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Palladium Mediated Substitutions and Rearrangements in Spiro[4,4]nonanes.

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Abstract:. The two-step $NaBH_4/CeCl_3$ 1,2-reduction of spiro[4,4]nonane-2,7-diene-1,6-dione gave a *trans*-alcohol as a first product which reacted further to the corresponding *cis,trans*-diol. Pd(II)-catalysis was used to effect an allylic rearrangement from the 1,6-diacetate to the corresponding 2,7-diacetate. Both diacetates were substrates for Pd(0)-catalyzed allylic alkylations. The relative stereochemistry was retained.

Introduction

Spirocyclic structural units are present in a number of natural products, and several approaches have been developed for the synthesis of spiranes as intermediates in total syntheses of natural products.[1] Spirane skeletons composed of small to medium sized rings are rigid and confer stiffness onto the molecule in which they are embedded. Such structures would appear to be useful for relative fixation of the geometry of pharmacophoric groups in bioactive molecules, or as appropriately substituted ligands for organometallic complexes.

There are several methods available for the construction of spirane systems. More recent methods include palladium induced spiroannelations,[2] nickel catalyzed spiroannelations,[3] radical promoted cyclizations,[4] rearrangement reactions,[5] and rhodium-catalyzed hydroacylations.[6] We have reported on spiroannelation by carbenoid rhodium insertion into C-H bonds.[7] Both Pd-catalysis,[8] and Ru(II)-catalyzed ring closing metathesis,[9] can be used to effect spiroannelation onto dihydropyrazines.

In contrast to synthetic procedures, relatively little information is available on carbosubstitutions and transformations in spiranes. Simple symmetrical systems such as the spiro[4,4]nonane system have been studied in connection with C_2-symmetry and chiroptical properties; preparations involving chemical or enzymatic resolution of oxo or hydroxy derivatives have provided single enantiomers of the corresponding 1,6-diene.[10,11] Preparations of the spiro[4,4]nona-1,3-diene, the 1,3,7-triene and the tetraene have also been described.[12] Benzo-fused analogues such as spirobis(indenes) have been prepared enatiomerically pure.[13]

Results and discussion

We have initiated work with emphasis on transition metal catalyzed transformations in cyclospiranes, and herein we report results from studies with spiro[4,4]nona-2,7-diene-1,6-dione (**2**) as substrate (Scheme 1).

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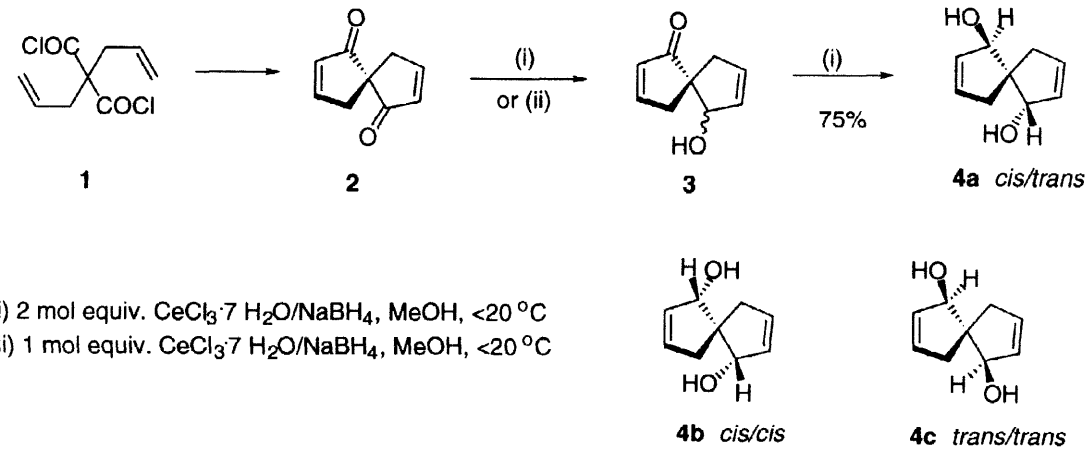
The dione **2** was available by Friedel-Crafts acylation of diallylated malonic acid dichloride.[12] For the π-allyl substitution reactions the diketone **2** was to be reduced to a diallylic alcohol. Three sets of enantiomeric pairs of diols can be formed in the reduction of the diketone **2**, *viz.* the *cis,trans*-diols **4a**, the *cis,cis*- and the *trans,trans*-diols **4b** and **4c** (Scheme 1). Sodium borohydride and cerium trichloride in methanol was used to effect selective 1,2-reduction. By keeping the temperature below 20 °C the reduction could be controlled to almost exclusive formation of the *cis,trans* isomer **4a** which was isolated in 85% yield. At higher temperatures mixtures of the stereoisomers were formed; flash chromatograpy allowed separation of the *cis,trans* isomer **4a** from the mixture of the other two isomers **4b** and **4c**. Previous work with aluminum hydride as reducing agent had led to isolation of **4a** in 30% yield.[12] In the past, reductive studies have mainly been run on the saturated spiro[4,4]nonane-1,6-dione system which furnished exclusively the *cis,cis*[4,4]nonane-1,6-diol isomer when lithium *tert*-butyldiisopropylaluminum hydride was the reducing agent,[10] whereas reductions with LAH or Red-Al^R yielded mixtures of the *cis,cis*- and the *trans,trans*-1,6-diols.[14]



