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ITERATIVE PD CATALYZED ADDITIONS FOR A SYNTHESIS OF METHYL 7,8,11,12 TETRADEHYDRORETINOATE

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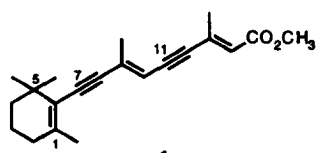
Summary: A 6 step synthesis of the title compound derives from a palladium catalyzed addition of terminal alkynes to acceptor alkynes.

The retinoids play a role in a myriad of biological functions including cell differentiation, cell proliferation, embryonic development, etc. beyond their well known role in vision. These variable roles have made them a target for the development of therapeutic agents.[1] The nuclear receptors, the RAR's and RXR's, recognize various geometric and conformational isomers of the retinoids. Conformationally restricted retinoids represent interesting analogues to probe the specificity of the various retinoid receptors for differentiation of biological function.[2] Repetitive use of a palladium catalyzed cross coupling of terminal alkynes with activated internal alkynes[3] suggested a potentially simple approach to a conformationally rigidified tetra-dehydro analogue **1** in which the two disubstituted double bonds are replaced by alkynes.[4]



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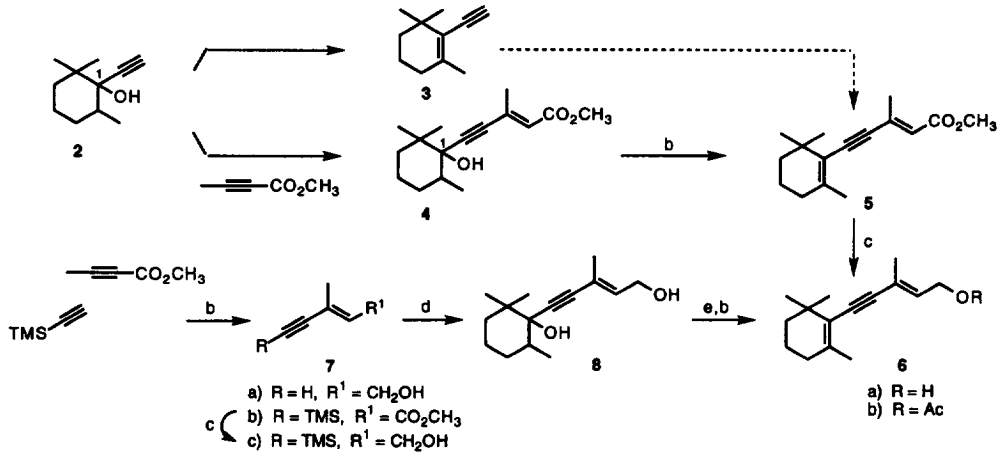
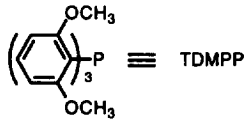
The initial effort focused on the coupling of methyl 2-butynoate with 1-ethynyl-2,6,6-trimethylcyclohexene **3**, available by dehydration of the corresponding alcohol **2** as shown in Scheme 1.[5] Surprisingly, our attempts to effect the simple dehydration did not proceed satisfactorily. Thus, the two steps were inverted. The coupling of equimolar quantities of **2**, an epimeric mixture at C-1, and methyl 2-butynoate (1-2 M conc) occurred smoothly using 3 mol% palladium acetate with 3 mol% tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as ligand (1:1 Pd:P) at rt in THF followed by applying the reaction mixture directly to a column to give the ynenoate **4**[6] in 88% isolated yield. While the major diastereomer of **4** is readily separated from the minor one, the dehydration step destroys the stereogenic centers and thereby makes this issue irrelevant. The reaction was performed on scales as large as 64 mmol with virtually identical yields. Normal dehydration conditions proceeded quite satisfactorily here to give **5**[6,7] which was uneventfully reduced to the alcohol **6** to set the stage for the second cross coupling event.

