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Palladium-Catalyzed Oxaspirocyclizations

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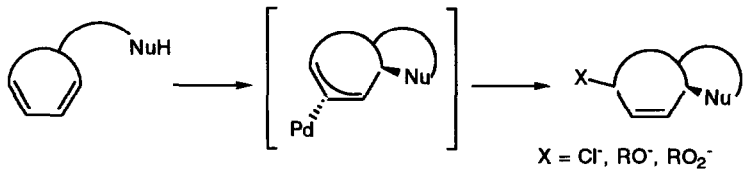
Abstract: *Palladium-catalyzed oxidation of 1-(3-hydroxyalkyl) and 1-(4-hydroxyalkyl)-1,3-cycloalkadienes results in a stereocontrolled oxaspirocyclization. The reaction proceed via a spirocyclic (π-allyl)palladium intermediate, which is attacked by an acetate or a chloride nucleophile leading to an overall 1,4-addition across the diene. The intermediate (π-allyl) palladium complex was independently prepared and characterized. The stereochemistry of the 1,4-addition can be controlled to give either cis or trans 1,4-addition across the double bonds. The oxaspirocyclization was applied to the total synthesis of theaspirone.*

Palladium-catalyzed intramolecular 1,4-additions to conjugated dienes have emerged as a synthetically versatile method for constructing heterocyclic systems.[1-4] Two principal types of reactions have been developed: one leading to an annulation type reaction and the other leading to spirocyclic products (Scheme I).

Scheme I.

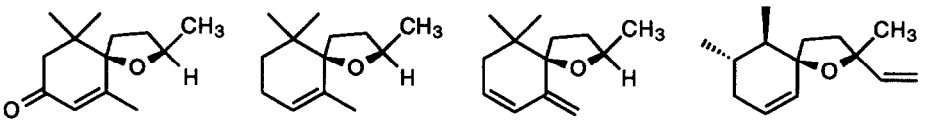


The first step involves coordination between the diene and Pd(II) yielding a η^4-complex which is readily attacked by the internal nucleophile to give a (π-allyl)palladium complex as an intermediate. This complex can then be attacked by a second, external nucleophile (Cl^-, RO^-, RCO_2^-) resulting in the liberation of the product. The Pd(0) formed is reoxidized by 1,4-benzoquinone to Pd(II) and this closes the catalytic cycle.

An interesting feature of these 1,4-oxidations is the possibility to direct the second nucleophile to either a *cis* or a *trans* addition over the 1,3-diene. If the external nucleophile consists of chloride or alkoxy, a *cis*-adduct will be obtained. However, if acetate is used as the second nucleophile and is allowed to coordinate to palladium a *cis* migration will take place, resulting in the *trans*-acetate. Coordination of acetate to palladium can be prevented if a catalytical amount of chloride is present. In this case, the chloride will block the coordination site on palladium and direct the acetate to an *anti* attack on the π-allyl complex, yielding a *cis* addition product.

Depending on where the chain containing the intramolecular nucleophile is situated, either fused[1-3] or spirocyclic[1,4] systems can be obtained. In a preliminary communication we reported on the palladium-catalyzed, stereocontrolled spirocyclization of diene-alcohols yielding oxaspirocycles in good yield and stereoselectivity.[4] These transformations are synthetically interesting since the spirocyclic products obtained are structually very similar to naturally occurring nor-isoprenoid spiroethers,[5] compounds such as theaspiranes and vetispirane, which are known aroma components in tea and vanilla, respectively.

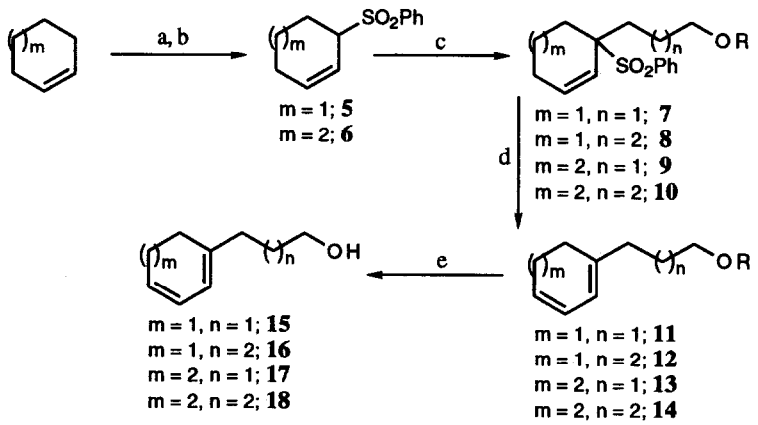
Fig. I



Theaspirone **1** Theaspirane **2** Vetispirane **3** Dactyloxene B **4**

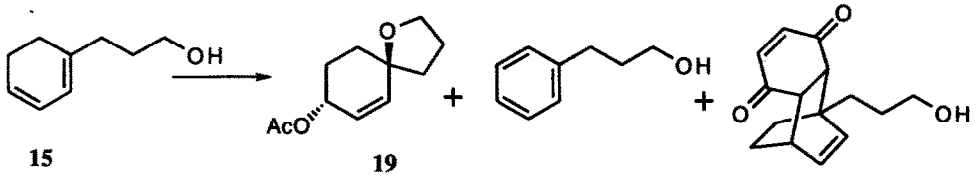
The requisite starting materials for oxaspirocyclization were readily synthesized employing a procedure recently developed in our laboratories[6] (Scheme II). The synthesis originates from cyclohexene or cycloheptene which is transformed to the corresponding allylic bromide by treatment with NBS in CCl_4. The bromide is unstable and therefore used immediately in the subsequent reaction with sodium benzenesulfinate which gives a stable allylic sulfone. The allylic sulfone is then treated with *n*-BuLi and alkylated with an *O*-protected haloalcohol. A regioselective 1,4-elimination of benzenesulfinate gives the 1-substituted 1,3-diene which is deprotected to furnish the diene-alcohol in good overall yield from the corresponding cycloalkene.

Scheme II



a. NBS, AIBN, CCl_4, 60 - 70 %; b. $NaSO_2Ph$, DMF, 80 - 90 %; c. *n*-BuLi, $XCH_2(CH_2)_nCH_2OR$, X = Br or I, R = THP or $SiMe_2(t\text{-Bu})$, THF, 61 - 97 %; d. *t*-BuOK, *t*-BuOH, 76 - 96 %; e. HCl, THF / H_2O, 81 - 87 %.

When substrate **15** was subjected to a catalytic amount of $Pd(OAc)_2$ with 1,4-benzoquinone as reoxidant in acetic acid only ~30% of the spirocyclic compound could be isolated. The reason for this low yield is due to competing Diels-Alder reaction between the diene and 1,4-benzoquinone and aromatization of the diene to benzene. It was possible to suppress the Diels-Alder reaction by changing the solvent to a 4:1 mixture of acetone - acetic acid. The change of solvent resulted in a slower but more selective reaction. As can be seen in Table I the rate of the cyclization was retarded and the amount of Diels-Alder adduct decreased from 17 to 7 %.