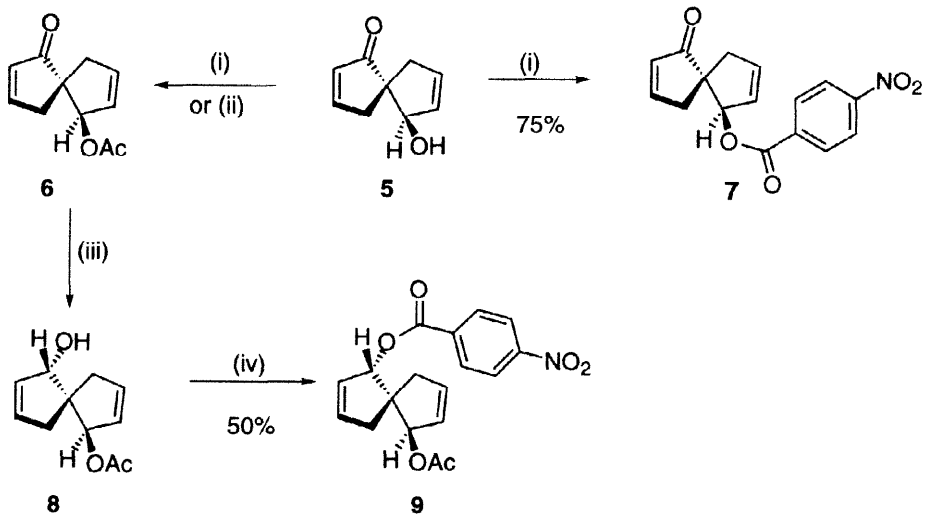
Scheme 1

The structural assignment of the diol as the *cis,trans* product **4a** was based on NMR data. The isomers **4b** and **4c** have C_2-symmetry and hence the NMR signals from both rings coincide. In the *cis,trans* isomer **4a**, however, the hydrogens as well as the carbons in the two rings are all magnetically nonequivalent. Hence there is a set of signals from each ring unless there is some partial overlapping of the signals.

The reduction of the two carbonyl groups is a two-step process. Using one equivalent of the reducing agent below 20 °C, the main product was a monohydroxy ketone which was formed together with the diol **4a** (Scheme 1). The monohydroxy ketone **3** was difficult to separate from unreacted diketone **2** on chromatography, but this mixture was readily separated from the diol **4a**. Treatment of the mixture with acetic anhydride gave a monoacetate which was separated from the diketone **2** by chromatography (Scheme 2). NMR techniques failed to identify the stereochemistry of the oily acetate. Acylation of the mixture was therefore repeated using *p*-nitrobenzoyl chloride. The crystalline benzoate was isolated by chromatography. A single crystal X-ray analysis showed the product to have the *trans* structure **7** (Fig. 1).

The monoacetate **6** was subsequently hydrolyzed back to the hydroxyketone **5** which was subjected to reductive conditions as above to furnish the *cis,trans*-diol **4a**. The monoacetate **6** was also chemoselectively reduced by the cerium trichloride-sodium borohydride reagent to a monoacetoxy hydroxy spirane which was converted into a crystalline *p*-nitrobenzoate. A single crystal X-ray analysis showed the product to have the *cis,trans* structure **9** (Fig. 2).

Formation of the *trans* structure **5** requires that the addition of the hydride to the carbonyl carbon is from the more shielded face. This may be rationalized as to proceed by initial complexation of the reducing agent to the two close carbonyl oxygens before intramolecular hydride transfer. Reduction of the acetate **6** to the hydroxy acetate **8** is consistent with hydride transfer to the carbonyl carbon from the less hindered face. Since reduction of the hydroxy ketone **5** also yielded the *cis,trans*-diol, it is suggested that the OH-group is blocked as a metal complex and hence the hydride is transferred from the less shielded face.



(i) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 3 h; (ii)*p*-$NO_2C_6H_4COCl$, DMAP, CH_2Cl_2, 20 °C, 2h; (iii) 1 mol equiv. $CeCl_3 \cdot 7\ H_2O/NaBH_4$, MeOH, <20 °C, 0.5 h, (iv) as (iii), but 1 h.

