia,M.,and Arnold., *Bull.Soc.Chim.Fr.*, 1973, 746. b) Fishi,A.,Mayer,H.,Simon,W.,and Stoller,H.J., *Helv.Chim.Acta*.,**1978**, 59, 397.
6. a) Bhat,S.V.,*J.Indian Inst.Sci*.,**1994**, 74, pp 257-276.
   b) Desai, S.R., Gore, V.K., Mayelvaganan, T., Padmakumar, R and Bhat, S.V., *Tetrahedron.*, **1992**, 48, 481. c) Lee, S.J and Chou, T.S., *Chem. Commun.*, **1988**, 1188. d) Padmakumar, R., Subramanian , T. and Bhat, S.V., *Org. Prep. Proc. Int.*, **1995**, 27, 463.
7. Chou, T.S., Tso, H.H., and Chang, L.J., *J.Chem.,Soc., Chem.*Commun., **1984**,1323.
8. Chou, T.S. and Wang, C.T., *Tetrahedron*., **1996**, 52, 12459.
9. a) Isler,O., Huber, W., Ronco, A. and Koffler, M. *Helv Chim.Acta.*, **1947**, 30, 1911. b) Isler, O., Ronco, A.,Guex, W., Hindley, N.C., Huber, W., Dialer, K and Kofler, M., *Helv.Chim. Acta*., **1949**, 32, 489. c) Reddy, A.M. and Rao, V.J. *J.Org. Chem.*, **1992**, 57, 6727.
10. Selected spectral values : Compound 6 : IR ν_{max} (Neat) 3413, 2930, 1625, 1445, 992, 885. cm^{-1} ^1H NMR (300 MHz,$CDCl_3$). δ 6.25 (1H. d. J=15.70 Hz , H-12), 5.68 (1H, dd. J=15.70. 5.85 Hz H-11), 5.60 (1H. t, J=6.60 Hz, H-14), 5.33 (1H, t, J=6.40 Hz, H-8), 4.59 (1H,d. J=5.85 Hz ,H-10), 4.05 (2H, d, J=6.60 Hz, H-15), 3.34 (3H, s -OCH_3), 2.73 (2H, d, J=6.40 Hz, H-7), 1.93 (2H, t, J=6.2 Hz), 1.78 (3H, d, J=1.09 Hz),1.65 (3H, d, J =1.0 Hz), 1.6 (3H, m), 1.53 (3H, s), 1.41 (2H, m), 0.96 (6H, s).
    Compound 10: IR ν_{max} (Neat) 2937, 1625. 1451, 898. cm^{-1}. UV (Heptane): λ max:328 nm, (ε 3.66 $\times 10^4$).^1H NMR (300 MHz,$CDCl_3$), δ 6.52 (1H,dd, J=10.60, 17.0 Hz, H-13), 6.44 (1H, d, J=11.70 Hz ,H-7), 6.40 (1H, d. J=11.70 Hz, H-8), 6.17 (2H, s, H-11 & 12), 5.24 (1H, d, J=17.0 Hz, H-14), 5.05 (1H, d, J=10.60 Hz. H-14), 2.02 (2H, t, J=6.20 Hz), 1.95 (3H, d. J=0.70 Hz), 1.90 (2H, d. J=0.73 Hz), 1.72 (3H. s), 1.62 (2H, m), 1.45 (2H, m), 1.02 (6H, s)

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