Scheme 1. First Stage Yne Coupling

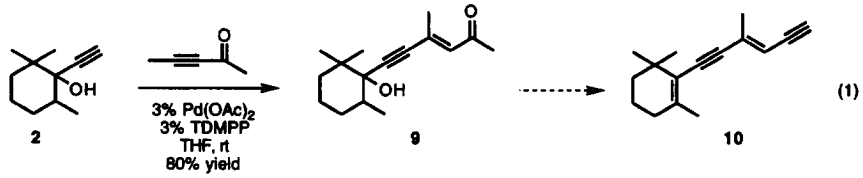


a) 3% $Pd(OAc)_2$, 3% TDMPP, THF, rt, 88% for **4**, 95% for **7b**. b) $POCl_3$, C_5H_5N, reflux, 64% for **5**, 66% for **6b**. c) DIBAL-H, $PhCH_3$, -78°, 63% for **6a**, 59% for **7c**. d) C_2H_5MgBr, then 2,2,6-trimethylcyclohexanone, THF, reflux, 60%. e) Ac_2O, C_5H_5N, 76%.



An alternative strategy envisioned pre-construction of the enyne and then its attachment to the cyclohexyl unit.[8] Considering the importance of **7** as a general building block for natural product synthesis,[9] we examined its synthesis via our palladium catalyzed addition reaction. Trimethylsilylacetylene added to methyl 2-butynoate to form **7b**[6,7] in 95% yield in 1 h under the above conditions. The latter was reduced as before to the alcohol **7c**[6] which could be desilylated to **7a**. Alternatively, **7a** is available commercially. Protection of the primary alcohol as the acetate was required for the dehydration to proceed satisfactorily to give **6b**[6] which must now be hydrolyzed to continue the synthesis. The requirement of a protection-deprotection scheme and a lower overall yield from **7a** made this route less attractive than the initial one.

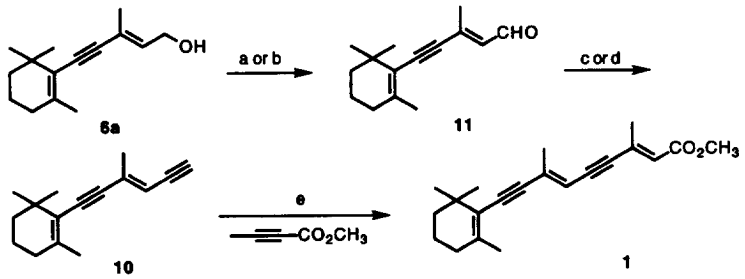
The second stage initially envisioned use of the methyl ketone **9** as a precursor of the terminal alkyne **10** by a double dehydration.[10] Accordingly, the requisite cross-coupling of the terminal alkyne **2** with 3-butyn-2-



one (eq. 1) proceeded smoothly in good yield to give a single geometric isomer **9**[6,7] assigned E based upon the low field shift of the vinyl methyl group in the ^1H nmr spectrum (δ 2.18) and the mechanism.[3] Unfortunately,

the attempts to effect dehydration[10] were for nought. On the other hand, the desired diyne **10** was readily accessed as outlined in Scheme 2 from alcohol **6a**. Oxidation to the aldehyde **11**[6] proceeded exceptionally well either

Scheme 2. Second Stage Yne Coupling

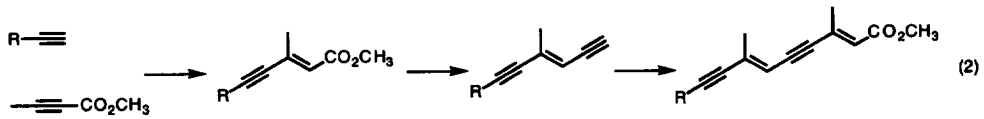


a) Dess-Martin periodinane, CH_2Cl_2, 0°, Q. b) NMO, TPAP, 3Å MS, CH_2Cl_2, rt, 87%. c) Ph_3P, CBr_4, CH_2Cl_2, 0°, then *n*-C_4H_9Li, -78° to rt, 58%. d) $TMSCHN_2$, LDA, THF, -78° to rt, 72%. e) 3% Pd $(OAc)_2$, 3% TDMPP, THF, rt, 53%.

