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Enantiocontrolled Formal Total Synthesis of Paeonilactone A and B from (*S*)-(+)-Carvone

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Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

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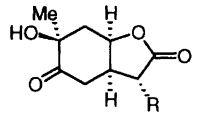
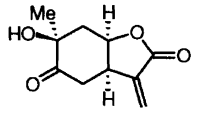
A synthesis of enantiomerically pure lactone **11a** from commercially available (*S*)-(+)-carvone has been developed. The synthesis constitutes a formal synthesis of paeonilactone A and B and involves a stereoselective palladium-catalyzed 1,4-oxylactonization of a conjugated diene to introduce two of the oxygen substituents required for the target.

Paeony root, the root of *Paeonia Albiflora* PALLAS, has been extensively used in traditional Chinese and Japanese treatment of pain mainly in the abdominal region. From this root a number of different constituents have been isolated including paeonilactone A (**1**), B (**2**), and C (**3**).[1]



1 : R=Me
3 : R=CH_2OBz



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Paeonilactone A (**1**) seemed to be a suitable target for our recently developed palladium-catalyzed 1,4-oxylactonization of conjugated dienes.[2] A retrosynthetic analysis is given in Scheme 1 which indicates that diene **4a** is an appropriate starting material for this approach.

The synthesis of **1** has earlier been carried out in racemic[3] as well as enantiospecific[4,5] form. In the previous approaches the oxygens in the 3- and 6-positions of **1** were introduced in a stepwise manner. With the use of our palladium-catalyzed 1,4-addition the oxygens are selectively introduced in the 3- and 6-positions via the oxylactonization reaction.

Results and discussion

The requisite diene acid **4** was prepared according to Scheme 2. The synthesis starts from commercially available (*S*)-(+)-carvone (**5**), which was subjected to a Shapiro reaction[6] to give triene **6** in 77% yield. The triene **6** was transformed to a 1:1 epimeric mixture of the alcohol **7** in 90% yield via a hydroboration–oxidation sequence employing 9-BBN–H_2O_2–NaOH. The direct oxidation of alcohol **7** to the corresponding diene acid **4** is difficult, since aromatization of the ring occurs under such oxidation conditions. Hence, the oxidation of **7** to acid **4** was performed in two steps via the aldehyde. The best conditions for this transformation were found to be Swern oxidation of **7** followed by treatment of the aldehyde produced with Ag_2O under basic conditions.[7] This gave the desired acid **4** in 77% overall yield from **7** together with less than 5% of the corresponding aromatic acid.

The lactonization of diene acid **4** was first performed under conditions giving the *trans* acetate **8** (1:1 mixture of C-7 epimers) in 66% yield (Scheme 3). Oxymercuration[8] of acetate **8** or alcohol **9**, obtained from **8** by methanolysis, was tried for the introduction of the oxygen in the tertiary position required for the target. Unfortunately, only recovered starting material was obtained on attempted oxymercuration of **8** or **9** using either $Hg(OAc)_2$ or $Hg(O_2CCF_3)_2$. Because of these discouraging results we turned our attention to the lactone acetate **10** and lactone alcohol **11** as intermediates to introduce the oxygen into the tertiary position. Alcohol **11** in a mixture with its C-7 epimer has previously been transformed into paeonilactone A (*vide infra*).[4] However, attempts to form the *cis* acetate **10** in the palladium-catalyzed lactonization employing the benzoquinone-based procedure gave a low yield of the desired *cis* acetate, and this route was not considered synthetically useful. One way to obtain the desired alcohol **11** would be to invert the stereochemistry of the

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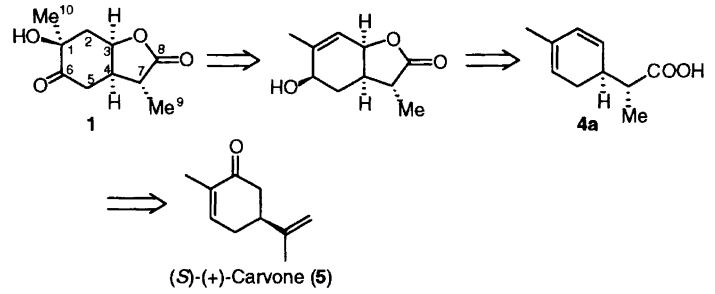
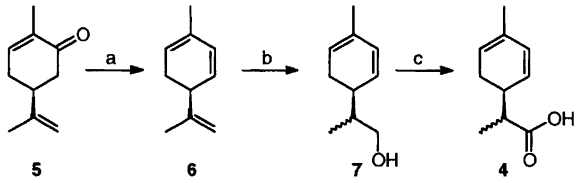


Scheme 1. A retrosynthetic analysis of paeonilactone A.



Scheme 2. (a) (i) $TsNHNH_2$, MeOH, H^+(cat.), (89%), (ii) 3 equiv. MeLi, Et_2O (87%); (b) (i) 9-BBN, THF, (ii) H_2O_2/OH^- (90%); (c) (i) oxalyl chloride–DMSO, CH_2Cl_2 (85%), (ii) $AgNO_3$–OH^-, EtOH (91%).