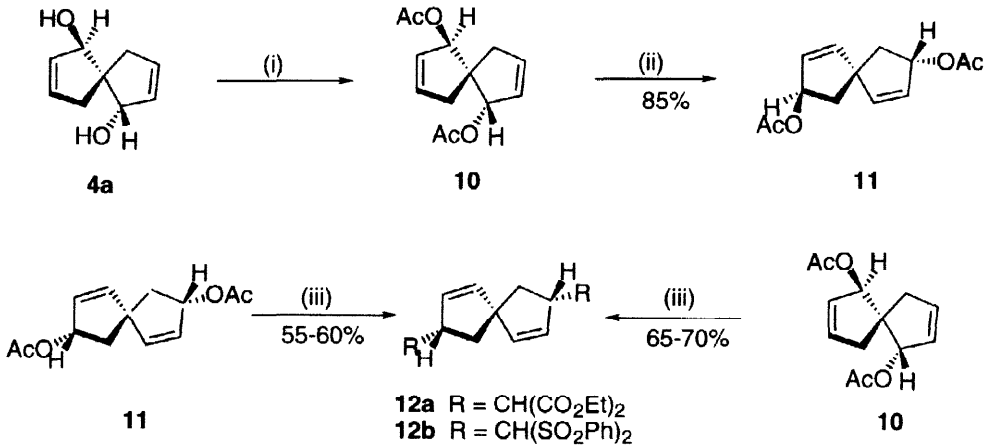
Scheme 2

Pd-mediated π-allyl transformations have been carried out with the diacetate **10** derived from the diol **4a**. A 1,3-acetate shift was effected by the $PdCl_2(PhCN)_2$ reagent in THF. The rearrangement with acetate transfer proceeded from the more shielded α-position next to the spirocenter to the less shielded β-position to furnish the diacetate **11**. It was anticipated that Pd(II) as an electrophile would initiate the rearrangement by complexation with the double bond at a distance from the spirocenter, and that this would result in an intramolecular 1,3-shift of the acetoxy group. The rearrangement proceeded with full retention of the relative stereochemistry, the product being the *cis,trans* isomer **11**.

Pd(0)-catalysis was used to effect carbosubstitution reactions in the diacetate **11** with the soft nucleophiles sodium malonate or the metallated derivative of di(phenylsulfonyl)methane. The catalyst was generated *in situ* from $Pd_2(dba)_3 \cdot CHCl_3$ and 1,2-bis(diphenylphosphino)ethane (dppe). The coupling reaction with the 2,7-diacetate **11** proceeded to the extent of 60% with sodiomalonate in THF solution. NMR spectra

were consistent with retention of relative stereochemistry, *viz.* with the *cis,trans* product **12a**. The regioisomeric 1,6-diacetate **10** was also dicoupled under the same conditions to furnish product **12a**. The reaction is initiated by metal coordination to the double bond before the acetate becomes a leaving group. The regiochemistry is in accordance with the normal addition of a nucleophile to the less substituted or less shielded allylic terminal carbon. DME was a better solvent than THF for reactions with the sodium salt of di(phenylsulfonyl)methane because of higher solubility of the salt in this solvent; the yield of the coupled product **12b** was 65% from the 2,7-diacetate **11**.

In conclusion we have deduced the stereochemical course in the 1,2-reduction of spiro[4,4]nona-2,7-diene-1,6-dione (**2**), and shown that allylic acetates of either regiochemistry are substrates for Pd-mediated carbylations in spiranes.



(i) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 3 h; (ii) $PdCl_2(PhCN)_2$, THF, 20 °C, 14 h;
(iii) $Pd_2(dba)_3$, dppe, NaR, THF, 20-50 °C, 2 h

Scheme 3

X-Ray data.

X-ray crystallographic analysis data for the compounds **7** and **9.**

The compounds **7** and **9** crystallized in centric space groups and are thus racemates. In Figs. 1 and 2 (*vide infra*) only one of the enantiomers is shown.

The X-ray data were collected on a Siemens SMART CCD diffractometer[15] using graphite monochromated Mo*K*α radiation (λ = 0.71073 Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[15] Absorption corrections were applied by the use of the SADABS program.[16] The structure was determined and refined using the SHELXTL program package.[17] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen positions were determined from difference Fourier plots and refined with isotropic thermal parameters. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Crystal data for $C_{16}H_{13}NO_5$ (7): M = 299.27, triclinic, P-1, a = 7.080(1), b = 8.239(1), c = 12.998(1) Å, α = 105.08(2), β = 92.84(2), γ = 109.01(2)°, V = 684.6(1) Å^3, Z = 2, D_x = 1.452 Mg m^{-3}, μ = 0.109 mm^{-1}, F(000) = 312, T = 150 K, measured 11259 reflections in 2θ range 3.3 - 80.5°, R_{int} = 0.014. 251 parameters refined against 7312 F^2, R = 0.043 for $I_o > 2\sigma(I_o)$ and 0.055 for all data (residual $\Delta\rho$ < 0.55 e Å^{-3}).

