Tetrahedron Vol. 49, No. 16, pp. 3313-3324, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
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Palladium-Mediated Cyclization of 1,5-Hexadien-3-ols to 1-Methyl-1,3-cyclopentadienes

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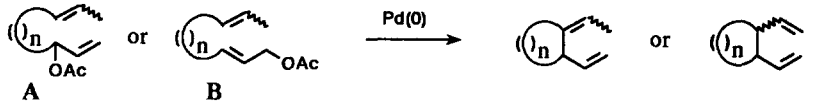
(*Received in Belgium* 9 *February* 1993)

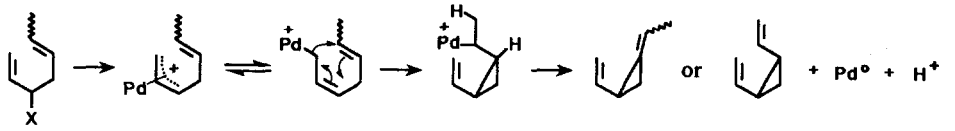
Abstract: *Treatment of 1,5-hexadien-3-ols in acetic acid by Pd(0) [$Pd(PPh_3)_4$] led to 1-methyl-1,3- cyclopentadienes. Cyclization is improved by the presence of catalytic amount of trifluoroacetic acid. Mechanism is discussed from the observed results with deuterated alcohols.*

The reaction of palladium complexes with C-nucleophiles is an attractive synthetic tool.[1-9] In particular, the intramolecular olefin allylation of olefinic allylacetates **A** or **B** constitutes a ring closure leading to 1-methylene-2-vinylcycloalkanes or 1,2-divinylcycloalkanes.[2-4]

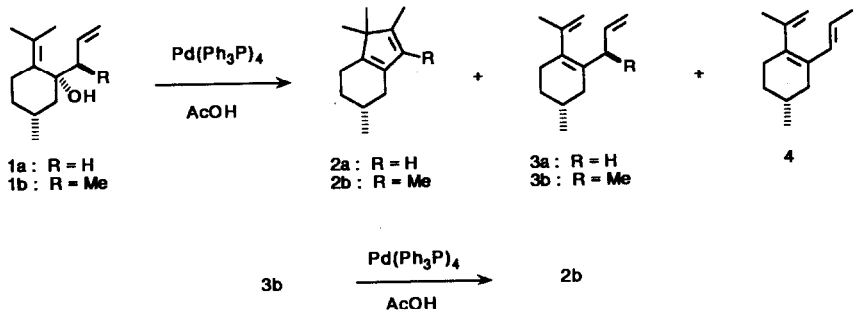


A **B**

These cyclizations provide a variety of five- (six-) membered carbocyclic systems from olefinic allylacetates with n = 3 or 4, and, to our knowledge, no report concerns the case n = 1, corresponding to 1,5-hexadien-3-ol derivatives. The expected palladium-catalyzed intramolecular metallo-ene reaction[4d] should lead to the formation of attractive cyclopropane derivatives or resulting products:

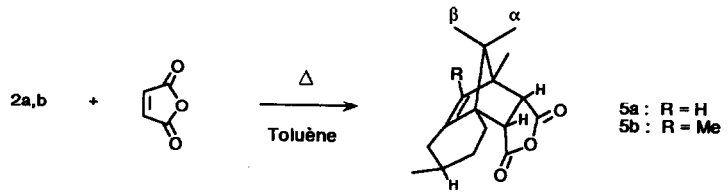


In this context, we studied the cyclization of some 1,5-hexadien-3-ols [10] easily obtained by allyl Grignard reagent addition to unsaturated ketones.[11] First, we have observed that allylpulegols **1a,b** treated in acetic acid solution by $Pd(PPh_3)_4$ (3 mole %, 80 °C, 4 h.) cyclized in bicyclo[4.3.0]nona-1(6),7-dienes **2a,b** along with trienes **3a,b** and **4**. The relative proportions are variable, the main product being **2a,b**. To increase the proportion of cyclopentadienes, we operated to reflux (c.a. 4 h), the only hydrocarbon isolated was **2a,b** in 70-75 % yield. Clearly, the trienes **3a,b** are precursors of **2a,b**: the treatment of **3b** by $Pd(PPh_3)_4$ under reflux of acetic acid led to **2b** : *1,3,6-heptatrienes could be cyclized into 1-methyl-1,3-cyclopentadienes.*

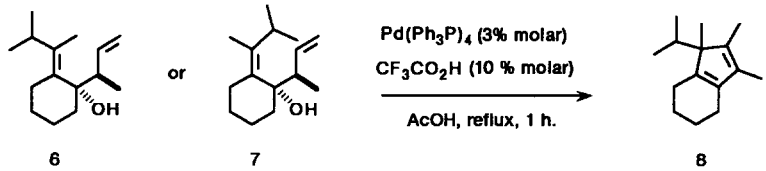


As heating in acetic acid solution with $Pd(PPh_3)_4$ afforded cyclization, a stronger acid should activate the process. In the same conditions, the addition of 0.1 equivalent of trifluoroacetic acid reduced the reaction time to c.a. 1 h. A clean reaction occurred leading to **2a** or **2b** with excellent yields (up to 90 %).

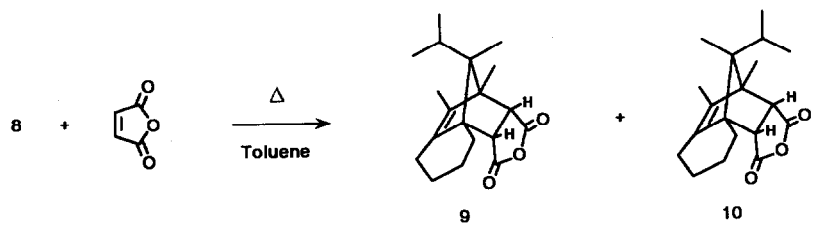
1,3-Cyclopentadienes **2a,b** were characterized as Diels-Alder adducts **5a,b** with maleic anhydride (75 % yield)(minor isomers were present in the crude product and discarded).



