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PALLADIUM CATALYZED FRAGMENTATION REACTION AS AN APPROACH TO VITAMIN A ESTER

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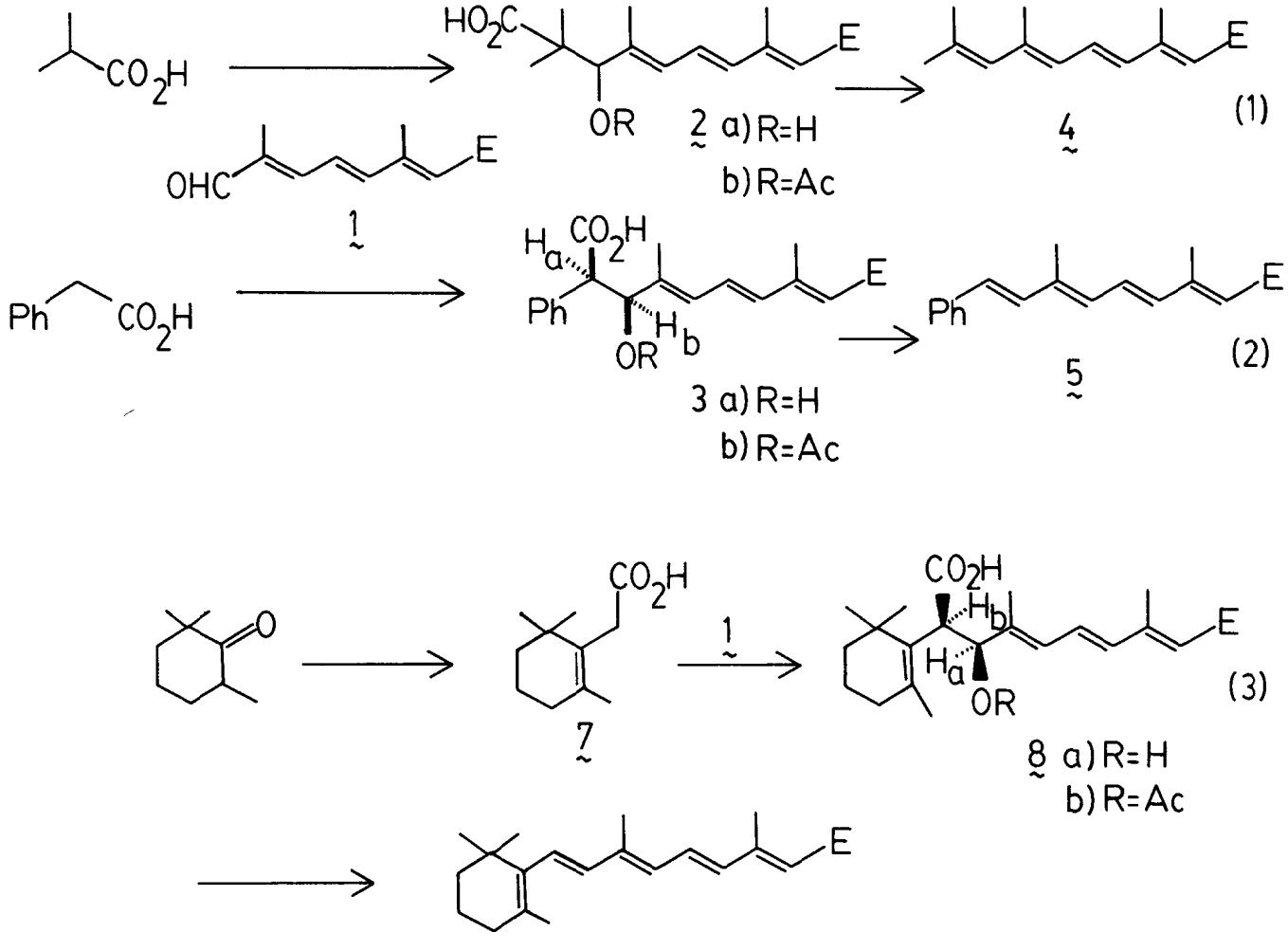
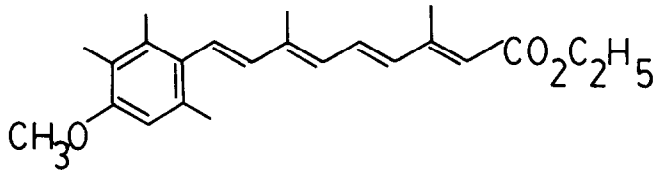
ABSTRACT: A novel C_{10} + C_{10} approach to retinoids employing a palladium induced decarboxylative elimination is described.