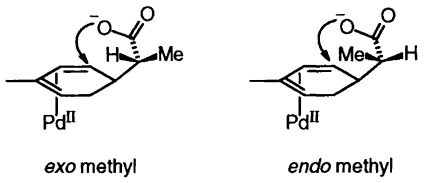


Fig. 1. Transition state structures for the lactonization of the different diastereoisomers of **4**.

alcohol **9** by a Mitsunobu reaction[9] to give, after hydrolysis, the *cis* alcohol **11.** This was tried and afforded **11** and its C-7 epimer in 46% yield from **8** (Scheme 3).

During the work on this project we developed a procedure for the palladium-catalyzed intramolecular 1,4-oxidation of 1,3-dienes utilizing DMSO–O_2 as the reoxidant.[10,11] With this new procedure a high selectivity for *cis*-acetoxylactonization was obtained with cyclohexa-2,4-dienylacetic acid. Applying these conditions to **4** gave the *cis* acetate **10** with the correct stereochemistry of the α-methyl group in 23% yield from the 1 : 1 epimeric mixture of **4** (Scheme 4).

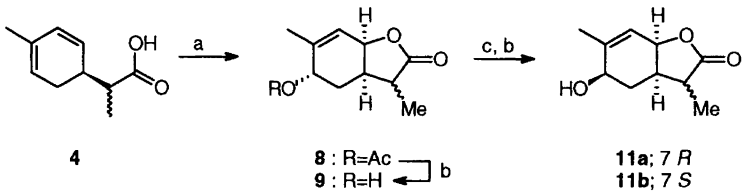
Hydrolysis of the lactone ester **10** gave the lactone alcohol **11a** in 91% yield. It was shown that **11a** was enantiomerically pure (>99% ee) by transformation into the corresponding Mosher ester and subsequent ^1H NMR analysis.

The selective formation of **10** from **4** can be explained according to Fig. 1. It is expected that the isomer with the methyl group pointing away from the cyclohexadiene in the lactonization will react faster than the epimer in which the methyl is pointing towards the cycohexadiene ring.

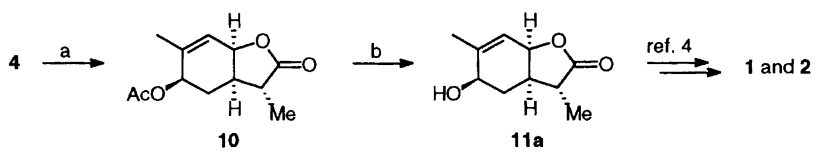
The alcohol **11** has previously been transformed into paeonilactone A and B by treatment with Cl_3CCHO and I_2 to form an iodo (trichloro)acetal.[4] Subsequent reduction of the iodide, opening of the acetal and oxidation gave paeonilactone A in 27% yield from **11**. Bromination of the α-position of the lactone ring followed by elimination of HBr before opening of the acetal and oxidation furnished paeonilactone B.

Conclusions

We have developed a formal total synthesis of paeonilactone A and B starting from commercially available (*S*)-(+)-carvone using aerobic Pd^{II}-catalyzed lactoniz-



Scheme 3. (a) 10% $Pd(OAc)_2$, *p*-BQ, HOAc–acetone (66%); (b) MeOH, K_2CO_3 (88–91%); (c) PPh_3, $EtO_2CN{=}NCO_2Et$, 2,4-dichlorobenzoic acid (58%).



Scheme 4. (a) 10% $Pd(OAc)_2$, LiOAc, DMSO–O_2 (23%); (b) MeOH, K_2CO_3 (91%).

ation in DMSO as a key step. In the synthesis of **11** presented in the literature[4] a 2:1 mixture of **11a**:**11b** was obtained in an overall yield of 11% after eight transformations from (*R*)-(−)-carvone. Our approach using (*S*)-(+)-carvone involves seven steps and gives the correct methyl epimer **11a** in 11% overall yield.

Experimental

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were run on a Varian Unity 400 spectrometer. $CDCl_3$ was used as the solvent unless otherwise stated, and the chloroform signal at 7.26 ppm (for ^{1}H) or 77.0 ppm (for ^{13}C) were used as references. IR spectra were obtained for thin films or $CDCl_3$ solutions on a Perkin–Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 25 °C. Merck silica gel 60 (240–400 mesh) was used for flash chromatography.

(S)-Carvone tosylhydrazone. To tosylhydrazine (9.31 g, 50 mmol) in MeOH (50 ml)was added conc. HCl (0.5 ml) followed by (*S*)-(+)-carvone (7.51 g, 50 mmol). The addition caused the solution to become clear and new crystals appeared after 5 min. The mixture was left to crystallize in a refrigerator overnight. The crystalline material was collected by filtration, washed with cold MeOH (50 ml) and dried to give carvone tosylhydrazone (14.3 g, 89%).