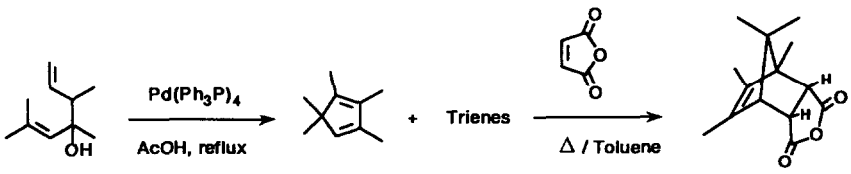
Similar results were observed with 2-alkylidene-1-allylcyclohexanols **6** and **7**.[11b] Exclusive formation of **8** occurred in excellent yield (up to 90 %).



In the case of **8**, two Diels-Alder adducts **9** and **10** were formed with maleic anhydride showing a low facial selectivity (overall yield 86 %, **9** : **10** = 55:45).

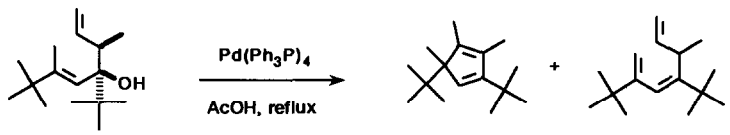


The acyclic 1,5-hexadien-3-ols underwent cyclization, but with the less substituted compounds, heavy products were formed. For alcohol **11**,[11a] the cyclopentadiene **12** was inseparable from the corresponding trienes and the formation of **12** was detected by the formation of the Diels-Alder adduct **13** (60 % overall yield).



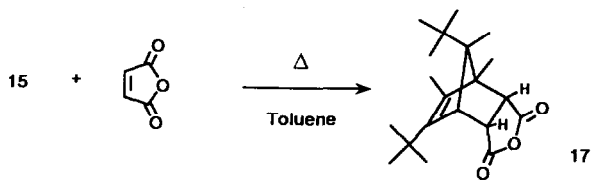
11 12 13

For the hindered alcohol **14**, [11b] the reaction was stopped when the triene **16** has almost disappeared (**15**, c.a. 65 % yield).



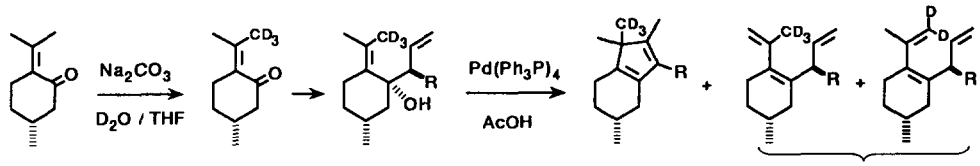
14 15 16

Only one adduct **17** was obtained by Diels-Alder reaction with maleic anhydride.



17

Intramolecular Pd(0)-catalyzed alkene allylations show an interesting potential for the stereocontrolled synthesis of carbocycles. We studied the facial selectivity for the cyclization of the isotopomers of **1a-d_3** and **1b-d_3**. These alcohols were obtained by addition of allyl Grignard reagents [11a] to (*R*)-pulegone-d_3 **18**. **18** was prepared by exchange with D_2O in the presence of Na_2CO_3.[12] In **18**, the deuterium was present only on the (*Z*)-methyl group : the ^1H NMR spectrum showed the sing. at 1.93 ppm was missing similarly for the signal at 22.08 ppm in the ^{13}C spectrum, futhermore, only one signal was present in the ^2D NMR spectrum.



18

1a-d_3: R = H
1b-d_3: R = Me

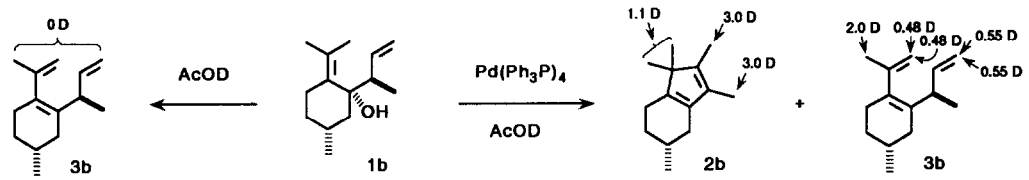
2a-d_3: R = H
2b-d_3: R = Me

3a-*d*: R = H
3b-*d*: R = Me

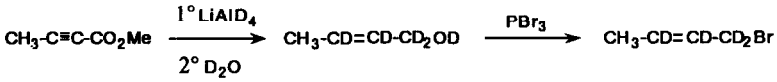
The reaction [$Pd(Ph_3P)_4$, acetic acid, 80 °C] was stopped when alcohols **1a-d_3** or **1b-d_3** have disappeared (TLC). NMR data indicated that trideuteromethyl groups are present at the two positions in cyclopentadienes **2a-d_3** or **2b-d_3** This result was clearly confirmed in the Diels-Alder adducts **5a-d_3** or **5b-d_3**, a mixture 1/1 of isotopomers was obtained (^1H NMR integration of each α- and β-methyl groups showed an intensity corresponding to c.a. 1.6 H) The topomerization of the isopropylidene moiety has occurred during the process of cyclization which is a non stereoselective process. Noteworthy was the fact that, for **2b-d_3**, ^2H NMR spectra indicated a slight incorporation of deuterium on allylic methyl. Trienes **3a-*d*** or **3b-*d*** were deuterated on methyl

and methylene groups (c.a. 72 % of trideuteromethyl and 28 % of dideuteromethylene groups)(the deuterium percentages are calculated from the integration values of protons): the proton was eliminated 2.53 times faster than the deuton.

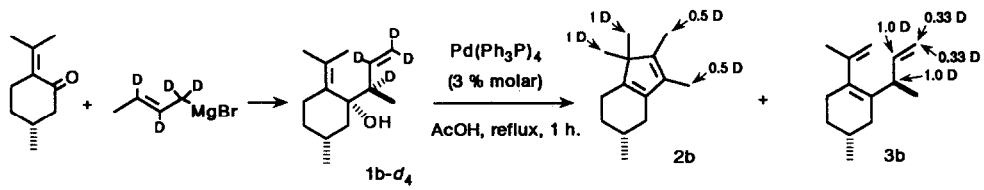
As a slight scrambling occurred, cyclization of **1a** or **1b** was carried out in monodeuteroacetic acid (acetic acid-*O*-*d*). ^2H NMR spectra indicated an incorporation of deuterium, in particular **3b** contained deuterium atoms on the 1 and 7 positions of the 1,3,6-heptatriene moiety and in the allylic methyl group. In contrast, when the alcohol **1b** was heated without catalyst in monodeuteroacetic acid solution, the only product was **3b** and no deuterium incorporation occurred.



