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A CONVENIENT SYNTHESIS OF STEREOCHEMICALLY PURE RETINOIDS. THE SYNTHESIS OF 10,14-DIMETHYL RETINALS.[1]

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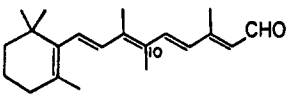
As part of our continuing studies of retinals and visual pigments,[2] we desired relatively large quantities of stereochemically pure retinoids. In particular, we desired the various geometric isomers of 10-methyl, 14-methyl and 10,14-dimethyl retinals (1,2,3),[3] since these are useful in studies directed toward the clarification of the steric factors involved in



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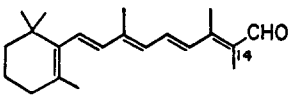

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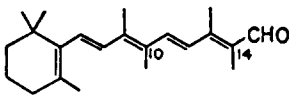

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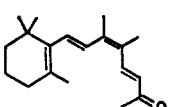
visual pigment formation.[2,4] The recent interest in retinoids as anticancer agents[5] has also stimulated research into the effect of modifications in the Vitamin-A skeleton upon the therapeutic and toxic properties of retinoids.

Syntheses of retinoids in this [2a,b,d,e] and other[6] laboratories have generally involved multistep procedures leading to low overall yields and mixtures of product isomers requiring tedious separation. In addition, most published procedures are not easily altered to allow modification of the side chain;[6a] our attempts to add 2-(diethylphosphono)-ethyl proprionate to β-ionone to yield triene esters convertible to 4 and 5 failed.[7,8] Recently, Stork and Kraus[9] described an improved synthesis of the key intermediate tetraene ketones 6 and 7; however, this method will not allow the preparation of "C_{19}" tetraene ketones 4 and 5.



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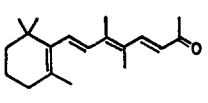

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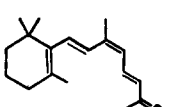

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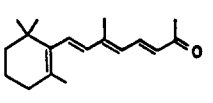

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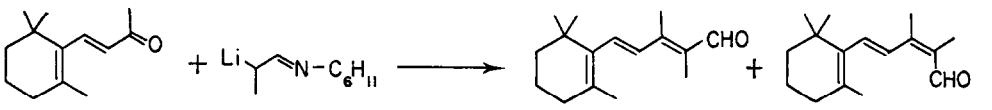
We wish to report a method by which certain retinoids can be prepared in 36-48 hours from β-ionone 8. Separation of more than two product isomers from starting materials is not required at any stage, allowing the synthesis of ≥ 200 mg quantities of stereochemically pure retinoids. Our approach is based on a modification of Wittig's directed aldol condensation[10] coupled with separation by preparative liquid chromatography (PLC).[11] The procedure is illustrated by the

synthesis of all-trans and 13-cis 10,14-dimethyl retinals.

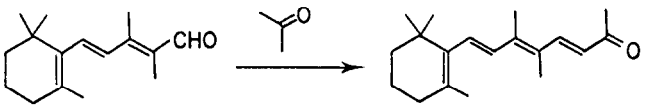
Preparation of tetraene ketone 5. A solution of 14.3 g (100 mmole) propylidene cyclohexylamine[10] in 80 mL ether was added over 30 minutes under N_2 at 0° to a stirred solution of 100 mmoles lithium diisopropyl amide (LDA) in 250 mL ether. After stirring 30 minutes at 0°, the mixture was cooled with a Dry Ice/acetone bath and 19.2 g (100 mmole) β-ionone[12] in 50 mL



8 10 9

ether was added over 20 minutes. The solution was stirred for 45 minutes at -78°, allowed to warm to room temperature over 45 minutes, then was cooled in an ice/water bath and the reaction quenched by the addition of 160 mL of water. The resulting mixture was stirred for 5 minutes, and the aqueous layer was separated and discarded. The organic layer was dried (Na_2SO_4) and evaporated in vacuo at ambient temperature.

The residual oil was dissolved in 500 mL anhydrous THF, cooled in a Dry Ice/CCl_4 bath to -23° under N_2 and 15.2 g (60 mmole, 0.6 eq.) I_2 was added in one portion. The solution was stirred 20 minutes at -23°, the bath removed and the solution allowed to come to room temperature The purple reaction mixture was poured into 1200 mL ether and 800 mL water, and the organic layer washed successively with 3x1200 mL water, 1x1200 mL 5% aqueous $NaHSO_3$, 2x1200 mL water, and 1x1200 mL saturated salt solution. The organic layer was dried (Na_2SO_4), evaporated and the resulting red-orange oil filtered through a column of 100 g of silica gel (1:1 ether:light petroleum). Purification by PLC (7.5% ether in hexane, 250 mL/min.) yielded 8.50 g (36.6 mmole) 9-cis triene aldehyde 9, and 3.21 g (13.8 mmole) all-trans 10 (combined yield 50% from β-ionone 8).