15 **19**

Table I. Solvent effects in oxaspirocyclization[a]

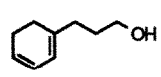
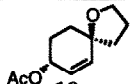
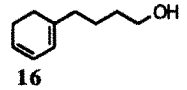
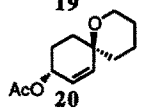
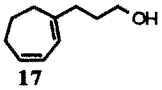
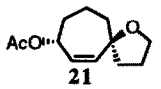
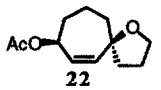
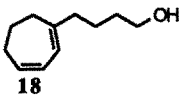
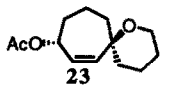
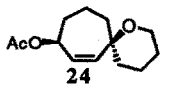
solvent	time, min	starting mat. %	spirocyclic product (**19**) (%)	aromatized product (%)	Diels-Alder product (%)
acetic acid (100%)	20	8	62	14	16
	30	0	68	15	17
acetone-acetic acid (80 : 20)	15	80	12	8	0
	33	51	36	8	5
	66	25	60	10	5
	132	0	81	12	7

a. The reaction was performed in an NMR tube employing deuterated solvents, and using 5 mol% of $Pd(OAc)_2$. The ratio between the compounds was determined by integration over appropriate peaks in the ^1H NMR.

By slow addition of the diene alcohol to the reaction mixture it was possible to further suppress the Diels-Alder reaction. Interestingly, the amount of aromatization was also decreased by this procedure. It was also found that the addition of Li_2CO_3 (as a source for LiOAc) accelerated the spirocyclization. This is probably due to an activation of the hydroxy nucleophile. With this modifications the substrates **15-18** were cyclized to their corresponding spiro acetates in good yields and good stereoselectivity (Table II). In the six-membered ring systems, the *trans*:*cis* ratio exceeded 98:2. In the seven-membered ring, the selectivity was slightly lower, and dienes **17** and **18** produced **21** and **23** in a *trans*:*cis* ratio of 88:12 and 94:6, respectively. All

attempts to direct these reactions towards *cis*-acetates in the six membered ring by inhibiting the *cis* migration of acetate from palladium (by addition of a catalytic amount of LiCl) resulted in poor yields and poor selectivity.[7] The only case in which stereoselective synthesis of both *cis*- and *trans*-acetates was possible from the same substrate was for the seven-membered ring substrate **17**. For **17**, omitting the Li_2CO_3 resulted in a *trans*:*cis* ratio of 88:12 mixture (*vide supra*), while the addition of 3 equiv. of Li_2CO_3 afforded a *trans*:*cis* ratio of 20:80. For **18** the corresponding ratios were 94:6 and 40:60 respectively. An explanation of this phenomena is that the increased acetate concentration by addition of Li_2CO_3 accelerates the external, *anti* attack on the π-allyl intermediate. If Li_2CO_3 is omitted, the external attack will decrease and now the *cis* migration of acetate from palladium to carbon will be the major reaction pathway.

Table II. Oxaspirocyclizations using acetates as the external nucleophile.

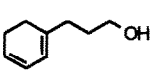
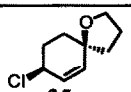
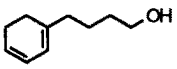
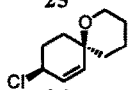
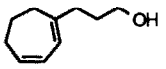
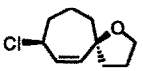
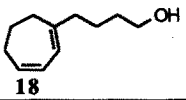
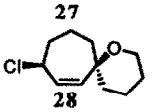
entry	starting material	method	reaction time (h)	product	ratio *trans* : *cis*	% yield
1	 **15**	A	24	 **19**	> 98 : 2	86
2	 **16**	A	24	 **20**	> 98 : 2	82
3	 **17**	A	100	 **21**	88 : 12	60
4		B	36	 **22**	20 : 80	54
5	 **18**	A	100	 **23**	94 : 6	82
6		B	72	 **24**	40 : 60	75

Method A: The diene was added to 2 eq. 1,4-Benzoquinone, 3 eq. Li_2CO_3 and 5 mol % $Pd(OAc)_2$ in HOAc / acetone 1 : 4. Method B: The diene was added to 2 eq. 1,4-Benzoquinone and $Pd(OAc)_2$ in HOAc / acetone 1 : 4.

As mentioned above a catalytic amount of chloride led to a poor result. If, however, a stoichiometric amount (2 equiv.) of LiCl was used in the reaction the *cis* chloro spirocyclic ethers were obtained in good yields and excellent stereoselectivity (Table III). In the case of cycloheptadienes **17** and **18** the reaction took place at a considerably lower rate. This was not a serious problem since triene formation and Diels-Alder addition are not facile in the seven membered ring. After extending the reaction time to 72 h and performing

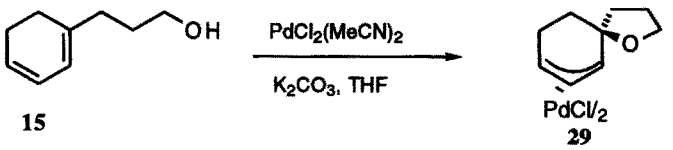
the reaction at a slightly elevated temperature (35 °C) the oxaspiro chlorides **27** and **28** were obtained in reasonable yields. The results from these chloro spirocyclizations are summarized in Table III.

Table III. Oxaspirocyclizations using chloride as the external nucleophile.

entry	starting material	reaction time (h)	product	% 1,4-*cis* selectivity	% yield
1	 **15**	24	 **25**	>98	73
2	 **16**	24	 **26**	>98	70
3	 **17**	72[a]	 **27**	>98	40
4	 **18**	72[a]	 **28**	>98	60

[a] 35 °C.

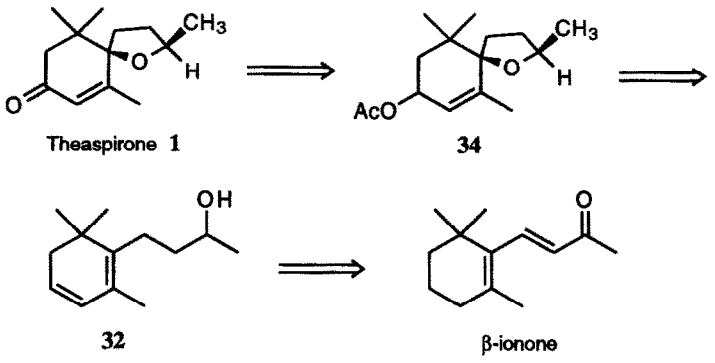
The proposed mechanism for the palladium-catalyzed spirocyclization involves formation of a (π-allyl)palladium intermediate (cf. Scheme I). In order to get more evidence for this mechanism we prepared the (π–allyl)palladium complex **29**, which is assumed to be the catalytic intermediate in the spirocyclization of **15**. Reaction of **15** with $PdCl_2(MeCN)_2$ in THF afforded a pale yellow complex which was isolated and characterized.