In order to check the exchange deuterium-hydrogene, we prepared the alcohol **1b-*d*$_4$**. Deuterated crotyl bromide was prepared according to the known procedure used for the synthesis of 1-bromo-1,1,2,3-tetradeutero-2-pentene.[13]

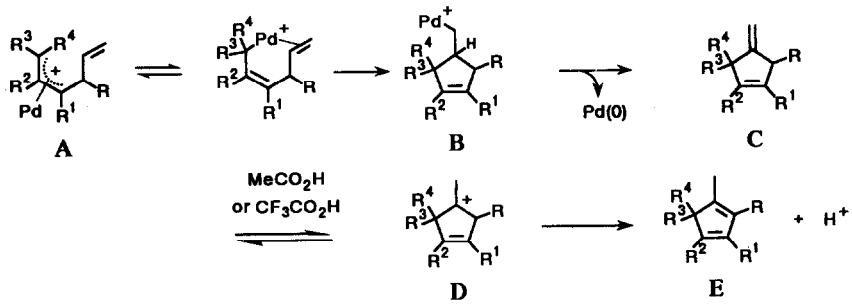


Cyclization of **1b-*d*$_4$**.in acetic acid solution containing catalyst led to **2b** bearing some deuterium atoms in several positions. Clearly, scrambling and exchange occurred. This was enhanced when trifluoroacetic acid (0.1 equiv.) was added, only allylic methyl groups are partly deuterated.

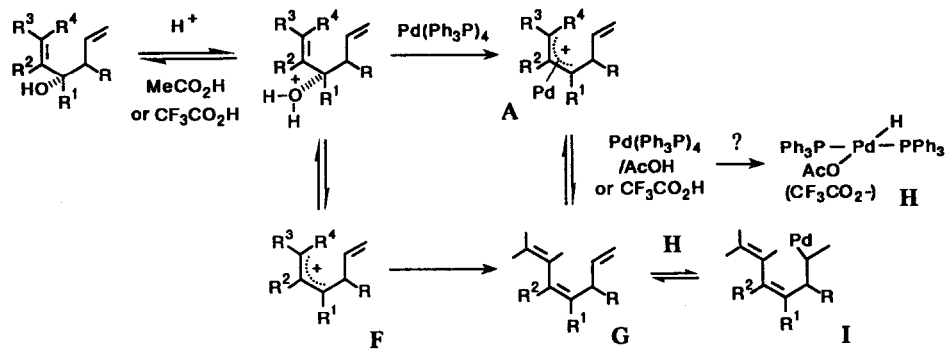


The deuterium labelled experiment demonstrated that acetic acid in the presence of $Pd(Ph_3P)_4$ can exchange proton with the 1,3,6-heptatriene moiety.

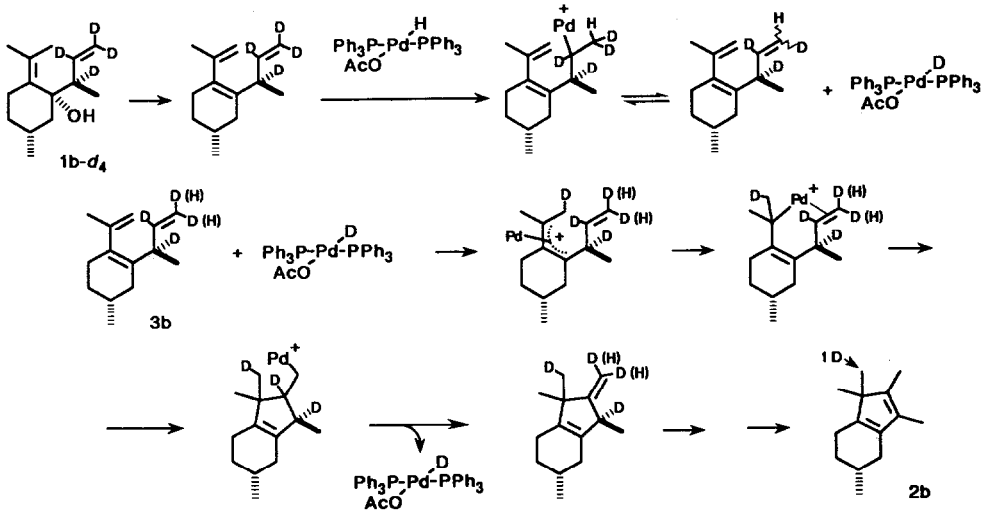
This cyclization can be rationalized by assuming the formation of a π-allylpalladium complex **A** which is then converted to a cyclopentenylmethylpalladium complex **B**, precursor of the cyclopentadiene.



Generally, η^3-allyl complex resulted from oxidative addition of an allylic substrate bearing a leaving group to a Pd^0 complex.[14] The formation of the π-allylpalladium complex **A** in acidic medium from the allylic alcohol is a seldom required process.[15] Formation from the corresponding 1,3,6-heptatriene **G** is not fully clear. As suggested earlier by B.M. Trost,[2f,h,l] a mechanism involving an intermediate such as $CH_3CO_2Pd(PPh_3)_2H$ may account for the above features and the tracer experiments. A large number of addition reactions have been observed with $Pd(PPh_3)_4$ and in particular it was reported the addition of HCl giving *trans*-$(PPh_3)_2Pd(H)Cl$.[1a,16,17] Addition of $CH_3CO_2Pd(PPh_3)_2H$ on the diene moiety of **G** should led to the π-allylpalladium complex **A**.



The presence of deuterium atoms on gem-dimethyl group of **2b** from **1b-d_4** cyclization can result from the equilibrium between the intermediates **G** and **I**. The reversible addition of $CH_3CO_2Pd(PPh_3)_2H$ on the allylic double bond of **1b-d_4** can release $CH_3CO_2Pd(PPh_3)_2D$ which after addition on the dienic moiety of **3b** would explain the presence of deuterium on gem-dimethyl group of **2b**.