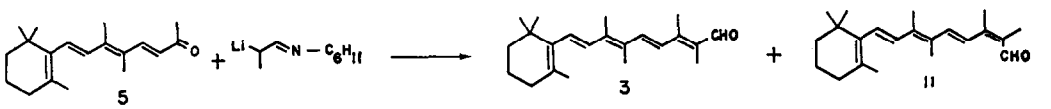
10 5

To a solution of 0.96 g (4.13 mmole) trans triene aldehyde 10 in 100 mL acetone[13] was added 32 mL 1N NaOH. The mixture was stirred under N_2 in the dark for 8 hours at room temperature then poured into 250 mL ether and 150 mL water. The organic layer was washed with 3x100 mL water, dried (Na_2SO_4) and evaporated. The resulting yellow-orange oil was filtered through a column of 25 g of silica gel (1:1 ether:light petroleum). Purification by PLC (7.5% ether in hexane, 250 mL/min.) yielded 0.936 g (3.41 mmole, 82%) all-trans tetraene ketone 5.

Preparation of 13-cis and all-trans 10,14-dimethyl retinals 11 and 3. Propylidene cyclohexylamine[10] (0.556 g, 4 mmole) in 10 mL ether was added over 20 minutes under N_2 at 0° to a stirred solution of 4 mmoles of LDA in 10 mL ether. The solution was stirred for 15 minutes at

0°, cooled with a Dry Ice/acetone bath, and 1.0 g (3.68 mmole) 5 in 10 mL ether was added over 30 minutes. The resulting pale-orange reaction mixture was stirred 30 minutes at -78°, allowed to warm to room temperature (45 minutes), then cooled in an ice/water bath and the reaction quenched by the addition of 25 mL of water. The mixture was stirred for 5 minutes, the aqueous layer separated and discarded, and the organic layer dried (Na_2SO_4) and evaporated.[14]

The residual oil was dissolved in 45mL anhydrous THF, cooled to -23° under N_2, and 0.561 g (2.21 mmole, 0.6 eq.) I_2 added in three portions. The solution was stirred 20 minutes at -23°, allowed to come to room temperature, then poured into 150 mL ether and 100 mL water. The organic layer was washed successively with 3x150 mL water, 1x150 mL 5% aqueous $NaHSO_3$, 2x150 mL water and 1x150 mL saturated salt solution, dried (Na_2SO_4), evaporated and the residual oil filtered through a column of 10 g of silica gel (1:1 ether:light petroleum). Purification by PLC (6% ether in hexane, 250 mL/min., two columns) yielded 216 mg 13-cis 10,14-dimethyl retinal 11 and 159 mg all-trans 10,14-dimethyl retinal 3.[15] (combined yield 36.4% from tetraene ketone 5)



5 3 11

This procedure has been applied to the preparation of tetraene ketones 4, 6 and 7, as well as the various 9-10 and 13-14 double bond isomers of retinals 1-3.[16] Extension of this method to the synthesis of more exotic retinoids is in progress.

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12. Purchased from Aldrich Chemical Company and distilled prior to use.
13. Spectral quality, purchased from Fisher Scientific Company.
14. The subsequent dehydration, hydrolysis and PLC purification were done under red light.
15. 3: NMR[17](CCl_4) δ 1.03 (s,6H), 1.72 (s,3H), 1.89 (s,3H), 2.01 (s,3H), 2.04 (s,3H), 2.33 (s,3H), 6.25 (d,1H,J=16Hz), 6.62 (d,1H,J=16Hz), 6.92 (d,1H,J=15Hz), 7.30 (d,1H,J=15Hz), 10.21 (s,1H); CI/MS (isobutane) m/e 313 (M^++1), 369 (M^++57); UV (Hexane) 375 nm (ε = 49,000).
11: NMR[17](CCl_4) δ 1.03 (s,6H), 1.72 (s,3H), 1.85 (s,3H), 1.99 (s,3H), 2.01 (s,3H), 2.10 (s,3H), 6.22 (d,1H,J=16Hz),6.65 (d,1H,J=16Hz), 7.05 (d,1H,J=15Hz), 7.32 (d,1H,J=15Hz), 10.30 (s,1H); CI/MS (isobutane) m/e 313 (M^++1), 369 (M^++57); UV (Hexane) 360 nm (ε = 30,000).
16. Complete details will be provided in our full paper.
17. See for comparison: a) Reference 2b; b) D.J. Patel, Nature, 221, 825 (1969).