15 **29**

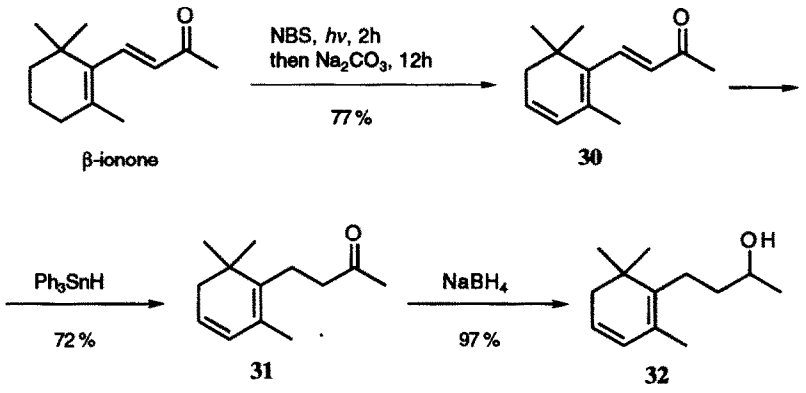
Theaspirone is a compound with a strong smell and taste. It is a flavor component of tea (hence its name) but it also occurs in passion fruit. Our strategy of creating oxaspirocycles would be particularly suited for the synthesis of this compound. A retrosynthetic analysis is given in Scheme III. Theaspirone would be readily available from **34**, which in turn would be obtained from palladium-catalyzed oxaspirocyclization of diene **32**. The latter diene is synthesized from β-ionone.

Scheme III. Retrosynthetic analysis of theaspirone



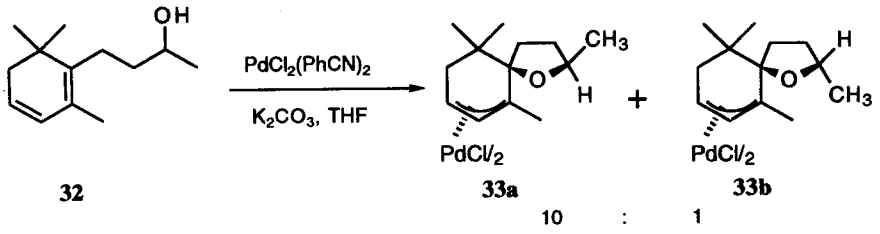
The transformation of β-ionone to trienone **30** was accomplished by a one-pot procedure involving an allylic bromination-elimination sequence[8] (Scheme IV). The α,β double bond was selectively reduced by triphenyltin hydride[9] and the ketone was transformed to alcohol by $NaBH_4$ reduction.

Scheme IV.



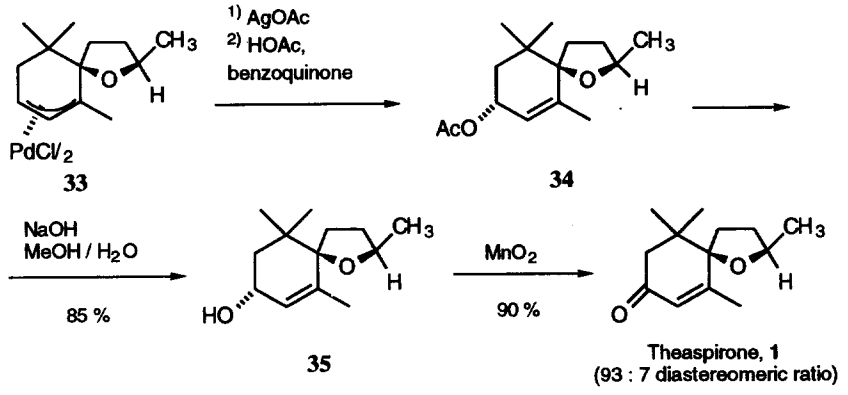
Initial attempts to cyclize diene **32** under the standard conditions for intramolecular 1,4-oxidation in acetone-acetic acid (4:1) failed. Because of the failure of diene **32** to undergo a catalytic reaction[10] we decided to try to prepare the intermediate (π-allyl)palladium complex. Reaction of diene **32** with $PdCl_2(PhCN)_2$, in THF in the presence of K_2CO_3 gave a quantitative yield of the spirocyclic π-allyl complex **33** as a 10:1 mixture of diastereoisomers (eq. 3.) The spirocyclization is expected to have a late transition state,[11] and therefore molecular modelling of the two possible diastereoisomers of the theaspirane skeleton (cf. Fig. I) should provide insight into this selectivity. Molecular mechanics calculations (MM2 parameters) showed that the diastereoisomer of theaspirane corresponding to **33a** is 2.2 kcal/mol more stable than that corresponding to **33b**.

The lower stability of the latter diastereoisomer largely results from interaction between the methyl group of the tetrahydrofuran and the vinylic methyl group.



We next studied the reactivity of the (π-allyl)palladium complex (Scheme V). Replacement of the chloride by acetate using AgOAc and subsequent reaction with benzoquinone in acetic acid afforded acetate **34**. The difference from the attempted catalytic reaction was that acetic acid was used as solvent in place of THF for the formation of the π-allyl.[10] The acetate **34** was hydrolyzed and oxidized to theaspirone which on analysis by ^{1}H NMR revealed a 93:7 diastereomeric ratio. Spectral data of the product were identical to those of the theaspirone reported in the literature.[12]

Scheme V.



Experimental Section

NMR spectra were recorded for $CDCl_3$ solutions with a Varian XL 300 spectrometer, ^{1}H at 300 or 400 MHz, and ^{13}C at 75.4 or 100.5 MHz, using tetramethylsilane (0.0 ppm, ^{1}H) or chloroform-d_1 (77.0 ppm, ^{13}C) as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer using a 0.1 mm KBr cell on neat samples or with $CDCl_3$ as solvent. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument in the electron impact mode using a potential of 70 eV volt. Commercial acetone (99.5%) and acetic acid (99.8%) were used as delivered. 1,4-benzoquinone, lithium chloride and lithium acetate dihydrate were

purchased from Aldrich. $Pd(OAc)_2$ was bought from Engelhard. $PdCl_2$ was obtained from Johnson Matthey. Merck silica gel 60 (240-400 mesh) was used for column chromatography.