In contrast to these results, cyclization of 1,5-hexadien-3-ols mediated by $TiCl_4$ in Et_2O solution gives rise to 1-chloro-3-cyclohexenes.[21]

The problems of five-membered ring synthesis have been posed in numerous natural product families over the past few decades. Cyclopentadienes, precursors of varied functional groups, are of value in the synthesis of polycyclic compounds.

Experimental Section

General. All reactions were run under an atmosphere of argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using Bruker AC 200 spectrometer. Carbon-proton couplings were determined by DEPT sequence experiments;[22] carbon multiplicities are listed as (s) quaternary, (d) or (q) methine or methyl, (t) methylene. Mass spectra were recorded on a Varian MAT 311 mass spectrometer and IR spectra were obtained on a Perkin-Elmer 298 spectrometer. The glassware was dried at 160 °C, assembled hot, and cooled in a desiccator with nitrogen atmosphere. Flash column chromatography used Merck grade silica gel (230-400 mesh) and thin-layer chromatography was performed on silica gel 60 F_{254}.

Materials. (+)-Pulegone was obtained by distillation of *Mentha pulegenium* oil. 1,5-Hexadien-3-ols were prepared by the Barbier process according to ref. 11a.

(2*Z*)-(5*R*)-2-(1-Trideuteromethylethylidene)-5-methylcyclohexanone ((*R*)-pulegone-d_3)(18). (*R*)-(+)-Pulegone (6g, 40 mmol) was added to a solution of anhydrous Na_2CO_3 (1g, 9.5 mmol) in deuterium oxide (20 ml) and anhydrous THF (20 mL). The solution was stirred and refluxed for 15 h. After cooling to room temperature, ether was added and the deuterium oxide solution was separated. The organic layer was washed with water until neutrality, dried ($MgSO_4$) and concentrated (bp 64 °C; 3.5 torr); ^1H NMR ($CDCl_3$): the signal at δ = 1.98 (3, s) is missing; ^{13}C NMR : the signal at δ = 22.08 (q) is missing;[23] ^2H NMR (CCl_4) δ = 1.78 (s) as a single signal; mass spectrum *m/z* 155 (45), 111 (27), 81 (100); HRMS calcd for $C_{10}H_{13}D_3O$ 155.1389, found 155.1385; IR (film) 2280-2040, 1675 cm^{-1}.

General Procedure for the Addition of Allyl chlorides to Unsaturated Ketones in the Presence of Magnesium. In a dry, two-necked reaction flask equipped with a magnetic stirrer, a reflux condenser and a dropping funnel, magnesium (4.4 g, 0.18 g-atom, 3 equiv.) was placed with anhydrous ether (40 mL). The reaction was started by the addition of one crystal of iodine and 0.5 mL of 1,2-dibromoethane. Upon cessation of gas evolution, the reaction flask was cooled with an ice bath and a solution of allyl chloride (120 mmol, 2 equiv.) and α,β-unsaturated ketone (60 mmol, 1 equiv.) in 250 mL of anhydrous ether was added over 3 h. The reaction mixture was stirred at room temperature for 12 h and poured onto ice-ammonium chloride. Excess magnesium was filtered with glass wool and washed with ether. After extractive work up, the ethereal solution was dried ($MgSO_4$). Concentration in vacuo gave the crude product that was subjected to flash chromatography on silica gel (pentane-ether, 9/1 containing triethylamine (1%))(85 % yield).

(1*S*, 5*R*)-1-(2-propen-1-yl)-2-(1-methylethylidene)-5-methylcyclohexanol (1a). ^1H NMR δ 5.80 (1, m), 5.07 (1, d *J* = 15.8 Hz), 5.07 (1, d *J* = 11.7 Hz), 2.63 (2, m), 1.95 (3, d *J* = 1.6 Hz), 1.66 (3, s), 0.85 (3, d *J* = 6.0 Hz); ^{13}C NMR δ 134.3 (d), 133.6 (s), 125.1 (s), 118.0 (t), 77.2 (s), 50.4 (t), 43.5 (t), 34.9 (t), 30.0 (d), 28.7 (t), 23.5 (q), 22.3 (q), 22.2 (q), for other spectral data, see ref.11a.

(2*Z*)-(1*S*, 5*R*)-1-(2-propen-1-yl)-2-(1-trideuteromethyl-ethylidene)-5-methylcyclohexanol (1a-d_3). ^1H NMR, the signal at δ = 1.95 (3, d *J* = 1.6 Hz) is missing;^{13}C NMR, the signal at δ = 22.2 is missing;

^2H NMR (CCl_4) δ 1.91 as alone signal; mass spectrum *m/z* 197 (0.1), 179 (5), 157 (14)($C_{10}H_{13}D_4O$), 156 (86)($C_{10}H_{14}D_3O$)(M^+ - C_3H_5), 155 (100)($C_{10}H_{15}D_2O$), 154 (19)($C_{10}H_{16}D_1O$); HRMS calcd for $C_{13}H_{17}D_3$ (M^+- H_2O) 179.1753, found 179.1756.

(2*Z*)-(1*S*, 5*R*)-1-((1*R*)-1-Methyl-2-propen-1-yl)-2-(1-trideuteromethyl-ethylidene)-5-methylcyclohexanol (1b-d_3). (85 % yield). ^1H NMR δ 5.93 (1, ddd *J* = 16.2, 11.2, 8.4 Hz), 5.08 (2, m), 1.71 (3, s), 0.98 (3, d *J* = 6.9 Hz), 0.85 (3, d *J* = 6.1 Hz), the signal at δ = 2.04 (3, d *J* = 1.4 Hz) ppm is missing; ^2H NMR (CCl_4) δ 1.92 as alone signal; ^{13}C NMR δ 140.21 (d), 133.20 (s), 124.96 (s), 115.33 (t), 79.55 (s), 49.91 (t), 42.56 (d), 35.34 (t), 29.50 (d), 28.54 (t), 23.51 (q), 22.02 (q), 14.22 (q), the signal at δ = 22.37 (q) is missing; mass spectrum *m/z* 193 (2)($C_{14}H_{20}D_3$)(M^+-H_2O), 178 (2), 163 (3), 157 (11), 156 (92)($C_{10}H_{14}D_3O$), 155 (100)($C_{10}H_{15}D_2O$), 154 (33)($C_{10}H_{16}D_1O$); HRMS calcd for $C_{10}H_{14}D_3O$ (M^+ - C_4H_7) 156.1467, found 156.1458, HRMS calcd for $C_{10}H_{15}D_2O$ 155.1404, found 155.1381; IR (film) 3500, 2180-2100, 1640, 1005, 915 cm^{-1}.