utilizing the Dess-Martin periodinane[11] or the catalytic perruthenate protocol as described by Ley.[12] The standard Corey-Fuchs procedure[13] was satisfactory for conversion of the aldehyde **11** into the requisite alkyne **10**;[6] however, the diyne **10** contained a minor by-product that was difficult to separate. On the other hand, the more recently developed one step procedure utilizing lithiated trimethylsilyldiazomethane[14] proved superior, forming a cleaner product in higher yield. Reactions using the diyne **10** prepared by the former route for the final palladium catalyzed addition invariably stopped short of completion under our usual catalyst conditions with 3 mol% palladium acetate. That the source of this problem lay in the presence of the trace impurity was revealed by the reaction going to completion at rt with the diyne prepared by the latter route (step d). Spectroscopic data support the assigned structure of diyne **1**. The new signal for the vinyl methyl group at δ 2.32 in the ^1H nmr spectrum indicates the *E*-geometry as predicted by the mechanistic rationale.

The palladium catalyzed addition of terminal alkynes to activated internal alkynes represents a mild method for C-C bond formation. The examples reported herein highlight the chemoselectivity and geometrical control. Although retinoids are notorious for the ease with which they can undergo *E-Z* interconversion, palladium does not catalyze this process under the conditions of the addition. The highly sensitive nature of the final diyne also attests to the selectivity of the method.

This iterative protocol represents a convenient entry into polydehydro retinoids and carotenoids (eq. 2). Thus, the tetradehydroretinoid **1** is available in 6 steps and 14% unoptimized overall yield from **2**. The triple bond also provides a focal point for further structural manipulation.[15] Thus, the dehydroretinoids reported herein should prove valuable for the synthesis of additional analogues.



(2)

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Spectrometry Facility, University of California-San Francisco, which is supported by the NIH Division of Research Resources. Johnson Matthey Alfa Aesar provided palladium salts under a loan program.

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6. This compound has been fully characterized spectroscopically and elemental composition established by high resolution mass spectrometry and/or elemental composition.
7. **5** IR(neat): 2182, 1717, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 1H), 3.69 (s, 3H), 2.34 (s, 3H), 2.03 (t, J = 6.6 Hz, 2H), 1.87 (s, 3H), 1.64-1.53 (m, 2H), 1.48-1.42 (m, 2H), 1.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 144.2, 139.3, 123.6, 121.5, 95.6, 93.9, 51.0, 37.4, 33.8, 32.1, 28.9, 22.7, 20.1, 18.8. Anal. Calcd for $C_{16}H_{22}O_2$: C, 77.90; H, 8.89. Found: C, 78.11; H, 8.73. **7b** IR(neat): 2120, 1715, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.06 (s, 1H), 3.67 (s, 3H), 2.14 (s, 3H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 137.8, 124.4, 106.3, 99.3, 51.2, 19.7, 0.3. Anal. Calcd for $C_{10}H_{16}O_2Si$: C, 61.81; H, 8.21. Found: C, 61.45; H, 7.97. **9** IR 3600-3200, 2206, 1677, 1586 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.40 (s, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 2.10-1.79 (m, 2H), 1.74-1.14 (m, 6H), 1.15-1.02 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 136.0, 130.5, 95.1, 89.7, 79.0, 39.2, 38.1, 37.1, 32.8, 31.8, 26.9, 21.1, 20.4, 19.8, 16.5. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.50; H, 9.84. **1** IR(neat): 2161, 1717, 1611, 1567 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.02 (s, 1H), 5.83 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H), 2.08 (s, 3H), 2.03 (t, J = 6 Hz, 2H), 1.86 (s, 3H), 1.65-1.54 (m, 2H), 1.50-1.43 (m, 2H), 1.10 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 143.0, 138.3, 134.4, 123.9, 122.8, 112.5, 99.8, 95.2, 94.1, 91.8, 51.1, 37.5, 33.9, 32.1, 29.0, 22.8, 20.8, 19.8, 18.8. HRMS: Calcd for $C_{21}H_{26}O_2$: 310.9334. Found: 310.9335.
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