$PdCl_2(PhCN)_2$.[13] Palladium(II) chloride (2 g) was dissolved in benzonitrile (45 mL) and the mixture was stirred at 110 °C for 30 min. Then the solution was filtered (to remove the unsoluble $PdCl_2$-polymer) and pentane was added to the mother liquid. The precipitate was collected on a filter, washed with pentane and dried under vacuum (0.1 mmHg) over night.

$PdCl_2(MeCN)_2$ was prepared as described in ref. 14.

Allylic sulphones 5 and 6 were synthesized according to ref. 6.

3-(3-(2-Tetrahydropyryloxy)propyl)-3-(phenylsulfonyl)cyclohexene (7) was prepared from **5** in 85% yield according to ref. 6 using the tetrahydropyrane-protected 3-bromopropanol as the alkylating agent. ^1H NMR (300 MHz) δ; 7.87 (d, 2 H), 7.63 (t, 1 H), 7.53 (t, 2 H), 6.15 (m, 1 H), 5.62 (m, 1 H), 4.55 (m, 1 H), 3.81 (m, 1 H), 3.70 (m, 1 H), 3.48 (m, 1 H), 3.36 (m, 1 H), 2.15 (m, 1 H), 2.00 - 1.45 (m, 15 H); ^{13}C NMR (75.4 MHz) δ; 136.4, 135.9, 133.4, 130.5, 128.5, 123.5, 98.7, 67.3, 66.4, 62.2, 31.7, 30.6, 27.0, 25.4, 24.6, 23.9, 19.5, 18.8.

Anal. Calcd. for $C_{20}H_{28}SO_4$: C, 65.90; H, 7.74. Found: C, 65.71; H, 7.56.

3-(4-(*t*-Butyldimethylsilyloxy)butyl)-3-(phenylsulfonyl)cyclohexene (8) was prepared from **5** in 87% yield according to ref. 6 using the *t*-butyldimethylsilyl-protected iodobutanol[15] as the alkylating agent. ^1H NMR (300 MHz) δ; 7.85 (d, 2 H), 7.62 (t, 1 H), 7.51 (t, 2 H), 6.13 (m, 1 H), 5.60 (m, 1 H), 3.57 (t, 2 H), 2.10 (m, 1 H), 1.95 - 1.32 (m, 11 H), 1.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75.4 MHz) δ; 136.4, 135.7, 133.3, 130.5, 128.4, 123.7, 66.7, 62.6, 34.5, 33.1, 26.9, 25.9, 23.9, 20.5, 18.8, 18.1, 14.1.

Anal. Calcd. for $C_{22}H_{36}SO_3Si$: C, 64.66; H, 8.88. Found: C, 64.47; H, 8.65.

3-(3-(2-Tetrahydropyryloxy)propyl)-3-(phenylsulfonyl)cycloheptene (9) was prepared from **6** in 97% yield following the procedure described for compound **7** and was used without further characterization.

3-(4-(*t*-Butyldimethylsilyloxy)butyl)-3-(phenylsulfonyl)cycloheptene (10) was prepared from **6** in 89% yield following the procedure described for compound **8** and was used without further characterization.

1-(3-(2-Tetrahydropyryloxy)propyl)-1,3-cyclohexadiene (11) was prepared from **7** in 96% yield according to ref. 6. ^1H NMR (300 MHz) δ; 5.87 (m, 1 H), 5.72 - 5.63 (m, 2 H), 4.58 (m, 1 H), 3.87 (m, 1 H), 3.75 (m, 1 H), 3.50 (m, 1 H), 3.40 (m, 1 H), 2.23 - 2.03 (m, 6 H), 1.88 - 1.65 (m, 4 H), 1.65 - 1.47 (m, 4 H); ^{13}C NMR (75.4 MHz) δ; 139.2, 124.6, 123.6, 118.6, 98.9, 67.2, 62.3, 33.9, 30.7, 27.6, 26.4, 25.5, 22.9, 19.6.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.74; H, 10.12.

1-(4-(*t*-Butyldimethylsilyloxy)butyl)-1,3-cyclohexadiene (12) was prepared from **8** in 82% yield following the procedure described for compound **11**. ^1H NMR (300 MHz) δ; 5.87 (m, 1 H), 5.70 - 5.62 (m, 2 H), 3.61 (t, 2 H), 2.21 - 2.01 (m, 6 H), 1.56 - 1.43 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75.4 MHz) δ; 139.9, 124.7, 123.5, 118.5, 63.1, 37.1, 32.5, 36.4, 26.0, 23.7, 22.9, 18.0, 14.1.

Anal. Calcd. for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 72.21; H, 11.18.

1-(3-(2-Tetrahydropyryloxy)propyl)-1,3-cycloheptadiene (13) was prepared from **9** in 90% yield following the procedure described for compound **11** and was used without further characterization.

1-(4-(*t*-Butyldimethylsilyloxy)butyl)-1,3-cycloheptadiene (14) was prepared from **10** in 86% yield following the procedure described for compound **12**. ^1H NMR (300 MHz) δ; 5.74 - 5.65 (m, 2 H), 5.54 (m, 1

H), 3.61 (t, 2 H), 2.36 - 2.23 (m, 4 H), 2.07 (t, 2 H), 1.87 - 1.78 (m, 2 H), 1.55 - 1.41 (m, 4 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75.4 MHz) δ; 146.4, 131.8, 124.9, 120.4, 63.1, 40.4, 34.5, 32.5, 32.1, 26.0, 25.7, 24.4, 18.4, 14.2.

1-(3-Hydroxypropyl)-1,3-cyclohexadiene (15) was prepared from **11** in 87% yield by deprotection with HCl in THF-water. ^{1}H NMR (300 MHz) δ; 5.87 (m, 1 H), 5.72 - 5.64 (m, 2 H), 3.66 (t, 2 H), 2.23 - 2.04 (m, 6 H), 1.78 - 1.67 (m, 2 H), 1.60 (br. s, 1 H); ^{13}C NMR (75.4 MHz) δ; 139.2, 124.5, 123.8, 118.8, 62.7, 33.6, 30.4, 26.3, 22.9.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.96; H, 10.29.

1-(4-Hydroxybutyl)-1,3-cyclohexadiene (16) was prepared from **12** in 98% yield following the procedure described for compound **15**. ^{1}H NMR (300 MHz) δ; 5.86 (m, 1 H), 5.69 - 5.61 (m, 2 H), 3.65 (t, 2 H), 2.20 - 2.02 (m, 6 H), 1.63 - 1.46 (m, 4 H), 1.30 (br. s, 1 H).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.83; H, 10.47.