(1*S*, 5*R*)-1-((1*R*)-1-Methyl-1,2,3,3-tetradeutero-2-propen-1-yl)-2-(1-methyl-ethylidene)-5-methylcyclohexanol (1b-d_4); 1-bromo-1,1,2,3-tetradeutero-2-butene was prepared from butynoic acid according to the known procedure (ref. 13). **1b-d_4** showed in ^1H NMR spectra no signal at δ > 2.7 ppm and a sing. at 0.936 ppm; mass spectrum *m/z* 212 (0.11), 194 (0.2), 179 (0.5), 154 (10), 154 (10), 153 (100), 152 (3), 109 (8), 107 (12), 93 (22), 81 (22); HRMS calcd for $C_{14}H_{20}D_4O$ 212.2078, found 212.2077; HRMS calcd for $C_{10}H_{17}O$ 153.1279, found 153.1284.

General Procedure for the Cyclization of 1,5-Hexadien-3-ols.

In a dry two necked flask equipped with a magnetic stirrer, a reflux condenser and a septum, were added $Pd(PPh_3)_4$ (prepared from palladiumdibenzylideneacetone (0.172 g, 0.3 mmol) and triphenylphosphine (0.711 g, 2.7 mmol) according to ref. 24), acetic acid (10 mL)(degassed by Ar bubbling), possibly trifluoroacetic acid (8 μL, 1 mmol) and 1,5-hexadien-3-ol (10 mmol). The mixture was refluxed for 4 h, (1 h with trifluoroacetic acid). After filtration, the filter cake was washed with Et_2O (100 mL) and the organic layers were washed with water (2 x 30 mL), dilute Na_2CO_3 solution until neutrality, brine and dried ($MgSO_4$), filtered and concentrated at reduced pressure. The residue was chromatographed (pentane) and if necessary fractions were purified by preparative gas chromatography.

(3*R*)-3,7,7,8-Tetramethylbicyclo[4.3.0]nona-1(6),8-diene (2a). IR (film) 3020, 2980 cm^{-1}; ^1H NMR δ 5.74 (1, br. s), 1.83 (3, s), 1.02 (3, d *J* = 6.80 Hz), 0.925 (3, s), 0.918 (3, s); ^{13}C NMR δ 152.1 (s), 146.2 (s), 133.3 (s), 125.6 (d), 51.8 (s), 33.0 (t), 31.7 (t), 29.7 (d), 22.0 (q), 21.8 (q)(2C), 21.5 (t), 12.2 (q); mass spectrum *m/z* 177 (9), 176 (65), 161 (78), 147 (22), 134 (43), 119 (100), 105 (78); HRMS calcd for $C_{13}H_{20}$ 176.1565, found 176.1568.

(5*R*)-5-Methyl-1-(2-propen-1-yl)-2-(2-propen-2-yl)cyclohexene (3a). IR (film) 3080, 1632, 910, 895 cm^{-1}; ^1H NMR δ 5.73 (1, ddt *J* = 17.0, 10.3, 6.5 Hz), 4.98 (1, br. s *J* = 17.0 Hz), 4.97 (1, br. s *J* = 10.3 Hz), 4.86 (1, br. s), 4.63 (1, br. s), 2.75 (2, d *J* = 6.5 Hz), 1.78 (3, s), 0.945 (3, d *J* = 5.8 Hz); ^{13}C NMR δ 147.1 (s), 137.8 (d), 135.4 (s), 127.6 (s), 114.9 (t), 111.9 (t), 38.8 (t), 37.2 (t), 31.4 (t), 29.6 (t), 29.0 (d), 22.5 (q), 21.7 (q); mass spectrum *m/z* 176 (19), 161 (34), 148 (8), 134 (11), 133 (14), 119 (30), 105 (100); HRMS calcd for $C_{13}H_{20}$ 176.1565, found 176.1568.

(5*R*)-5-Methyl-1-(1-propen-1-yl)-2-(2-propen-2-yl)cyclohexene (4). IR (film) 3080, 1632, 910, 895 cm^{-1}; ^1H NMR δ 6.44 (1, d J = 15.7 Hz), 5.59 (1, dd J = 15.7, 6.6 Hz), 4.96 (1, q J = 1.35 Hz), 4.64 (1, br. s), 1.81 (3, t J = 1.0 Hz), 1.75 (3, d J = 6.6 Hz), 1.0 (3, d J = 6.0 Hz); ^{13}C NMR δ 146.9 (s), 138.1 (s), 131.4 (d), 121.5 (d), 113.3 (t), 34.1 (t), 31.2 (t), 30.3 (t), 28.8 (d), 22.6 (q), 22.0 (q), 18.5 (q); mass spectrum *m/z* 176 (29), 161 (42), 133 (12), 119 (30), 105 (100); HRMS calcd for $C_{13}H_{20}$ 176.1565, found 176.1568.

(1*R*, 5*R*, 8*S*, 9*S*, 13*R*)-1,5,14,14-Tetramethyl-11-oxatetracyclo[6.5.1.0^{3,8}.0^{9,13}]tetradec-2-en-10,12-dione (5a). A solution of **3a** (211 mg, 1.2 mmol) and maleic anhydride (150 mg, 1.5 mmol) in toluene (6 mL) was refluxed for 2 h. The solvent was removed *in vacuo* and the crude product was chromatographed on silica gel (ether/pentane 1/9). Two isomers (3:1) were isolated; major isomer: mp 114 °C (pentane); IR (nujol) 1860, 1780, 1240, 1095, 930, 795 cm^{-1}; ^1H NMR δ 5.48 (1, br. s), 3.30 (2, m), 1.30 3, s), 0.95 (3, d J = 6.2 Hz), 0.74 (3, s), 0.73 (3, s); ^{13}C NMR δ 172.6 (s); 172.1 (s), 146.5 (s), 128.7 (d), 65.5 (s). 604 (s), 58.4 (s), 54.0 (d), 53.7 (d), 35.2 (t), 30.4 (t), 25.6 (t), 30.3 d), 22.1 (q), 17.3 (q)(2C), 12.6 (q); mass spectrum *m/z* 274 (30), 246 (21), 201 (50), 196 (36), 187 (40), 177 (24), 176 (100)(M^+- $C_4H_2O_3$), 175 (21), 161 (71), 134 (45), 119 (82), 105 (48); HRMS calcd for $C_{17}H_{22}O_3$ 274.1568, found 274.1559.