Heightened interest in the therapeutic applications of retinoids as well as in the chemistry of vision increases the desirability of alternative approaches to this important class of compounds.[1-3] One of the most important methods has been the Wittig reaction.[2] The undesirability of triphenylphosphine oxide as a by-product has provided an impetus for alternatives. For example, isonitrile anions have served.[4] We recently described a stereoselective approach to dienes based upon a Pd(0) catalyzed decarboxylative elimination of β-acetoxycarboxylic acids.[5] The advantage of the method stemmed from the propensity for formation of the E geometry for the newly introduced double bond regardless of the configuration of the starting material. In this letter, we wish to communicate that this method applies to the construction of linear polyenes and has been successfully applied to the ethyl ester of Vitamin A starting from 2,2,6-trimethylcyclohexanone, a compound recognized as a particularly convenient starting material.[6,7]

In model studies, the dianions[8,9] of isobutyric acid and phenylacetic acid (THF, 0°) were added to aldehyde ester 1[10] (THF, -20°), followed by acetylation (CH_3COCl, C_5H_5N, CH_2Cl_2, 0° then THF, H_2O, $NaHCO_3$, 25°) to give the β-acetoxycarboxylic acids 2b[11] and 3b[11] in ca 86% and 85% yields respectively (equation 1 and 2). In the case of 3a, a single diastereomer (>95%), mp 156-8° (dec), forms - tentatively assigned the threo stereochemistry depicted on the basis of J_{ab} = 9.5 Hz. Usually, the erythro isomers show such vicinal couplings on the order of 3-6 Hz.[12]


CO2H
HO2C
E
OR
2 a) R=H
b) R=Ac
4
(1)
OHC
1
Ph
CO2H
Ha
Hb
3 a) R=H
b) R=Ac
5
(2)
O
7
1
Ha
Hb
8 a) R=H
b) R=Ac
(3)

Treatment of 2b with 7 mol% $(Ph_3P)_4Pd$ in the presence of $(C_2H_5)_3N$ in DMSO at 80° led to a 68% yield of the all trans tetraene[13a] 4 contaminated by 15% of a by-product, tentatively identified as the 6-Z isomer by NMR spectroscopy[13b] of a sample enriched in the by-product. That the isomerization of the 6,7-double bond was not occurring as a result of palladium, the hydroxy acid 2a was subjected to elimination with DMF-acetal to also give a similar mixture of products. On the other hand, subjection of 3b to 5 mol% $(Ph_3P)_4Pd$ in the presence of $(C_2H_5)_3N$ in refluxing THF in the dark led to a single bright orange tetraene 5,[14] mp 116-8°, in 60% yield. The application to such aromatic systems has particular relevance since the substituted analogue 6 is useful in treating tumors and keratinizing dermatoses.[1,15]



6

The synthesis of Vitamin A ethyl ester utilizes the acid 7 which is available in ca 55-60% overall yield from 2,2,6-trimethylcyclohexanone.[6,16] Its dianion added smoothly to 1 to give an unstable hydroxy acid 8a[17a] as a single diastereomer (threo isomer assigned on the basis of J_{ab} = 9.2 Hz), which was acetylated in the usual fashion to the acetoxy acid 8b[17a] (see equation 3). In identical fashion to the preparation of 5, 8b smoothly underwent decarboxylative elimination in 60.2% yield to give a single tetraene identified as the all trans ethyl ester of Vitamin A by spectral comparison.[17b] From 7 to final product, the crude materials were directly reacted. Thus, the Vitamin ester is conveniently available in 35-40% overall yield from 2,2,6-trimethylcyclohexanone. Equally pertinent, these results firmly establish this method as a convenient stereocontrolled entry into very sensitive polyenes in addition to dienes.

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    b) NMR (270 MHz) from a mixture with 4: δ1.29 (3H, t, J=7.1 Hz), 1.68 (3H, s), 2.07 (6H, s), 2.30 (3H, s), 4.16 (2H, q, J=7.1 Hz), 5.68 (2H, s), 6.01 (1H, d, J=11.5 Hz), 6.17 (1H, d, J=15.1 Hz), 6.79 (1H, dd, J=15.1, 11.5 Hz).
14. Fully characterized by spectral means and combustion analysis. NMR (270 MHz): δ1.29 (3H, t, J=7.0 Hz), 2.07 (3H, d, J=0.7 Hz), 2.36 (3H, d, J=1.1Hz), 4.18 (2H, q, J=7.0 Hz), 5.81 (1H, s), 6.32 (1H, d, J=11.4 Hz), 6.35 (1H, d, J=15.1 Hz), 6.67 (1H, d, J=15.8 Hz), 6.89 (1H, d, J=15.8 Hz), 7.01 (1H, dd, J=15.1, 11.4 Hz).
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    b) NMR (270 MHz): δ1.03 (6H, s), 1.29 (3H, t, J=7.1 Hz), 1.46 (2H, m), 1.62 (2H, m), 1.71 (3H, s), 2.00 (3H,s), 2.02 (2H, m), 2.35 (3H, d, J= 1.1 Hz), 4.17 (2H, q, J=7.1 Hz), 5.79 (1H, s), 6.11 (1H, d, J=15 Hz), 6.13 (1H, d, J=11.4 Hz), 6.27 (2H, d, J=15 Hz), 6.99 (1H, dd, J=15.0, 11.4 Hz).

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