1-(3-Hydroxypropyl)-1,3-cycloheptadiene (17) was prepared from **13** in 81% yield following the procedure described for compound **15**. ^{1}H NMR (300 MHz) δ; 5.77 - 5.65 (m, 2 H), 5.58 (m, 1 H), 3.65 (t, 2 H), 2.37 - 2.25 (m, 4 H), 2.15 (t, 2 H), 1.89 - 1.78 (m, 2 H), 1.77 - 1.65 (m, 2 H), 1.59 (br. s, 1 H); ^{13}C NMR (75.4 MHz) δ; 145.7, 132.1, 124.7, 120.7, 62.7, 37.0, 34.5, 32.0, 31.1, 25.6.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.64; H, 10.77.

1-(4-Hydroxybutyl)-1,3-cycloheptadiene (18) was prepared from **14** in 90% yield following the procedure described for compound **15**. ^{1}H NMR (300 MHz) δ; 5.76 - 5.64 (m, 2 H), 5.55 (m, 1 H), 3.65 (t, 2 H), 2.37 - 2.23 (m, 4 H), 2.08 (t, 2 H), 1.87 - 1.78 (m, 2 H), 1.63 - 1.44 (m, 4 H), 1.38 (br. s, 1 H); ^{13}C NMR (75.4 MHz) δ; 146.0, 131.9, 124.8, 120.6, 62.9, 40.4, 34.4, 32.4, 32.0, 25.7, 24.3.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.59; H, 10.82.

Spiro [4,5] (5*R, 8*R**)-8-acetoxy-1-oxa-6-decene (19).** $Pd(OAc)_2$ (8.1 mg, 0.036 mmol), benzoquinone (160 mg, 1.45 mmol) and Li_2CO_3 (160 mg, 2.17 mmol) were dissolved in aceton / HOAc (2 mL, 4 : 1). To this solution was then added the dienol **15** (120 mg, 0.868 mmol, dissolved in 1 mL acetone) during 16 h. 1 h after the addition was completed ether (15 mL) was added and the resulting solution was washed with aqueos NaOH (2 M, 2x4 mL) and brine (3 mL). The solution was dried with $MgSO_4$, the solvent was evaporated and the residue subsequently Kugelrohr distilled under reduced pressure (1 mmHg, oven temperature 250 °C) to give **19** (147 mg, 0.749 mmol, 86%). ^{1}H NMR δ 5.78 (d, J = 10.0 Hz, 1 H), 5.72 (dd, J = 3.0, 10.0 Hz, 1 H), 5.29 (m, 1 H), 3.86 (t, J = 6.6 Hz, 2 H), 2.13 (m, 1 H), 2.05 (s, 3 H), 2.00-1.60 (m, 7 H); ^{13}C NMR δ 170.6, 136.5, 126.6, 79.3, 68.1, 67.4, 37.2, 32.0, 26.9, 26.0, 21.3; IR ($CDCl_3$) 2949, 2870, 1728, 1372, 1249, 1067, 1030; MS: m/z 196 (M^+, 0.2%), 154 (22), 136 (50), 126 (46), 110 (38), 94 (22), 91 (27), 84 (27), 55 (32), 43 (100).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.21; H, 8.35.

Spiro [5,5] (6*R, 9*R**)-9-acetoxy-1-oxa-7-undecene (20).** The same experimental procedure as for **19** was employed. Chromatography afforded **20** in 82% yield. ^{1}H NMR δ 6.04 (d, J = 10.2 Hz, 1 H), 5.79 (dd, J = 10.2, 3.6 Hz, 1 H), 5.27 (m, 1 H), 3.69 (m, 2 H), 2.12 (m, 1 H), 2.05 (s, 3 H), 1.93-1.53 (m, 9 H); ^{13}C NMR δ 170.6, 135.4, 127.4, 70.0, 68.2, 61.7, 34.8, 29.4, 25.7, 25.0, 21.3, 19.1; IR ($CDCl_3$) 2942, 2868, 1727, 1372, 1250, 1076, 1040; MS: m/z 210 (M^+, 1%), 150 (64), 140 (23), 124 (29), 94 (100), 91 (25), 66 (23), 55 (36), 43 (95), 41 (38).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.59; H, 8.55.

Spiro [4,6] (5*R, 8*R**)-8-acetoxy-1-oxa-6-undecene (21).** $Pd(OAc)_2$ (9 mg, 0.039 mmol), benzoquinone (170 mg, 1.58 mmol) and the dienol **17** (120 mg, 0.79 mmol) were dissolved in acetone / HOAc (2 mL, 4 : 1) and stirred for 100 h at ambient temperature. Ether (15 mL) was added and the resulting solution was washed with aqueous NaOH (2 M, 2x4 mL) and brine (3 mL). The solution was dried with $MgSO_4$, the solvent was evaporated and the residue subsequently chromatografied on silica. Eluation with pentane / ether (75 : 25) gave a 88 : 12 mixture of **21** and **22** (100 mg, 0.476 mmol, 60%). ^{1}H NMR δ 5.73 (d, J = 12.2 Hz, 1 H), 5.63 (dd, J = 3.5, 12.2 Hz, 1 H), 5.47 (m, 1 H), 3.83 (m, 2 H), 2.05 (s, 3 H), 1.99-1.66 (m, 10 H); ^{13}C NMR δ 170.0, 138.4, 131.1, 83.7, 72.0, 66.7, 37.6, 36.6, 32.5, 25.7, 21.2, 20.0; IR ($CDCl_3$) 2943, 2869, 1728, 1450, 1373, 1252, 1093, 1030; MS: m/z 210 (M^+, 0.6%), 150, (74), 123 (28),97 (33), 81 (28), 79 (29), 55 (42), 43 (100), 41 (35).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.65.

Spiro [4,6] (5*R, 8*S**)-8-acetoxy-1-oxa-6undecene (22).** The same experimental procedure as for **21** was used but Li_2CO_3 (170 mg, 2.36 mmol) was also added. After 36 h reaction time was the reaction mixture subjected to the same work-up as described above. Chromatography gave a 17 : 83 mixture of **21** and **22** (90 mg, 0.428 mmol, 54%). ^{1}H NMR δ 5.77 (d, J = 12.2 Hz, 1 H0, 5.47 (dd, J = 2.6, 12.2 Hz, 1 H), 5.38 (m, 1 H), 3.86 (m, 2 H), 2.05 (s, 3 H), 1.99-1.81 (m, 6 H), 1.80-1.63 (m, 4 H); ^{13}C NMR δ 170.3, 138.6, 130.3, 85.5, 73.3, 66.8, 37.4, 36.4, 33.3, 25.9, 22.1, 21.2; IR ($CDCl_3$) 2937, 2864, 1728, 1448, 1373, 1252, 1202, 1104, 1028; MS: m/z 210 (M^+, 0.7%), 150 (78), 123 (26), 107 (24), 97 (32), 81 (29), 79 (28), 55 (43), 43 (100), 41 (36).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.33; H, 8.75.