(3*R*)-3,7,7,8,9-Pentamethylbicyclo[4.3.0]nona-1(6),8-diene (2b). IR (film) 2975, 2960, 745 cm^{-1}; ^1H NMR δ 1.71 (6, br. s), 0.99 (3, d J = 6.1 Hz), 0.87 (3, s), 0.86 (3, s); ^{13}C NMR δ 145.5 (s), 143.1 (s), 135.0 (s), 130.8 (s), 51.0 (s), 31.6 (t), 31.3 (t), 29.6 (d), 21.92 (q), 21.86 (q), 21.7 (q), 21.2 (t), 10.4 (q), 9.2 (q); mass spectrum *m/z* 190 (84), 175 (74), 173 (17), 133 (100), 119 (95); HRMS calcd for $C_{14}H_{22}$ 190.1721, found 190,1722.

(5*R*)-5-Methyl-1-((1*R*)-1-methyl-2-propen-1-yl)-2-(2-propen-2-yl)cyclohexene (3b). IR (film) 3080, 1630, 910, 890 cm^{-1}; ^1H NMR δ 5.79 (1, ddd J = 16.9, 10.8, 5.2 Hz), 4.94 (1, dt J = 10.8, 1.8 Hz), 4.91 (1, dt J = 16.9, 1.8 Hz), 4.83 (1, s), 4.60 (1, d J = 2.6 Hz), 3.40 (1, qd J = 7.05, 5.2 Hz), 1.77 (3, d J = 1.0 Hz), 1.03 (3, d J = 7.0 Hz), 0.94 (3, d J = 6.1 Hz); ^{13}C NMR δ 147.5 (s), 143.1 (d), 134.6 (s), 131.8 (s), 112.7 (t), 111.7 (t), 39.4 (d), 32.0 (t), 31.6 (t), 30.1 (t), 29.0 (d), 22.8 (q), 22.1 (q), 17.2 (q); mass spectrum *m/z* 190 (16), 175 (46), 133 (25), 119 (100), 105 (30); HRMS calcd for $C_{14}H_{22}$ 190.1721, found 190.1724.

(1*R*, 5*R*, 8*S*, 9*S*, 13*R*)-1,2,5,14,14-Pentamethyl-11-oxatetracyclo[6.5.1.0^{3,8}.0^{9,13}]tetradec-2-en-10,12-dione (5b). mp 120 °C (pentane); IR (CCl_4) 1860, 1785, 1090, 930 cm^{-1}; ^1H NMR δ 3.25 (2, m), 1.52 (3, br. s), 1.21 (3, s), 0.93 (3, d J = 5.0 Hz), 0.67 (3, s), 0.62 (3, s); ^{13}C NMR δ 172.7 (s), 171.9 (s), 136.8 (s), 134.6 (s), 64.7 (s), 60.5 (s), 59.4 (s), 54.2 (d), 53.3 (d), 32.5 (t), 30.3 (t), 30.3 (d), 25.5 (t), 22.2 (q), 17.4 (q), 17.0 (q), 10.9 (q), 10.8 (q); mass spectrum *m/z* 288 (7), 260 (3), 191 (14), 190 (100), 175 (19); HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1728.

7,8,9-Trimethyl-7-(1-methylethyl)bicyclo[4.3.0]nona-1(6),8-diene (8). IR (film) 1655 cm^{-1}; ^1H NMR δ 1.72 (3, br. s), 1.68 (3, br. s), 0.92 (3, s), 0.78 (3, d J = 7.0 Hz), 0.64 (3, d J = 6.8 Hz); ^{13}C NMR δ 143.7 (s), 141.5 (s), 137.2 (s), 132.7 (s), 58.2 (s), 32.4 (d), 24.0 (t), 23.8 (t), 23.5 (t), 23.3 (t), 19.9 (q), 17.8 (q), 17.6 (q), 10.7 (q), 10.3 (q); mass spectrum *m/z* 204 (36), 189 (96), 175 (33), 173 (23), 162 (70), 161 (97), 157 (68), 147 (100), 133 (65); HRMS calcd for $C_{15}H_{24}$ 204.1878, found 204.1862.

(1*R, 8*S**, 9*S**, 13*R**, 14*R**)-1,2,14-Trimethyl-14-(1-methylethyl)-11-oxatetracyclo-[6.5.1.0^{3,8}.0^{9,13}]tetradec-2-en-10,12-dione (9).** IR 1865, 1785, 1250, 1100, 925 cm^{-1}; ^1H NMR δ 3.16 (1, 1/2 AB J = 6.9 Hz), 3.11 (1, 1/2 AB), 1.53 (3, d J = 1.9 Hz), 1.32 (3, s), 0.82 (6, d J = 6.75 Hz), 0.67 (3, s); ^{13}C NMR δ 172.8 (s), 171.7 (s), 136.6 (s), 135.5 (s), 70.1 (s), 61.9 (s), 61.1 (s), 54.1 (d), 52.7 (d), 31.1 (d), 26.2 (t), 23.5 (t), 23.1 (t), 21.7 (q), 21.6 (t), 19.9 (q), 13.7 (q), 11.8 (q); mass spectrum *m/z* 204 (60), 189 (100), 162 (66), 147 (35), 133 (30); HRMS calcd for $C_{19}H_{26}O_3$ 302.1881, found 302.1872 and calcd for M^+-$C_4H_2O_3$ 204.1878, found 204.1884.

