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A [3+2] NITRILE OXIDE CYCLOADDITION APPROACH TO RETINOIDS

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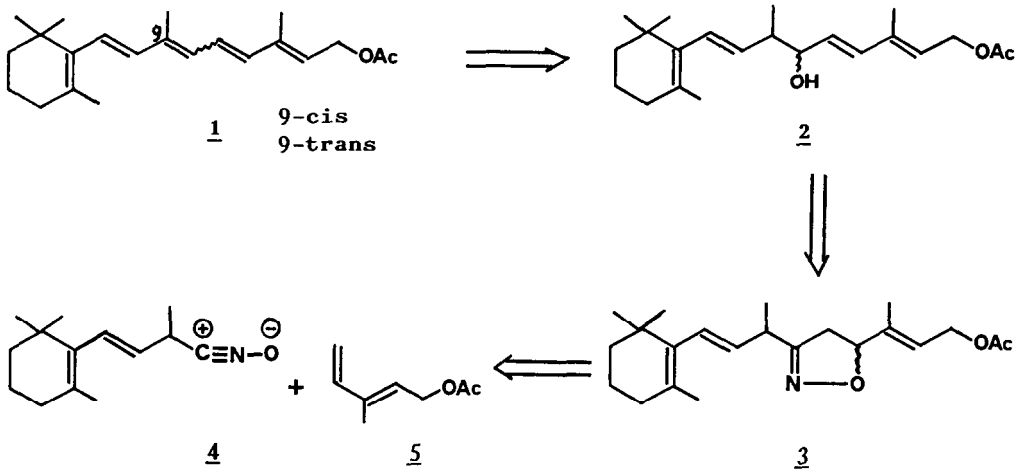
Summary: The C-20 retinoid carbon skeleton was assembled through a C(14) + C(6) approach by interception of the nitrile oxide derived from the C(14) aldehyde component with a C(6) diene dipolarophile, followed by $Mo(CO)_6$ -promoted ring opening of the derived 3,5-disubstituted isoxazoline.

Vitamin A and its various derivatives continue to receive considerable attention both from a synthetic and a pharmacological point of view.
Of particular importance are the biological roles which they play as anticancer agents. [1,2]
Consequently many synthetic routes have been developed and since the subject was comprehensively reviewed in 1978 [3], many more syntheses have appeared, [4,5] reflecting the substantially increased interest in the field.
One of the most convergent approach to the assemblement of the C(20) skeleton of this class of compounds, incorporating a pentaene system as the most salient structural feature, involves the coupling of a C(14) aldehyde component with a C(6) Grignard fragment.
We wish to report in this letter a new strategy that has evolved from our laboratories culminating in the construction of the C(20) carbon atoms framework of the immediate precursor **2** of Vitamin A and its 9-cis isomer, as retrosynthetically depicted in the Scheme.



1 9-cis 9-trans

2

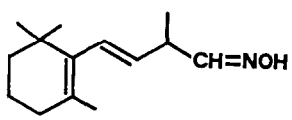
4 + 5

3

This approach differs significantly from the previous ones in the way it addresses the crucial carbon-carbon bond forming step. In fact we have employed a [3+2] cycloaddition of the nitrile oxide 4 to the alkene 5 to form the 3,5-disubstituted isoxazoline 3.

In recent years this key tactical element has emerged as a powerful tool for preparing highly functionalized carbon chains[6] and will be given further impetus by our recent discovery[7] that the masked functions retained in this versatile heterocyclic ring can be unveiled under non-hydrogenolytic conditions.

According to the scheme the opening move required the key materials 4 and 5, which were easily obtained starting from two commercially available compounds, namely ß-ionone and trans-3-methyl-2-penten-4-yn-1-ol. The first was converted via Darzens reaction by a known procedure[8] in 90% yield into the C-(14) aldehyde, the corresponding oxime 6 being the precursor of 4, while the second was easily taken to 5, the C(6) component, by selective hydrogenation of the triple bond of 7 in the presence of Lindlar catalyst, followed by standard acetylation (Ac_2O, Py, DMPA, r.t.).