Spiro [5,6] (6*R, 9*R**)-9-acetoxy-1-oxa-7-dodecene (23).** The same experimental procedure as for **21** was used. After 100 h the reaction mixture was subjected to the same work-up as described for **21**. Chromatography gave **23** (132 mg, 0.589 mmol, 82 %). ^{1}H NMR δ 5.80 (dd, J = 3.0, 12.2 Hz, 1 H), 5.68-5.55 (m, 2 H), 3.66 (m, 2 H), 2.20 (m, 1 H), 2.05 (s, 3 H), 1.85 (m, 1 H), 1.79-1.46 (m, 9 H), 1.40 (m, 1 H); ^{13}C NMR δ 170.1, 136.7, 132.8, 73.9, 73.3, 62.1, 37.8, 37.7, 32.8, 25.9, 21.2, 20.8, 19.1; IR ($CDCl_3$) 2941, 2864, 1724, 1443, 1373, 1249, 1206, 1090, 1070, 1028; MS: m/z 224 (M^+, 0.3%), 182 (26), 164 (61), 123 (20), 108 (32), 81 (26), 55 (51), 43 (100), 41 (40).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.59; H, 9.15.

Spiro [5,6] (6*R, 9*S**)9-acetoxy-1-oxa-7-dodecene (24).** The same experimental procedure as for **22** was used. After 72 h the reaction mixture was subjected to the same work-up as described for **22**. Chromatography gave **24** (75%). ^{1}H NMR (300 MHz) δ; 5.88 (dd, 1 H), 5.68 (m, 1 H), 5.40 (m, 1 H), 3.77 - 3.69 (m, 2 H), 2.36 - 1.30 (m, 15 H).

Spiro [4,5] (5*R, 8*S**)-8-chloro-1-oxa-6-decene (25).** $Pd(OAc)_2$ (8.1 mg, 0.036 mmol), benzoquinone (160 mg, 1.45 mmol) and Li_2CO_3 (160 mg, 2.17 mmol) were dissolved in aceton / HOAc (2 mL, 4 : 1). To this solution were then added the dienol **15** (110 mg, 0.796 mmol, dissolved in 1 mL acetone) and LiCl (62 mg, 1.45 mmol, dissolved in 1 mL HOAc) during 16 h. 1 h after the addition was completed ether (15 mL) was added and the resulting solution was washed with aqueos NaOH (2 M, 2x4 mL) and brine (3 mL). The solution was dried with $MgSO_4$, the solvent was evaporated and the residue subsequently Kugelrohr distilled under reduced pressure (0.01 mmHg, oven temperature 100 °C) to give **25** (100 mg, 0.579 mmol, 73%). ^{1}H NMR δ

5.81 (dd, J = 3.6, 9.7 Hz, 1 H), 5.70 (d, J = 9.7 Hz, 1 H), 4.52 (m, 1 H), 3.88 (t, J = 6.6 Hz, 2 H), 2.17-1.92 (m, 5 H), 1.86-1.69 (m, 2 H), 1.62 (m, 1 H); ^{13}C NMR δ 135.2, 128.6, 79.2, 67.4, 54.4, 36.9, 31.4, 30.9, 25.9; IR ($CDCl_3$) 2952, 2869, 1438, 1394, 1228, 1060, 1039; MS: m/z 172 (M^+, 2%), 144 (28), 137 (100), 95 (42), 91 (48), 77 (38), 67 (41), 41 (57), 39 (70).

Anal. Calcd. for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.78; H, 7.65.

Spiro [5,5] (6*R, 9*S**)-9-chloro-1-oxa-7-undecene (26).** The same experimental procedure as for **25** was used. Kugelrohr distillation at 0.1 mmHg and 200°C afforded **26** in 70% yield. ^{1}H NMR δ 5.96 (d, J = 10.2 Hz, 1 H), 5.85 (dd, J = 3.1, 10.2 Hz, 1 H), 4.51 (m, 1 H), 3.72 (m, 2 H), 2.20-1.99 (m, 3 H), 1.79-1.48 (m, 7 H); ^{13}C NMR δ 133.6, 129.7, 69.8, 61.7, 55.0, 34.5, 30.1, 29.4, 25.7, 18.9; IR ($CDCl_3$) 2942, 2868, 1441, 1230, 1082, 1044, 1029; MS: m/z 186 (M^+, 3%), 151 (100), 124 (32), 102 (34), 91 (38), 77 (33), 68 (47), 41 (57), 39 (49).

Anal. Calcd. for $C_{10}H_{15}ClO$: C, 64.34; H, 8.10. Found: C, 64.58; H, 8.15.

Spiro [4,6] (5*R, 8*S**)-8-chloro-1-oxa-6-undecene (27).** $Pd(OAc)_2$ (9 mg, 0.039 mmol), LiCl (60 mg, 1.41 mmol), Li_2CO_3 (170 mg, 2.36 mmol), benzoquinone (170 mg, 1.58 mmol) and **17** (120 mg, 0.788 mmol) were dissolved in acetone / HOAc (2 mL, 4 : 1). After 72 h at 35°C the reaction mixture was diluted with ether (5 mL) and washed with aqueos NaOH (2x3 mL, 2 M), brine (3 mL) and dried with $MgSO_4$. Evaporation and subsequent chromatography of the residue gave **27** (59 mg, 0.316 mmol, 40%) ^{1}H NMR δ 5.74 (br s, 2 H), 4.63 (ddd, J = 9.3, 3.0, 1.6 Hz, 1 H), 3.94-3.80 (m, 2 H), 2.21-1.80 (m, 8 H), 1.75-1.63 (m, 2 H); ^{13}C NMR δ 139.6, 131.2, 85.0, 66.9, 58.7, 37.5, 37.0, 36.5, 26.0, 22.7; IR ($CDCl_3$) 2936, 2863, 1447, 1248, 1222, 1071, 1049; MS: m/z 224 (M^+, 5%); 151 (100), 123 (75), 91 (45), 79 (49), 55 (48), 53 (46), 41 (56), 39 (63).

Anal. Calcd. for $C_{10}H_{15}ClO$: C, 64.34; H, 8.10. Found: C, 64.43; H, 8.23.

Spiro [5,6] (6*R, 9*S**)-9-chloro-1-oxa-7-dodecene (28).** The same experimental procedure as for **27** was used. Chromatography gave **28** (87 mg, 0.433 mmol, 60%) ^{1}H NMR δ 5.85 (br s, 2 H), 4.63 (ddd, J = 9.3, 4.3, 1.9 Hz, 1 H), 3.72 (app t, J = 4.8 Hz, 2 H), 2.15-1.93 (m, 3 H), 1.87-1.42 (m, 9 H); ^{13}C NMR δ 136.3, 132.6, 75.7, 61.8, 58.4, 37.5, 36.8, 34.6, 25.8, 21.4, 19.6; IR ($CDCl_3$) 2939, 2964, 1444, 1375, 1242, 1196, 1108, 1087, 1018; MS: m/z 224 (M^+, 8%), 165 (98), 109 (40), 91 (42), 81 (100), 79 (44), 55 (69), 53 (41), 41 (68), 39 (48).

