# AN EFFICIENT STEREOSELECTIVE SYNTHESIS OF Z-2-(2-METHYLENE CYCLOHEXYLIDENE)ETHANOL BY THE PHOTOSENSITIZED OXYGENATION OF 1-VINYLCYCLOHEXENE. A MODEL FOR RING A OF CALCITRIOL ◊

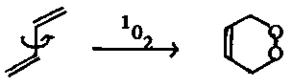
**Jacqueline Ficini*, Claude Barbara, and Ouathek Ouerfelli**

Laboratoire de chimie organique de synthèse, UA 408, Université P. et M. Curie,
8, rue Cuvier 75005 Paris, France

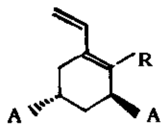
Abstract - The reaction of singlet oxygen with the vinylcyclohexene leads to an endoperoxide which is a model for a possible route to ring A of calcitriol.

The reaction of singlet oxygen with conjugated homoannular dienes is well known to yield endoperoxides via a 1,4-cycloaddition[1]. A similar reaction takes place readily with those acyclic dienes which are held in an S-cis conformation.

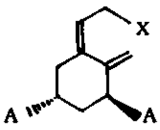
When, however, a particular diene can assume an S-trans as well as an S-cis conformation the 1,4-cycloaddition of singlet oxygen competes with an ene reaction which leads to acyclic hydroperoxides[2]. The proportion of the two products depends on the steric environment and on the nature of the substituents on the diene system. It is not surprising, therefore, that endoperoxides from homoannular dienes have seldom been used as intermediates in synthesis.



1 2



3 a : A=H, b : A=OH



4

a : A=H, $X=PO\phi_2$ or OH
b : A=OH, $X=PO\phi_2$ or OH

We were attracted to the potential of endoperoxide intermediates (1 → 2) such as those which might be derived from 3, in connection with our work on the synthesis of natural products related to ring A of cholecalciferol, (eg 4b), because the S-cis configuration of the endoperoxide correlates with the required Z geometry of the desired product.

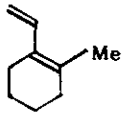
---

◊ This paper is dedicated in honor of Professor D.H.R. Barton's 70th birthday.

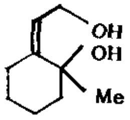
Two problems must be solved to make this approach successful. The required diene (e.g. 3) has to be able to adopt easily the S-cis conformation required to lead to the Z methylenecyclohexylidene system shown, in 4. The second problem, posed by the presence of the trans hydroxyl groups on the cyclohexene ring, was solved in previous work from our laboratory[4]. we now report on the feasibility of the endoperoxide route to the Z diene system of 4, using the vinylcyclohexenes 3 as models which lack the ring hydroxyls of 4.

Our first attempts started with 2-methyl-1-vinylcyclohexene 3a as a substrate ($R=CH_3$) in which the methyl group was intended to serve as precursor of the eventual methylene of 4.

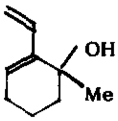
It soon became clear that the presence of a methyl group on the endocyclic double bond (3a, $R=CH_3$) completely suppressed the desired 1,4-cycloaddition, presumably by preventing the formation of the required *coplanar S-cis arrangement of the diene.* Oxidation took place, instead, by other reaction pathways and led ($CH_2Cl_2$, tetraphenylporphine 0-10°C, 495 nm, or acetonitrile, dicyanoanthracene, 420 nm), after reduction ($LiAlH_4$, 0°C, ether) only to a mixture of alcohols [6[5] (46 %), 7[6] (27 %) and 8[7] (27 %)] in combined yield of 42 %. None of the desired 5 could be detected.



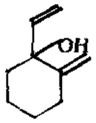
3a (R=Me)



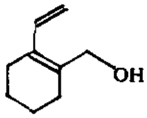
5



6



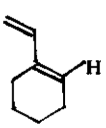
7



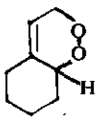
8

It was, therefore, decided to examine the oxidation of the vinylcyclohexene 3a (R=H) *in which the proper* coplanar S-cis arrangement should now be accessible. The eventual addition of the missing carbon which is present as a methylene in the final product should occasion no difficulty.

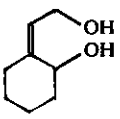
Our initial experiments indeed showed that, in $CCl_4$, the major product of the singlet oxygen reaction was the desired endoperoxide 9. It was characterized as its reduction product the enediol 10[8].



3a (R= H)



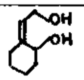
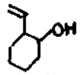
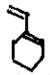
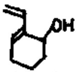
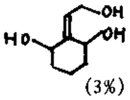
9



10

As anticipated, a protic solvent as carbon tetrachloride[9] gives the best results. Lithium aluminium hydride was a more satisfactory reducing reagent than sodium borohydride or thiourea.

The following table shows the results of this oxidation under various conditions of solvent, temperature, sensitizer and reducing reagent.