Crystal data for $C_{18}H_{17}NO_6$ (9): M = 343.33, monoclinic, $P2_1/c$, a = 13.152(1), b = 9.250(1), c = 14.077(1) Å, β = 106.47(1)°, V = 1642.2(1) Å^3, Z = 4, D_x = 1.389 Mg m^{-3}, μ = 0.105 mm^{-1}, F(000) = 720, T = 150 K, measured 21321 reflections in 2θ range 3.2 - 66.3°, R_{int} = 0.033. 294 parameters refined against 4868 F^2, R = 0.060 for $I_o > 2\sigma(I_o)$ and 0.087 for all data (residual $\Delta\rho$ < 0.34 e Å^{-3}).

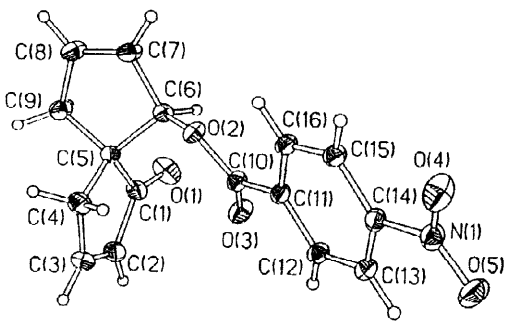


Fig.1

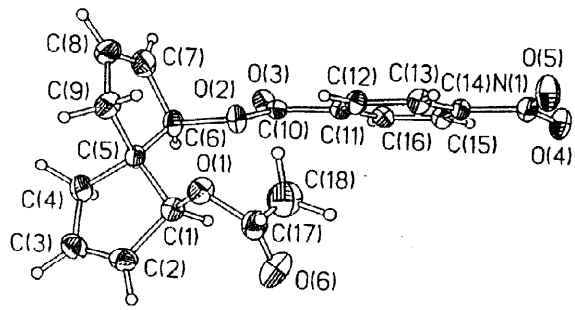


Fig. 2

Fig 1. ORTEP plot of *trans*-6-oxospiro[4,4]nona-2,7-dien-1-yl *p*-nitrobenzoate (**7**). In the thermal-ellipsoid plot of the X-ray structure of compound **7**, ellipsoids are shown a 50% probability. The conformation of the C5-C6 is *ac* the torsion angle C1-C5-C6-O2 being -103.1(1)°

Fig. 2. ORTEP plot of *cis,trans*-spiro[4,4]nona-6-acetoxy-2,7-diene-1-yl *p*-nitrobenzoate (**9**). In the thermal-ellipsoid plot of the X-ray structure of the *cis*-trans compound **9**, ellipsoids are shown at 50% probability. The conformations of the C1-C5 and C5-C6 bonds are *ac* and *sc*, respectively. The torsion angle O1-C1-C5-C6 is 96.0(2)° and the torsion angle C1-C5-C6-O2 is -37.6(2)°.

Experimental.

^{1}H NMR spectra were recorded in $CDCl_3$ at 500, 300 or 200 MHz with Bruker DRX 500, DPX 300 or DPX 200. The ^{13}C spectra were recorded in $CDCl_3$ at 125, 75 or 50 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77.00 ppm) as references. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.).

Solvents were degassed by bubbling argon through them. Dry dichloromethane and NMP were distilled from CaH_2 under argon. Dry THF was distilled from sodium and benzophenone under argon.

cis/trans-Spiro[4,4]nona-2,7-diene-1,6-diol (**4a**). Sodium borohydride (384 mg, 10.15 mmol) was added in portions to a solution of spiro[4,4]nona-2,7-diene-1,6-dione[12] **2** (750 mg, 5.07 mmol) and $CeCl_3 \cdot 7H_2O$ (3.774 g, 10.13 mmol) in methanol (60 mL) at 20 °C. The solution was cooled to keep the temperature inside the flask at 20 °C when $NaBH_4$ was added. The solution was stirred for 2 h at ambient temperature. Water was added and the methanol was evaporated. The solution was extracted with EtOAc (3x), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using EtOAc; yield 578 mg (75%) of a white solid, m.p. 125 °C. Found: C, 70.75; H, 8.02. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. ^{1}H NMR (200 MHz, CD_3OD): δ 2.0-3.0 (m, 4H, CH_2), 3.99 (s, 1H, CH), 4.83 (s, 1H, CH), 5.7-6.1 (m, 4H, CH=). ^{13}C NMR (50 MHz, CD_3OD): δ 39.9 (CH_2), 46.5 (CH_2), 57.4 (C), 77.9 (CH), 84.5 (CH), 132.9 (CH=), 134.2 (CH=), 134.4 (CH=), 136.4 (CH=). MS(EI): *m/z* 152 (M^+, 1), 134 (94), 116 (34), 105 (55), 91 (64), 82 (47), 79 (55), 78 (42), 77 (65), 28 (100).