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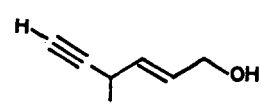


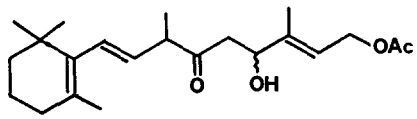
7

The cycloaddition of the nitrile oxide 4 generated from the oxime 6 following

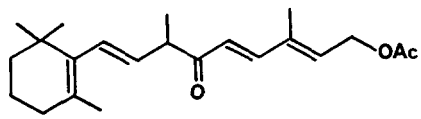
Torrsell's directions[9] into the diene 5 took place regio- and chemoselectively to produce the 3,5-disubstituted-isoxazoline 3, accomodating the C(20) carbon atom framework of the targets 1, in good yield.*

Cleavage of the labile N-O bond was then easily accomplished by treatment of 3 with $Mo(Co)_6$ in wet acetonitrile[7] to afford in 60% yield the ß-hydroxy-ketone 8.

Conversion of 8 to the α,ß-unsaturated ketone 9 was facilitated by prior conversion to the corresponding methansulfonate ester.



8



9

Thus exposure of 8 to methansulfonyl chloride and triethylamine (0.5 h at 0°C, 5 h at room temperature) afforded 9 as an oil in 70% yield as sole product (HPLC). A doublet centered at 6.2 (J=16Hz) and a doublet centered at 7.1 (J= 16Hz) allowed the assignement of the E-geometry of the newly generated double bond.

Completion of the synthetic pathway was achieved by treatment of 9 with sodium borohydride at -10°C for 10 min. providing the known 2 yield in 90%, whose efficient transformation to both Vitamin A and its 9-cis isomer had been already described in the literature.[10,11]

In conclusion we have developed a flexibile approach to retinoids which not only constitutes a formal synthesis of these compounds through a protocol easily amenable to large scale preparation, but is also applicable to the preparation of analogues which can be used to probe the functional groups responsible for biological activity.

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Notes and references

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* All compounds gave spectral and analytical data consistent with the assigned structures. The spectroscopic data of selected compounds are reported:

2: oil; UV (MeOH): λ_{max} 235 nm (ε 18000); IR (neat) 3450, 1740, 1640, 1610 cm^{-1}; HNMR δ 0.95 (s, 6H), 1.2-1.6 (m, 4H), 1.15 (d, 3H, J=6Hz), 1.68 (s, 3H), 1.74 (s, 3H), 1.9 (m, 2H), 2.1 (s, 3H), 2.35 (m, 2H), 3.9 (m, 1H), 4.7 (d, 2H, J=6.5Hz), 5.3 (dd, 1H, J=15.5Hz and 8Hz), 5.5 (brt, 1H), 5.67 (dd, 1H, J=16Hz and 8Hz), 5.95 (d, 1H, J=15.5Hz), 6.3 (d, 1H, J=16Hz).

3: oil; IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 0.95 (s,6H), 1.2-1.6 (m,4H), 1.3 (d,3H,J=6Hz), 1.62 (s,6H), 1.9 (m,2H), 2.0 (s,3H), 2.85 (m,2H), 3.3 (m, 1H), 4.5 (d,2H,J=6.5Hz), 4.87 (brt,1H), 5.25 (dd,1H,J=15.5 and 8Hz), 5.6 (brt,1H), 5.9 (d,1H,J=15.5Hz).

8: oil; IR (neat) 3450, 1740, 1710 cm^{-1}; ^{1}H NMR δ 0.95 (s,6H), 1.1-1.6 (m,4H), 1.2 (d,3H,J=6Hz), 1.6 (s,3H), 1.67 (s,3H), 1.9 (m,2H), 2.02 (s, 3H), 2.7 (m,2H), 3.2 (m,2H), 4.4 (m,1H), 4.5 (d,2H,J=6.5Hz), 5.25 (dd, 1H,J=15.5 and 8Hz), 5.6 (brt,1H), 6.0 (d,1H,J=15.5Hz).

9: oil; UV (MeOH): λ_{max} 278nm (ε 24400); IR (neat) 1740, 1680, 1630, 1600 cm^{-1}; ^{1}H NMR δ 0.95 (s,6H), 1.1-1.6 (m,4H), 1.2 (d,3H,J=6Hz), 1.6 (s,3H), 1.9 (m,2H), 2.05 (s,3H), 3.4 (m,1H), 4.6 (d,2H,J=6.5Hz), 5.2 (dd, 1H, J=15.5 and 8Hz), 5.8 (brt, 1H), 5.95 (d, 1H, J=15.5Hz), 6.2 (d,1H,J=16Hz), 7.1 (d,1H,J=16Hz).

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