(1*R, 8*S**, 9*S**, 13*R**, 14*S**)-1,2,14-Trimethyl-14-(1-methylethyl)-11-oxatetracyclo-[6.5.1.0^{3,8}.0^{9,13}]tetradec-2-en-10,12-dione (10).** IR 1865, 1785, 1250, 1100, 925 cm^{-1}; ^{1}H NMR δ 3.37 (1, 1/2 AB *J* = 6.9 Hz), 1.46 (3, d *J* = 2.0 Hz), 1.32 (3, s), 0.74 (6, d *J* = 6.9 Hz), 0.59 (3, s);

***(Endo)*-1,8,9,10,10-Pentamethyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3,5-dione (13).** M.p. 100 °C; IR 1860, 1780 cm^{-1}; ^{1}H NMR δ 3.63 (1, dd *J* = 7.6, 4.7 Hz), 3.23 (1, d, *J* = 7.6 Hz), 2.66 (1, d *J* = 4.7 Hz), 1.66 (3, s), 1.54 (3, s), 1.20 (3, s), 0.82 (3, s), 0.79 (3, s); ^{13}C NMR δ 171.6 (s)(2C), 136.1 (s), 134.7 (s), 63.1 (s), 60.7 (s), 58.7 (d), 52.3 (d), 47.4 (d), 19.5 (q), 18.4 (q), 13.7 (q), 11.0 (q), 10.7 (q); mass spectrum *m/z* 234 (13), 161 (8), 147 (20), 137 (38), 136 (100), 121 (75); HRMS calcd for $C_{14}H_{18}O_3$ 234.1255, found 234.1247.

2,4-*Bis*(1,1-dimethylethyl)-5-methyl-1,3,6-heptatriene (16). IR 3070, 900 cm^{-1}; ^{1}H NMR δ 6.04 (1, ddd *J* = 17.0, 10.8, 5.0 Hz), 6.01 (1, br. s), 4.93 (1, d *J* = 1.9 Hz), 4.92 (1, dd *J* = 17.0, 2.2 Hz), 4.91 (1, dd *J* = 10.8, 2.1 Hz), 4.75 (1, d *J* = 1.9 Hz), 3.56 (1, qdt *J* = 7.2, 5.0, 2.2 Hz), 1.25 (3, d *J* = 7.2 Hz), 1.06 (9, s), 1.03 (9, s); ^{13}C NMR δ 155.9 (s), 151.8 (s), 145.1 (d), 125.2 (d), 111.9 (t), 109.8 (t), 38.5 (d), 36.2 (s), 31.0 (s), 31.5 (q)(3C), 29.7 (q)(3C), 19.9 (q).

(1*R, 2*R**, 6*R**, 7*S**, 10*R**)-8,10-*Bis*(1,1-dimethylethyl)-1,9,10-trimethyl-4-oxa-tricyclo-[5.2.1.0^{2,6}]dec-8-en-3,5-dione (17).** mp 126 °C (pentane); IR (CCl_4) 1860, 1780 cm^{-1}; ^{1}H NMR δ 3.55 (1, dd *J* = 7.7, 4.7 Hz), 3.24 (1, d, *J* = 4.7 Hz), 3.14 (1, d *J* = 7.7 Hz), 1.66 (3, s), 1.33 (3, s), 1.10 (9, s), 0.88 (9, s), 0.80 (3, s); ^{13}C NMR δ 173.1 (s), 171.5 (s), 142.4 (s), 138.4 (s), 71.7 (s), 62.3 (s), 56.2 (d), 53.6 (d), 48.5 (d), 35.8 (s), 32.2 (s), 31.1 (q)(3C), 30.5 (q)(3C), 16.9 (q), 13.9 (q), 13.6 (q); mass spectrum *m/z* 318 (8), 220 (32), 164 (91), 149 (76), 108 (45), 57 (100); HRMS calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2187.

Cyclization of 1a-*d*$_3$. 2a-*d*$_3$: IR 2215-2060 cm^{-1}; mass spectrum *m/z* 180 (20)($C_{13}H_{16}D_4$), 179 (90)($C_{13}H_{17}D_3$), 178 (73)($C_{13}H_{18}D_2$), 177 (48)($C_{13}H_{19}D_1$), 176 (13)($C_{13}H_{20}$), 164 (41), 163 (45), 162 (31), 161 (52), 150 (10), 137 (43), 136 (65), 119 (100), 107 (45); HRMS calcd for $C_{13}H_{17}D_3$ 179.1753, found 179.1756. **3a-*d***: IR 2230-2060 cm^{-1}; ^{1}H NMR δ 4.86 (0.7 H), 4.63 (0.7 H), 1.78 (0.33 H); ^{2}H NMR (CCl_4) δ 4.86, 4.64, 2.0, 1.76, 1.59, 1.0 (relative intensity : 1:1:3:16:2.5:1); ^{13}C NMR signals at δ = 111.9 (t) and 22.5 (q) shows low intensity; mass spectrum *m/z* 181 (6)($C_{13}H_{15}D_5$), 180 (13)($C_{13}H_{16}D_4$), 179 (12)($C_{13}H_{17}D_3$), 178 (7)($C_{13}H_{18}D_2$), 177 (3)($C_{13}H_{19}D_1$), 165 (15), 164 (19), 163 (21), 162 (13), 107 (100), 105 (80); HRMS calcd for $C_{13}H_{16}D_4$ 180.1816, found 180.1816, for $C_{13}H_{17}D_3$ 179.1753, found 179.1756. **5a-*d*$_3$**: IR 2280-2140 cm^{-1}; ^{1}H NMR δ 0.74 (1.6 H), 0.73 (1.6 H); ^{13}C NMR signal at δ = 17.3 shows low intensity; mass spectrum *m/z* 276 (2), 248 (1), 204 (5), 203 (5), 180 (10), 179 (29)($C_{13}H_{17}D_3$)(M^+- $C_4H_2O_3$), 178 (40), 177 (17), 176 (13),175 (6), 163 (20), 136 (26), 122 (24), 43 (100); HRMS calcd for $C_{17}H_{19}D_3O_3$ 277.1768, found 277.1757.