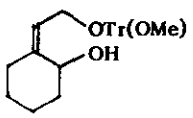
| | OXYGENATION | | | | | REDUCTION | | isolated products after oxygenation and reduction |
|---|---|---|---|---|---|---|---|---|
| | mmol | solvent | sensitizer | t°C | time lamp power | reducing reagent (solvent) | time | (yield) |
| 1 | 5 | $CH_2Cl_2$ | TPP* | 20° | 2 h<br>(500 W) | $LiAlH_4$<br>(Ether) | 8 h |   <br>(42%) **10** (9%) (3%) |
| 2 | 18,5 | Ether<br>3% MeOH | TPP | 20° | 3 h<br>(1500W) | $LiALH_4$<br>(Ether) | 12 h |  unchanged |
| 3 | 5 | MeOH | R. B.* | 20° | 16 h<br>(500 W) | $LiALH_4$<br>(Ether) | 12 h | **10**<br>(33%)  (10%) |
| 4 | 5 | $^{i}Pr$OH | R. B. | 19° | 10 h<br>(500 W) | $LiALH_4$<br>(Ether) | 12 h | **10** (19%) |
| 5 | 5 | $^{i}Pr$OH | R. B. | 19° | 10 h<br>(500 W) | Thiourea<br>($^{i}Pr$OH) | 15 days | undeterminated mixture |
| 6 | 5 | $CCl_4$ | TPP | 20° | 9 h<br>(500 W) | $LiALH_4$<br>(Ether) | 12 h | **10** (53%) |
| 7 | 20 | $CCl_4$ | TPP | 20° | 9 h<br>(1500 W) | $LiALH_4$<br>(Ether) | 12 h | **10**<br>(52%)  (3%) |
| 8 | 2 | $CCl_4$ | TPP | 20° | 8 h<br>(500 W) | Thiourea<br>aq.10% MeOH | 2 h | polymers |
| 9 | 5 | $CCl_4$ | TPP | 20° | 8 h<br>(500 W) | $NaBH_4$<br>($^{i}Pr$OH) | 3 days | **10** (19%) |
| 10 | 5 | $CCl_4$ | TPP | 5° | 21 h<br>(500 W) | $LiALH_4$<br>(Ether) | 7 h | **10** (37%) |
| 11 | 5 | $CCl_4$ | TPP | 5° | 21 h<br>(500 W) | $H_2$/Pd Lindler<br>(MeOH) | 18 h | **10** (20%) |

* TPP = Tetraphenylporphine        * R.B. = Rose Bengal

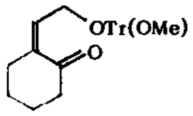
In all cases, irradiation was performed at ≥ 495 nm by passing through a solid filter (Schott 495 or GG 420). All compounds described have showed correct elemental analysis, and/or spectral data.

Under the best conditions we uncovered (experiments 6, 7), yields are as high as have been recorded previously for flexible dienes. Even though yields are relatively modest ( ≯ 50 %), the transformation 3a → 10 is quite acceptable, given the simplicity and the efficiency of this approach to the A ring of the vitamins D.

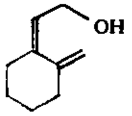
To complete our model study, it remained to transform enediol 10 into dienol 4a. This was accomplished in four steps 10 → 11 → 12 → 4a in an overall yield of 90 %. There was no isomerization of the Z ketone 12[10] to the more stable E isomer[11] under the conditions outlined below :



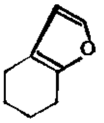
11



12



4a (X=OH)



13

Protection of the primary alcohol in 10 with a 4-methoxytrityl group was followed by oxidation with manganese dioxide (unless the primary alcohol is protected, manganese dioxide oxidation leads to the expected furan 13[12]).

The use of manganese dioxide is essential : oxidation by pyridinium chlorochromate (PCC), even in buffered medium, leads to isomerization of enone 12 to its more stable E isomer. Final methylenation by Wittig reaction (without isomerisation of the Z enone 12, under Conia's procedure[14]), followed by deprotection of the primary alcohol then led to the desired dienol 4a[13] (R=OH).

*The sequence just described leads from a diene of type* 3a to a system 4 with the required geometry of the A ring of 1S,25-dihydroxycholecalciferol. We are now studying the application of this strategy to the synthesis of the properly substitued ring A (cf 4b) necessary for the synthesis of cholecalcitriol.

## NOTES AND REFERENCES

1. For review see : a) K. Gollnick and G. O. Schenk, "1,4-Cycloaddition Reactions", ed. by J. Hamer, Academic Press, Inc., New York, 1967, p. 255; b) J. Bloodworth and H. J. Eggelte, "Singlet Oxygen", vol. II, Chapter 4, ed. by A. A. Frimer, C.R.C. Press, 1985.
2. For instance : a) D. Kearns, J. Amer. Chem. Soc., 1969, 91, 6554 ; b) M. Matsumoto, S. Dobashi, K. Kuroda, and K. Kondo, Tetrahedron, 1985, 41, 2147.
3. E. G. Baggiolini, J. A. Iaccobelli, B. M. Henessy, A. D. Batcho, J. F. Sereno, and M. R. Uskokovic, J. Org. Chem., 1986, 51, 3098.