cis/trans-Spiro[4,4]nona-2,7-diene-1,6-diol (**4a**) can be also made by treating *trans*-6-hydroxyspiro[4,4]nona-2,7-dien-1-one (**5**) with one equivalent of sodium borohydride. Thus a solution of *trans*-6-hydroxyspiro[4,4]nona-2,7-dien-1-one **5** (50 mg, 0.33 mmol) and $CeCl_3 \cdot 7H_2O$ (262 mg, 0.7 mmol) in methanol (3 ml) was treated with sodium borohydride (15 mg, 0.39 mmol) at 0 °C. The mixture was stirred for 20 min at this temperature when TLC monitoring showed the reaction to be complete. The solvent was evaporated at reduced pressure, and the product was purified by flash chromatography using EtOAc; yield 35 mg (70%) of the *title compound* **4a**.

trans-6-Hydroxyspiro[4,4]nona-2,7-dien-1-one (**5**). Sodium borohydride (152 mg, 4 mmol) was added gradually to a solution of spiro[4,4]nona-2,7-diene-1,6-dione **2** (592 mg, 4 mmol) and $CeCl_3 \cdot 7H_2O$ (1.49 g, 4 mmol) in methanol (40) with cooling in order to keep the temperature inside the flask below 20 °C. The mixture was stirred at ambient temperature for 2 h before water was added and the methanol was evaporated. The reaction gave a mixture of spiro[4,4]nona-2,7-diene-1,6-dione (**2**), *trans*-6-hydroxyspiro[4,4]nona-2,7-dien-1-one (**5**) and *cis/trans*-spiro[4,4]nona-2,7-diene-1,6-diol (**4a**). The diol **4a** was separated from the other two spiro compounds using flash chromatography, eluting initially with hexane:EtOAc 1:2, then with EtOAc; yield 150 mg. The starting material and product **5** could not be separated and were isolated as a mixture. The ratio of the compounds **2**:**5** was 2:3 by ^{1}H NMR estimation; yield 376 mg. ^{1}H NMR (200 MHz): δ 2.27-2.29 (m, 2H, CH_2), 2.57-2.69 (m, 1H, one H in CH_2), 2.77 (d, *J* 7.12 Hz, 1H, OH), 3.35-3.46 (m, 1H, one H in CH_2), 4.73-4.79 (m, 1H, CH), 5.66-5.72 (m, 1H, CH=), 5.85-5.90 (m, 1H, CH=), 6.05-6.12 (m, 1H, CH=), 7.70-7.75 (m, 1H, CH=). ^{13}C NMR (50 MHz): δ 38.3 (CH_2), 42.9 (CH_2), 57.8 (C), 80.7 (CH), 131.8 (CH=), 132.2 (CH=), 132.6 (CH=), 164.8 (CH=), 213.5 (CO).

trans-6-Acetoxyspiro[4,4]nona-2,7-dien-1-one (**6**). Acetic anhydride (163 mg, 1.6 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution from the mixture of spiro[4,4]nona-2,7-diene-1,6-dione **2** and *trans*-6-hydroxyspiro[4,4]nona-2,7-dien-1-one **5** (243 mg; ratio 2:3) and DMAP (215 mg, 1.76 mmol) in dry dichloromethane (5 mL) under argon at 0 °C. The solution was stirred at 0 °C for 2 h, washed with aq. $CuSO_4$ (3x), aq. $NaHCO_3$ (2x) and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using hexane:EtOAc 3:1; yield 147 mg of a colourless oil. Found: C, 69.07; H, 6.66. Calc. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. HRMS: *M* 192.0796. Calc. for $C_{11}H_{12}O_3$: 192.0786. ^{1}H NMR (200 MHz): δ 2.33-2.36 (m, 2H, CH_2), 2.66-2.77 (m, 1H, one H in CH_2), 3.10-3.15 (m, 1H, one H in CH_2), 5.67-5.77 (m, 2H, CH= and CHO), 5.99-6.04 (m, 1H, CH=), 6.12-6.18 (m, 1H, CH=), 7.62-7.68 (m, 1H, CH=). ^{13}C NMR (50 MHz): δ 21.3 (CH_3), 39.4 (CH_2), 44.4 (CH_2), 55.6 (C), 82.2 (CH), 128.7 (CH=), 131.8 (CH=), 133.4 (CH=), 161.9 (CH=), 169.4 (CO), 210.1 (CO). MS (EI): *m/z* 192 (M^+, 4), 150 (58), 149 (51), 133 (33), 132 (78), 121 (36), 104 (62), 43 (100).