Anal. Calcd. for $C_{11}H_{17}ClO$: C, 65.83; H, 8.54. Found: C, 65.69; H, 8.43.

π-Allyl Complex 29. To dienol (**15**) (0.138 g, 1.0 mmol) in THF (20 mL) at 0 °C was added $PdCl_2(CH_3CN)_2$ (0.259 g, 1.0 mmol) together with K_2CO_3 (0.145 g, 1.05 mmol). The mixture was stirred for 30 min at 0 °C and left in a refridgerator over nigth. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (120 mL) and washed with water (10 mL). The water was back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were evaporated to give a yellow solid which was dissolved in a small amount of CH_2Cl_2 and run through a short flash column (ether). Complex **29** was obtained as yellow crystals in 40% yield. ^{1}H NMR (400 MHz) δ 5.47 (dt, J = 0.7, 6.4 Hz, 1 H), 5.20 (m, 1 H), 4.83 (d, J = 6.4 Hz, 1 H), 3.92 (m, 1 H), 3.76 (m, 1 H), 2.42 (m, 1 H), 2.30 (m, 1H), 2.06-1.84 (m, 4 H), 1.56-1.42 (m, 2 H); ^{13}C NMR (100.5 MHz) δ 100.6, 81.8, 81.6, 81.1, 68.2, 37.5, 35.0, 26.1, 25.5.

3,4-Dehydro-β-ionone (30). A refluxing solution of β-ionone (3.84 g) and N-bromo-succinimide (46 g) in dry CCl_4 (180 mL) in a 250 mL round bottomed flask (Pyrex) was irradiated with a tungsten lamp (100 W) for two hours. After cooling to room temperature the precipitate was filtered off. Anhydrous sodium carbonate (5.2

g) and DMF (50 mL) were added to the mother liquid which was stirred over night at room temperature. The bulk of the CCl_4 was distilled off. Then the reaction mixture was cooled to room temperature, diluted with ether (300 mL) the sodium carbonate was filtered off and the mother liquid was washed with 5% aqueous HCl (2 x 100 mL), brine (100 mL) and finally dried over $MgSO_4$. Evaporation of the solvent by rotary evaporator gave a brown liquid which was purified by flash chromatography, using pentane:ether 90:10 as eluent, giving the product as a light-brown liquid (2.95 g, 77%). Spectral data were in accord with those reported in ref. 8. ^{1}H NMR δ 7.27 (d, J = 16.6 Hz, 1 H), 6.2 (d, J = 6.38 Hz, 1 H), 5.87 (bs, 2 H), 2.31 (s, 3 H), 2.12 (d, J = 2.07 Hz, 2 H), 1.91 (s, 3 H), 1.08 (s, 3 H),; MS: m/z 190 (M^+, 11%), 175 (33), 157 (5.2), 147 (10), 130 (14), 115 (13), 91 (19), 43 (100).

7,8-Dihydro-3,4-dehydro-β-ionone (31). Dehydro-β-ionone **30** (1.0 g, 5.3 mmol) and Ph_3SnH (5.0 g, 14 mmol) were dissolved in dry benzene (45 mL) in a 250 mL round bottomed flask fitted with a reflux condenser The whole apparatus was covered with alumina foil to avoid exposure to light. The reaction mixture was refluxed under N_2 atmosphere for six days. After cooling to room temperature, methanol was added (80 mL) and the reaction mixture was stirred for four hours at room temperature, then it was filtered through celite and the solvent was removed by rotary evaporator. Bulb-to-bulb distillation (90 °C / 0.06 mmHg) afforded **31** (0.71 g, 72%). Spectral data were in accord with those reported in ref. 9. ^{1}H NMR (400 MHz) δ 5.72 (dt, J = 9.5, 1.6 Hz, 1 H), 5.64 (m, 1 H), 2.51 (m, 2 H), 2.35 (m, 2 H), 2.15 (s, 3 H), 2.02 (dd, J = 4.2, 1.6, Hz, 2 H), 1.78 (s, 3 H), 0.97 (s, 6 H); ^{13}C NMR (100.5 MHz) δ 138.0, 129.2, 128.7, 125.5, 123.5, 43.7, 39.9, 34.4, 29.8, 26.2 (2 C), 22.2, 18.0; IR (neat) 3033 (m), 2957 (s), 1716 (s), 1359 (s), 1160 (m), 723 (m); MS: m/z 192 (M^+, 6.9%), 177 (2), 133 (13), 121 (26), 105 (20), 91 (24), 77 (15), 43 (100).

7,8-Dihydro-3,4-dehydro-β-ionol (32). To 7,8 -Dihydro-3,4-dehydro-β-ionone (**31**) (0.71 g, 3.69 mmol) was added a solution of MeOH (20 mL), water (2 mL) and NaOH (2 M, 0.1 mL). To the stirred solution was added sodium borohydride (0.18 g, 4.76 mmol) in small portions. The reaction was stirred at room temperature for 30 min. By that time the reaction was complete according to TLC. Acetone (5 mL) was added to the mixture to destroy the excess $NaBH_4$. The solvents were removed by rotary evaporator and the residue was dissolved in ether (75 mL) washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by elution through a short column of silica. (pentane : ether, 1:1) The alcohol (**32**) (0.64 g, 89%) was obtained as a colorless liquid. ^{1}H NMR (400 MHz) δ 5.74 (dt, J = 9.4, 1.7 Hz, 1 H), 5.62 (m, 1 H), 3.83 (m, app hex, J = 6.0 Hz, 1 H), 2.28-2.19 (m, 1 H), 2.13- 2.04 (m, 1 H), 2.0 (dd, J = 4.3, 1.8 Hz, 2 H), 1.72 (s, 3 H), 1.65-1.5 (m, 2 H), 1.22 (d, J = 6.1 Hz, 3 H), 0.98 (s, 6 H); ^{13}C NMR (100.5 MHz) δ 139.2, 129.4, 124.8, 123.2, 68.6, 40.0, 39.2, 34.4, 26.3, 24.6, 23.4, 18.5; IR (neat) 3354 (vs), 3032 (m), 2964 (s), 1465 (m), 1128 (m), 725 (m); MS m/z 194 (M^+, 19%), 121 (41), 119 (100), 105 (25), 91 (25), 77 (12), 45 (23).