4. D. Desmaële, Thesis, Paris, 1984 ; Tetrahedron Lett., 1985, 26, 4941.
5. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.40 (3H, s, $CH_3$), 1.50-2.00 (4H, m, $-[CH_2]_2-$), 2.00-2.30 (3H, m, OH, $=CH-\underline{CH_2}-$), 5.07 (1H, dd, J=2,11 Hz, $\underset{H}{\overset{H\quad H}{>C=C<}}$), 5.50 (1H, dd, J=2,18 Hz, $\underset{\underline{H}}{\overset{H\quad H}{>C=C<}}$), 5.95 (1H, t, J=5 Hz, $CH_2-\overset{H}{C}=$ ), 6.45 (1H, dd, J=11,18 Hz, $\underset{H}{\overset{H\quad H}{>C=C<}}$).
6. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.25-2.50 (9H, m, OH, $-[CH_2]_4-$), 4.85 (1H, broad band, $=\underset{H}{\overset{H}{C<}}$), 5.00(1H, b.b., $=\overset{H}{C<}$), 5.22 (1H, dd, J=2,16 Hz, $\underset{\underline{H}}{\overset{H\quad H}{>C=C<}}$), 5.40 (1H, dd, J=2,10 Hz, $\underset{H}{\overset{H\quad H}{>C=C<}}$), 6.17 (1H, dd, J=10,16 Hz, $\underset{H}{\overset{H\quad HH}{>C=C<}}$).
7. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.25-2.45 (9H, m, OH, $-[CH_2]_4-$), 4.30 (2H, s, $-CH_2-O$), 5.09 (1H, dd, J=2,10 Hz, $\overset{H\quad H}{>C=\underset{H}{C<}}$), 5.27 (1H, dd, J=2,17 Hz, $\overset{H\quad H}{>C=\underset{\underline{H}}{C<}}$), 6.95 (1H, dd, J=10,17 Hz, $\overset{H\quad H}{>C=\underset{H}{C<}}$).
8. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.25-2.75 (8H, m, $-[CH_2]_4-$), 2.80-3.50 (2 OH, b.b.), 4.05 (1H, dd, J=7,13 Hz, $-\underset{\underline{H}}{\overset{H}{C}}-OH$), 4.35 (1H, dd, J=7,13 Hz, $-\underset{H}{\overset{H}{C}}-OH$), 4.67 (1H, t, J=2 Hz, $>\underset{OH}{\overset{H}{C}}$ ), 5.50 (1H, t, J=7 Hz, $>\underset{\underline{H}}{\overset{CH_2}{C<}}$) ; ir (neat) : 3320, 2900, 1600 $cm^{-1}$.
9. M. Matsumoto and K. Kuroda, a) J. Chem. Soc., Chem. Comm., 1981, 11, 987 ; b) Tetrahedron lett., 1985, 23, 1285.
10. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.60-2.60 (8H, m $-[CH_2]_4-$), 3.82 (3H, s, $CH_3$), 4.02-4.20 (2H, m, $CH_2-O$), 5.93 (1H, bt, J=7 Hz, $>\overset{\underline{H}}{C<}$), 6.80-7.70 (14H, m, aromatic protons) ; ir (neat) 2920, 1680, 1600 $cm^{-1}$
11. $^1H$ nmr, $CDCl_3$, $\delta$ : 6.75, broad triplet, whereas the shift is 5.93 for the Z isomer.
12. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.50-2.80 (8H, m, $-[CH_2]_4$), 6.22 (1H, d, J=2Hz), 7.30 (1H, d, J=2Hz). For examples of furan formation via endoperoxides see for instance : a) B. Harirchian and P. D. Magnus, Synth. Comm., 1977, 7, 119 ; b) K. Kondo and M. Matsumoto, Tetrahedron Lett., 1976, 5, 391.
13. $^1H$ nmr, $CDCl_3$, $\delta$ : 1.50-1.80 (4H, m, $-[CH_2]_2-$), 2.10-2.40 (4H, m, $-CH_2-C=$), 4.30 (2H, d, J=7Hz, $CH_2-O$) 4.67 (1H, d, J=2Hz, $=\underset{H}{\overset{H}{C<}}$), 4.95 (1H, d, J=2Hz), 5.50 (1H, t, J=7Hz, $=\overset{H}{C<}$ ).
14. J. M. Conia and J. C. Limasset, Bull. Soc. Chim. Fr., 1967, 1936.

Received, 25th July, 1988