Cyclization of 1b-*d*$_3$. 2b-*d*$_3$: IR 2220, 2140, 2062 cm^{-1}; ^{1}H NMR δ 0.87 (1.5 H, s), 0.86 (1.5 H, s); ^{2}H NMR (CCl_4) δ 1.75 (br s)(rel. intens. 1), 0.92 (br s)(rel. intens. 6.7); ^{13}C NMR signals at δ = 21.9 and 21.7 shows low intensity; mass spectrum *m/z* 194 (43)($C_{14}H_{18}D_4$), 193 (96)($C_{14}H_{19}D_3$), 192 (100)($C_{14}H_{20}D_2$), 191 (55)($C_{14}H_{21}D_1$), 190 (17)($C_{14}H_{22}$), 178 (47), 177 (41), 176 (38), 175 (32), 138 (16), 137 (33), 136 (71), 135 (64), 133 (57); HRMS calcd for $C_{14}H_{19}D_3$ 193.1909, found 193.1915, calcd for $C_{14}H_{20}D_2$ 192.1847 or $C_{14}H_{18}D_3$ 192.1831, found 192.1836. **3b-*d***: IR 2180-2040 cm^{-1}; ^{1}H NMR δ 4.83 (0.73 H, s), 4.60 (0.73 H, s), 1.78 (0.81 H, s); ^{2}H NMR (CCl_4) δ 4.90, 4.65, 2.0, 1.82, 1.5 (relative intensity : 1,1, shoulder, 10.4, 1.4); ^{13}C NMR signals at δ = 111.7 and 22.8 show low intensity; mass spectrum *m/z* 194 (1.8), 193 (3.4), 192 (3),

191 (2), 190 (0.3), 178 (19), 177 (21), 176 (25) 175 (18), 165 (15), 164 (28), 163 (24), 162 (13), 136 (14), 135 (18),134 (18), 133 (11), 122 (80), 121 (74), 120 (58), 119 (100); HRMS calcd for $C_{14}H_{18}D_4$ 194.1972, found 194.1974, $C_{14}H_{19}D_3$ 193.1909, found 193.1911, $C_{14}H_{20}D_2$ 192.1847, found 192.1848, $C_{14}H_{21}D$ 191.1784, found 191.1785. **5b-d_3** : IR 2220, 2262, 2130 cm^{-1}; ^1H NMR δ 0.67 (1.68 H, s), 0.62 (1.68 H, s); ^{13}C NMR signals at δ = 17.4 and 17.0 shows a very low intensity; mass spectrum *m/z* 291 (4), 290 (4), 263 (3), 262 (3), 194 (27), 193 (100), 192 (99), 191 (42), 178 (19), 177 (23), 176 (15), 175 (19); HRMS calcd for $C_{18}H_{21}D_3O_3$ 291.1913, found 291.1916.

Cyclization of 1b-d_4. 2b : ^1H NMR δ 1.7 (5 H, br. s), 0.87 (2H, s), 0.86 (2H, s); ^2H NMR (CCl_4) δ 2.08, 1.67, 1.5, 0.86 (relat. intens. : 3.3, 3.3, 1, 6.7); mass spectrum *m/z* 194 (9.3)($C_{14}H_{18}D_4$), 193 (5)($C_{14}H_{19}D_3$), 192 (11)($C_{14}H_{20}D_2$), 191 (52)($C_{14}H_{21}D$), 190 (70)($C_{14}H_{22}$), 177 (20), 176 (43), 175 (73), 174 (17), 173 (35), 172 (10), 171 (25), 135 (38), 134 (53), 133 (100), 119 (60); HRMS calcd for $C_{14}H_{21}D_1$ 191.1784, found 191.1784, $C_{14}H_{22}$ 190.1721, found 190.1724. **3b** : ^1H NMR δ 4.92 (1.4 H), 4.85 (1H), 4.61 (1H), 1.77 (3H), 1.01 (3H, br. s); ^2H NMR (CCl_4) δ 5,73, 4.90, 3.36 (rel. inten. 0.6, 0.6, 1); mass spectrum *m/z* 194 (20), 179 (55), 178 (22), 165 (12), 164 (73), 163 (35), 149 (15), 137 (18), 136 (23), 124 (14), 123 (78), 122 (100); HRMS calcd for $C_{14}H_{18}D_4$ 194.1972, found 194.1969.

Table I. Deuterium incorporation in compounds 1, 2, 5.

	1a-d_3	2a-d_3	5a-d_3	1b-d_3	2b-d_3	5b-d_3
D_0 (% of total)	1	5	5	2	5	4
D_1 (% of total)	8	20	17	11	20	18
D_2 (% of total)	43	33	35	45	40	37
D_3 (% of total)	42	37	35	42	32	35
D_4 (% of total)	6	5	8	4	4	5
Deuterium total	2.44	2.17	2.16	2.43	2.12	2.17

Cyclization of 1b in the Presence of Acetic Acid-*O*-*d*. 2b : ^1H NMR, the singlet at δ = 1.7 is missing, 0.87 and 0.86 (c.a. 4.4 H); ^2H NMR (CCl_4) δ 2.2, 2.0, 1.7, 0.9 (relat. intens. : 1.6, 1.6, 5.8, 1); ^{13}C NMR signals at δ = 10.4 and 9.2 have almost totally disappeared. **3b** : ^1H NMR δ 5.8 (0.94 H), 4.9 (0.9 H), 4.86 (0.52 H), 4.63 (0.52 H), 3.4 (1H), 1.7 (1H); ^2H NMR (CCl_4) δ 4.94, 4.64, 1.78 (relat. intens. : 3.2, 0.8, 1); ^{13}C NMR signals diminished at δ = 112.7, 111.7 and 22.8; enlargement of the 112-110 ppm region shows a singlet at 112.7 (=CH_2), one triplet at 112.45 (J_{CD} = 24.0 Hz, CDH), a sing. at 111.67 (=CH_2), a triplet at 111.4 (J_{CD} = 24.0 Hz, CDH), a CD_2 group (even if present) cannot be detected; mass spectrum *m/z* 195 (5), 194 (5), 193 (8), 192 (8), 191 (3.5), 190 (2.2), 179 (16), 178 (39), 177 (30), 176 (31), 175 (11), 164 (24), 163 (36), 150 (12), 136 (12), 135 (26), 134 (25), 123 (46), 122 (61), 121 (100); HRMS calcd for $C_{14}H_{19}D_3$ 193.1909, found 193.1911, $C_{14}H_{20}D_2$ 192.1847, found 192.1848.

Acknowledgment. T.Z. is grateful to Morocco Government for a grant.

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