π–Allyl Complex 33. To the dienol, **32** (0.377 g, 1.03 mmol) in THF (20 mL) was added $PdCl_2(PhCN)_2$ (0.743 g, 1.03 mmol) followed by K_2CO_3 (0.283 g, 1.08 mmol) at room temperature. The mixture was stirred under N_2 for two hours at room temperature, then put into the refrigerator over night. The solvent was removed *in vacuo*. The remaining solid was dissolved in CH_2Cl_2 (45 mL) and washed with water (6 mL). The aqueous phase was back extracted with CH_2Cl_2 (30 mL) and the solvent of the combined organic phases was evaporated

by rotary evaporator. The remaining solid was rinsed with n-hexane (4 x 5 mL) the π-allyl complex was obtained quantitatively. It was analyzed without recrystallization in order to see the diastereomeric ratio. By ^{1}H NMR the ratio was determined to 10:1. ^{1}H NMR δ **major isomer (33a)**: 5.49 (m, 1 H, π-allyl, overlapped by other isomer), 4.58 (m, 1 H), 4.14 (m, 1 H), 2.8-3.0 (m, 1 H, overlapped by other isomer), 2.51 (m, 1 H), 1.97 (m, 1 H), 1.56 (d,2 H), 1.45 (s, 3 H), 0.85 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR δ 102.6, 102.0, 90.5, 77.5, 68.1, 41.2, 35.8, 35.1, 34.4, 24.2, 23.6, 20.4, 19.1. **minor isomer (33b)**: ^{1}H NMR δ 5.49 (m, 1 H, p-allyl, overlapped), 4.65 (m, 1 H), 4.23 (m, 1 H), 2.8-3.0 (m, 1 H, overlapped), 2.42 (m, 1 H), 2.08 (m, 1 H), 1.58 (d, 2 H), 1.41 (s, 3 H), 0.88 (s, 3 H), 0.85 (s, 3 H).

Spiro [4,5] (2*R, 5*R**, 8*R**)-8-acetoxy-2,6,10,10-tetramethyl-1-oxa-6-decene (34)**. To a stirred solution of π-allyl complex **33** (335 mg; 0.5 mmol) in acetic acid (2 mL) was added a solution-suspension of AgOAc (183 mg, 1.1 mmol) in acetic acid (3 mL). The mixture was stirred for 20 min and then a solution of *p*-benzoquinone (216 mg, 2.0 mmol) in acetic acid (3 mL) was added. The reaction turned dark brown and was stirred for 8 h at room temperature. Brine (4 mL) was added and the mixture was extracted with pentane:ether, 9:1 (4 x 15 mL). The combined organic layers were washed with water (15 mL), saturated Na_2CO_3-solution (2 x 4 mL), 2 M NaOH (3 mL) and brine (4 mL) followed by drying ($MgSO_4$). The solvent was removed by rotary evaporator to give the product (184 mg, 73 %), which was contaminated with some elimination product (diene). Flash chromatography (pentane-ether 90:10) on silica afforded 106 mg, 42 % of pure product as a mixture of diastereoisomers. **Major isomer**: ^{1}H NMR (400 MHz) δ 5.34 (m, 1 H), 5.16 (m, 1 H), 4.21-4.09 (m, 1 H), 2.06-1.36 (m, 6 H), 2.02 (s, 3 H), 1.84 (dd, J = 14.9, 6.0 Hz, 1H), 1.78 (t, J = 1.5 Hz, 3 H), 1.26 (d, J = 5.7 Hz, 3 H), 1.02 (s, 3 H), 0.88 (s, 3 H); **Minor isomer**: ^{1}H NMR (400 MHz) δ (Important peaks) 5.31 (m, 1 H), 5.28 (m, 1 H), 2.03 (s, 3H), 1.77 (t, J = 1.6 Hz, 3 H), 1.00 (s, 3 H), 0.91 (s, 3 H).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.21.

Spiro [4,5] (2*R, 5*R**, 8*R**)-8-hydroxy-2,6,10,10-tetramethyl-1-oxa-6-decene (35)**. The allylic acetate (**34**) (0.095 g, 0.38 mmol) was dissolved in 2 M NaOH (1.88 mL) and MeOH (7.5 mL) and heated to 60 °C for 20 min. and cooled to room temperature. The solvent was removed *in vacuo*. Ether (75 mL) was added and the solution was washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Flash chromatography on silica (pentane-ether 50:50) afforded the alcohol as a colorless oil with a strong smell in 85% yield. **Major isomer**: ^{1}H NMR (400 MHz) δ 5.33 (m, 1 H), 4.25-4.06 (m, 2 H), 2.10-1.36 (m, 6 H), 1.74 (dd, J = 2, 1.5 Hz, 3 H), 1.26 (d, J = 6.0 Hz, 3 H), 0.95 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (100.5 MHz) δ 143.3, 124.8, 88.5, 77.02, 65.9, 45.1, 39.2, 34.4, 31.2, 24.8, 22.1, 20.6, 18.0.

Spiro [4,5] (2*R, 5*R**)-2,6,10,10-tetramethyl-1-oxa-8-oxo-6-decene (Theaspirone, 1)**. To a solution of the allylic alcohol (**35**) (0.052 g, 0.25 mmol) in CH_2Cl_2 (10 mL) was added MnO_2 (0.248 g, 2.85 mmol). The mixture was stirred at room temperature over night. Ether (70 mL) was added and the solution was washed with brine (15 mL). The aqueous layer was back extracted with ether (25 mL). The combined organic layers were dried ($MgSO_4$). Evaporation of the solvent gave theaspirone (47 mg, 90% yield, containing 7% of the 2S*,5R* diasteroisomer) as a colorless oil with a strong smell. Spectral data were in accord with those reported in ref. 12. **Major isomer (1)**: ^{1}H NMR (400 MHz) δ 5.72 (m, 1 H), 4.21 (m, 1 H), 2.40 (dd, J = 17, 0.7 Hz, 1 H), 2.33 (ddd, J = 13.5, 8.5, 0.7 Hz, 1 H), 2.21 (dd J = 17, 1.2 Hz, 1 H), 2.03 (dddd, 11.8, 8.0, 5.3, 1.0 Hz, 1 H), 1.99

(dd, J = 1.2, 0.5 Hz, 3 H), 1.80 (ddd, J = 8.2, 12.0, 13.5 Hz, 1 H), 1.50 (tdd, J = 11.8, 10.5, 8.3 Hz, 1 H), 1.31 (d, J = 6.0 Hz, 3 H), 1.02 (s, 3 H), 0.948 (s, 3 H); ^{13}C NMR (100.5 MHz) δ 198.3, 168.2, 124.8, 88.4, 77.6, 50.2, 40.7, 34.2, 32.6, 24.3, 22.9, 20.4, 18.9; IR ($CDCl_3$) 2974 (m), 1660 (s), 1085 (m). **Minor isomer**: ^{1}H NMR (400 MHz) δ (Resolved peaks) 5.76 (m, 1 H), 1.97 (dd, J = 1.2, 0.5 Hz, 1 H).

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References and Notes

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