trans-6-Oxospiro[4,4]nona-2,7-dien-1-yl *p*-nitrobenzoate (**7**): *p*-Nitrobenzoyl chloride (280 mg, 15 mmol) was added to the mixture of the compounds **2** and **5** obtained as above (240 mg) and DMAP (200 mg, 1.65 mmol) in dry dichloromethane (15 mL) at ambient temperature. TLC monitoring showed the reaction to be complete after 3 h. The reaction mixture was extracted with water, dried ($MgSO_4$), the solvent distilled off and the residual material subjected to flash chromatography using hexane:EtOAc 3:1; yield 200 mg. The product was a yellow crystalline material, m.p. 148 °C (from $CHCl_3$). HRMS: *M* 299.0797. Calc. for $C_{16}H_{13}NO_5$: 299.0793. ^{1}H NMR (300 MHz): δ 2.4-2.6 (m, 2H, CH_2), 2.8 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 5.85, 6.1-6.2 (m, 1H, CH=), 5.98 (t., 1H, CHOH), 6.12 (m, 1H, CH=), 6.20 (m, 1H, CH=), 7.70 (m, 1H, CH=), 8.13 and 8.27 (ABA′B′, *J* 9.5 Hz, 4H, C_6H_4). ^{13}C NMR (200 MHz): δ 39, 44 (CH_2), 55 (C_q.), 84 (CHOH), 124, 130, 135, 150 (Ph), 128, 133 (CH=), 163 (CO-O), 212 (C=O). MS(EI): *m/z* 299 (M^+, 7), 300 (2), 77 (30), 104 (73), 132 (84), 150 (100).
The structure was confirmed by a single crystal X-ray analysis (Fig. 1).

cis,trans-6-Acetoxyspiro[4,4]nona-2,7-dien-1-yl *p*-nitrobenzoate (**9**): $CeCl_3 \cdot 7H_2O$ (418 mg) was added to a solution of *trans*-6-acetoxyspiro[4,4]nona-2,7-dien-1-one **6** (80 mg, 0.416 mmol) in MeOH (5 mL), the solution cooled to 0 °C and sodium borohydride (15.83 mg, 0.416 mmol) added slowly at this temperature. The mixture was stirred at ambient temperature for 0.5 h, the solvent distilled off and the product subjected to flash chromatography using hexane:EtOAc 2:1. The product thus obtained contained some of the starting material. Part of the product mixture (50 mg) was dissolved in dichloromethane (5 mL), DMAP (63.44 mg, 0.52 mmol) added and the mixture was stirred for 10 min before *p*-nitrobenzoyl chloride (96.2 mg, 0.52 mmol) was added. The reaction mixture was stirred for 1 h at ambient temperature when TLC monitoring showed the reaction to be complete. The solvent was distilled off, the residual material dissolved in diethyl ether, the solution shaken with $NaHCO_3$, with brine, dried ($MgSO_4$) and the product purified by flash chromatography using hexane:EtOAc 1:1. Product **9** (53 mg) was a white solid, m.p. 149 °C. This

corresponds to an overall yield of 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.0 (s, 3H, CH_3), 2.3-2.4 (d, *J* 15.3 Hz, 1H, CH_2), 2.4-2.5 (s, 2H, CH_2), 2.9-3.0 (d, *J* 15.3 Hz, 1H, CH_2), 5.45 (s, 1H, CHOAc), 5.8 (m, 1H, CH=CH), 6.0 (m, 3H, CH=CH, CHOCO), 6.2 (m, 1H, CH=CH), 8.2 (q, 4H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20(CH_3), 38, 45 (CH_2), 55 (Cq), 80, 86 (CH), 123, 131 (Ar), 127, 128, 136, 139 (CH=CH, Ar), 163, 165 (CO).
The structure has been verified by a single crystal X-ray analysis (Fig. 2).

cis/trans-Spiro[4,4]nona-2,7-diene-1,6-diacetate (**10**). Acetic anhydride (1.074 g, 10.53 mmol) in dry dichloromethane (15 mL) was added dropwise to a solution of *cis/trans*-spiro[4,4]nona-2,7-diene-1,6-diol (667 mg, 4.39 mmol) and DMAP (1.34 g, 10.97 mmol) in dry dichloromethane (15 mL) under argon at 0 °C. The solution was stirred for 2 h at 0 °C, washed with aq. $CuSO_4$ (3x), aq. $NaHCO_3$ (2x) and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using hexane:EtOAc 2:1; yield 964 mg (93%) of a colourless oil. Found: C, 65.66; H, 7.06. Calc. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. ^{1}H NMR (200 MHz): δ 1.97 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.1-2.9 (m, 4H, CH_2), 5.2-6.1 (m, 6H, CH and CH=). ^{13}C NMR (50 MHz): δ 21.3 (CH_3), 38.9 (CH_2), 45.4 (CH_2), 54.5 (C), 79.1 (CH), 84.3 (CH), 128.4 (CH=), 129.7 (CH=), 134.8 (CH=), 137.2 (CH=), 170.0 (CO).

cis/trans-Spiro[4,4]nona-1,6-diene-2,7-diacetate (**11**). *cis/trans*-Spiro[4,4]nona-2,7-diene-1,6-diacetate **10** (410 mg, 1.74 mmol) and $PdCl_2(PhCN)_2$ (100 mg, 0.26 mmol) were dissolved in dry THF (40 mL) under argon and the solution stirred at ambient temperature for 20 h. The solution was evaporated and the crude residual material subjected to flash chromatography using hexane:EtOAc 3:1; yield 349 mg (85%) of a colourless oil, b.p. 228 °C. Found: C, 65.97; H, 6.89. Calc. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. ^{1}H NMR (200 MHz): δ 2.01 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.6-2.5 (m, 4H, CH_2), 5.4-6.1 (m, 6H, CH= and CH). ^{13}C NMR (50 MHz): δ 21.2 (CH_3), 43.1 (CH_2), 44.4 (CH_2), 59.6 (C), 79.1 (CH), 79.3 (CH), 128.7 (CH=), 129.2 (CH=), 143.2 (CH=), 143.7 (CH=), 170.8 (CO). MS(EI): *m/z* 236 (M^+, 1), 176 (14), 134 (100), 116 (56), 105 (24), 43 (62).

Tetraethyl *cis,trans*-spiro[4,4]nona-2,7-diene-2,7-bismalonate (**12a**).
(i). From 2,7-diacetate **11**: $Pd_2(dba)_3$ (108.6 mg, 0.105 mmol) was added to dppe (83.58 mg, 0.21 mmol) in THF (1 mL). The mixture was stirred under argon at ambient temperature for 10 min and then added to a solution of spiro[4,4]nona-2,7-diene-2,7-diacetate **11** (0.5 mL, 2.118 mmol) in THF (5 mL). The mixture was stirred for 10 min before a solution of sodium malonate was added. The malonate solution was prepared from diethyl malonate (1.01 mL, 6.4 mmol) and sodium hydride (55% in oil; 335.12 mg, 7.68 mmol) in THF (5 mL). The resultant solution was stirred at ambient temperature for 1 h, and at 50 °C for 1 h when TLC monitoring showed the reaction to be complete. Water and diethyl ether were added to the cold reaction mixture, the ether phase collected, the water phase extracted with diethyl ether, the combined ether solutions dried ($MgSO_4$) and evaporated. Excess diethyl malonate was removed from the residual material by

distillation (b.p. 50 °C/1 mmHg) and the residual material subjected to flash chromatography using hexane:EtOAc 2:1; yield 0.554 mg (60%) of a colourless oil, b.p. 290 °C. Found: C, 63.59; H, 7.47; Calc. for $C_{23}H_{32}O_8$: C, 63.28; H, 7.36. ^{1}H NMR (500 MHz): δ 1.35 (t, 12H, CH_3), 1.70-2.19 (quartet of multiplets, 4H, CH_2), 3.28 (d, 2H, CH-CO), 3.48 (m, 2H, CH, spiro), 4.27 (q, 8H, CH_2), 5.63-5.73 (m, 4H, vinyl). ^{13}C NMR (75 MHz): δ 14 (s, CH_3), 42 (d, CH_2), 44.6 (d, CH, spiro), 57.3 (d, CH-CO), 61 (s, C_{quat}), 61.3 (s, CH_2), 130, 138 (doublets, CH, vinyl), 168.3 (s, CO). MS(EI): *m/z* 436 (M^+, 4), 276 (63), 235 (54), 203 (76), 161 (80), 131 (100), 116 (52).

(ii). From 1,6-diacetate **10**: The reaction was run under the same conditions as above; yield 70% (GC).

cis/trans-2,7-Bis[di(phenylsulfonyl)methyl]spiro[4,4]nona-1,6-diene (**12b**).

(i) From diacetate **11**. $Pd_2(dba)_3{\cdot}CHCl_3$ (29 mg, 0.028 mmol) and dppe (22 mg, 0.055 mmol) were dissolved in dry THF (2 mL) under argon at ambient temperature and the mixture stirred for 10 min before a solution of *cis/trans*-spiro[4,4]nona-1,6-diene-2,7-diacetate (130 mg, 0.55 mmol) in dry THF (5 mL) was added. The resultant solution was stirred for 10 min at ambient temperature and added slowly by means of a syringe to a stirred suspension of di(phenylsulfonyl)methane (408 mg, 1.37 mmol) and NaH (55% in oil; 56 mg, 1.27 mmol) in dry THF (10 mL). The mixture was stirred at ambient temperature for 1 h and at 50 °C for 1 h. Diethyl ether was added and the solution was washed with water and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using hexane:EtOAc 1:1; yield 214 mg (55%) of a white solid, mp. > 230 °C. Found: C, 59.11; H, 4.79. Calc. for $C_{35}H_{32}O_8S_4$: C, 59.30; H, 4.55. ^{1}H NMR (200 MHz): δ 1.99-2.53 (m, 4H, CH_2), 3.77-3.88 (m, 2H, C<u>H</u>-CH_2), 4.72-4.75 (m, 2H, CH), 5.38-5.63 (m, 4H, CH=), 7.49-7.95 (m, 20H, Ph). ^{13}C NMR (50 MHz,): δ 41.8 (CH_2), 42.3 (CH_2), 43.9 (CH_2), 44.2 (CH_2), 61.4 (C), 85.2 (CH), 85.3 (CH), 126.8, 127.3, 128.6, 128.7, 128.9, 129.4, 133.8, 133.9, 134.2, 137.8, 138.2, 139.0, 139.2, 139.8 (Ar). MS(EI): *m/z* 568 (14), 143 (41), 142 (41), 141 (53), 128 (100), 125 (39), 78 (81), 77 (36).

(ii). From 1,6-diacetate **10**: The reaction was run under the same conditions as above, using DME as solvent; yield 65% (isolated).

References

1. (a) Vandervalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1767-1831; (b) Galvez, J. M. G.; Angers, P.; Canonne, P. *Tetrahedron Lett.* **1994**, *35*, 2849-2852.
2. (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2411; (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635-662; (c) Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y., Liu, F. *Chem. Rev.* **1996**, *96*, 365-393; (d) Grigg, R.; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1996**, *37*, 695-698 and references therein; (e) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595-602; (f) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421-9438; (g) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636-644; (h)

Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813-1819; (i) Wu, G.-z.; Lamaty, F.; Negishi, E. J. Org. Chem. **1989**, 54, 2507-2508.

3. Kong, K.-C.; Cheng, C.-H. *Organometallics* **1992**, *11*, 1972-1975.
4. (a) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806-3814; (b) Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* **1998**, *63*, 3141-3146.
5. (a) Liu, P.-Y.; Wu, Y.-J.; Burnell, D. J. *Can. J. Chem.* **1997**, *75*, 656-664; (b) Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104-110; (c) Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3295-3304; (d) Patra, D.; Ghosh, S. *J. Chem. Soc. Perkin Trans 1* **1995**, 2635-2641.
6. Sattelkau, T; Hollmann, C; Eilbracht, P. *Synlett* **1996**, 1221-1223.
7. Aburel, P. S.; Undheim, K. *Tetrahedron Lett.* **1998**, *39*, 3813-3814.
8. Möller, B.; Undheim, K. *Tetrahedron* **1998**, *54*, 5789-5804.
9. (a) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309-2322; (b) Krikstolaityté, S.; Hammer, K.; Undheim, K. *Tetrahedron Lett.* **1998**, *39*, 7595-7598; (c) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, 53, 10603-10614.
10. Nieman, J. A.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1973-1976.
11. (a) Gerlach, H.; Müller, W. *Helv. Chim. Acta* **1972**, *55*, 2277-2286; (b) Sumiyoshi, M.; Kuritani, H.; Shingu, K. *J. Chem. Soc., Chem. Commun.* **1977**, 812-814; (c) Cram, D. J.; Duuren, B. L. V. *J. Am. Chem. Soc.* **1955**, *77*, 3576-3579.
12. Semmelhack, M. F.; Foos, J. C.; Katz, S. *J. Am. Chem. Soc.* **1973**, *95*, 7325-7336.
13. (a) Brewster, J. H.; Prudence, R. T. *J. Am. Chem. Soc.* **1973**, *95*, 1217-1229; (b) Hill, R. K.; Cullison, D. A. *J. Am. Chem. Soc.* **1973**, *95*, 1229-1239.
14. (a) Srivastava, N.; Mutal, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493-494; (b) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1954**, *76*, 2753-2757; (c) Hardegger, E.; Maeder, E.; Semarene, H. M; Cram, D. J. *J. Am. Chem. Soc.* **1959**, *81*, 2727-2737; (d) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587-1593 (e) Harada, N.; Ai, T.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 232-233.
15. SMART and SAINT Area-detector Control and Integration Software, Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
16. Sheldrick, G. M. *Private communication,* 1996.
17. Sheldrick, G. M. SHELXTL, Version 5. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.