Triene 6. To carvone tosylhydrazone (13.2 g, 41.2 mmol) in dry Et_2O (50 ml) at 0 °C was added MeLi (82 ml of a 1.5 M in Et_2O, 123 mmol) over a period of 30 min. When the addition was complete the reaction was stirred for another 30 min at 0 °C and then at room temperature for 3 h. The reaction was stopped by addition of H_2O (100 ml) and the two layers were separated. The aqueous layer was extracted with pentane (2 × 50 ml) and the combined organic layers were washed with H_2O (2 × 50 ml) and brine (1 × 50 ml), and dried ($MgSO_4$). Careful evaporation of the solvent afforded the unstable triene **6** (4.8 g, 87%), which was used in the next step without further purification. ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.83 (1 H, ddd, J=9.6, 2.4, 1.6 Hz), 5.68 (1 H, dd, J=9.6, 3.7 Hz), 5.46 (1 H, m), 5.76 (2 H, m), 2.91 (1 H, m), 2.20 (2 H, m), 1.75 (3 H, dd, J=1.4, 0.9 Hz), 1.73 (3 H, app q, J=1.9 Hz).

Alcohol 7. To the triene **6** (4.8 g, 35.8 mmol) was added 9-BBN (80 ml of a 0.5 M solution in THF, 40 mmol) in THF. The reaction was stirred under N_2 at RT for 48 h. Oxidation of the boron intermediate was performed by adding EtOH (45 ml), aqueous NaOH (15 ml of a 6 M solution) and 30% H_2O_2 (30 ml). The oxidation was completed by heating the reaction to 50 °C for 3 h. The solvent was removed under reduced pressure and Et_2O (100 ml) was added to the residue. The organic solution was washed once with saturated aqueous K_2CO_3 (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography using pentane–Et_2O 75:25 as the eluent to give the alcohol **7** (4.9 g, 90%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.81 (1 H, m), 5.70 (1 H, m), 5.44 (1 H, br), 3.61 (1 H, m), 3.48 (1 H, m), 2.36 (1 H, m), 2.09 (2 H, m), 1.71 (3 H, m), 1.65 (1 H, br), 1.51 (1 H, m), 0.95 (3 H, one isomer, d J=7 Hz), 0.92 (3 H, other isomer, d, J=7 Hz). ^{13}C NMR (100 MHz; $CDCl_3$), mixture of isomers: δ 131.3+131.2, 129.8+128.8, 128.5+128.3, 120.3+120.0, 66.0+65.8, 39.3+39.1, 35.1+34.8, 26.2+25.0, 21.0 (two), 14.14+14.11.

Acid 4. To freshly distilled oxalyl chloride (1.01 ml, 11.6 mmol) in dry CH_2Cl_2 (10 ml) at −50 °C was carefully added dry DMSO (1.64 ml, 23.1 mmol). The solution was stirred at −50 °C for 2 min after which the alcohol **7** (1.6 g, 10.5 mmol) dissolved in CH_2Cl_2 (15 ml) was introduced. After an additional reaction of 30 min at this temperature NEt_3 (7.3 ml, 53 mmol) was added. The mixture was stirred at −50 °C for another 10 min, then the vessel was allowed to warm to room temperature and water (40 ml) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with brine (25 ml) and dried ($MgSO_4$). Careful evaporation of the solvent followed by flash chromatography of the residue using pentane–Et_2O 95:5 as the eluent gave the aldehyde (1.34 g, 85%), which was further oxidized immediately.

To this aldehyde (1.2 g, 8.0 mmol) in EtOH (40 ml) at 0 °C was added $AgNO_3$ (2.99 g, 17.6 mmol) in H_2O (5 ml). To this solution was added dropwise KOH (20 ml of a 1 M solution, 20 mmol) with vigorous stirring at 0 °C, which resulted in the formation of a black precipitate. After 5 min of reaction no aldehyde remained according to TLC and the silver salts was filtered off and washed with H_2O (50 ml). The alkaline aqueous phase was washed once with Et_2O (50 ml), acidified with conc. HCl and extracted with EtOAc (3 × 50 ml). The organic phase was subsequently washed with water (50 ml) and brine (25 ml), dried ($MgSO_4$) and evaporated to give the acid **4** (1.2 g, 91%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.3 (1 H, br), 5.84 (1 H, m), 5.75 (1 H, dd, J=9.8, 3.2 Hz, one isomer), 5.68 (1 H, dd, J=9.8, 3.2 Hz, other isomer), 5.44 (1 H, br), 2.55 (2 H, m), 2.20 (1 H, m), 2.08 (1 H, m), 1.72 (3 H, m), 1.20 (3 H, d, J=6.9 Hz, one isomer), 1.17 (3 H, d, J=6.9 Hz, other isomer). IR: 1702 cm^{-1}.

Lactone acetate 8. To a stirred solution of $Pd(OAc)_2$ (20 mg, 0.09 mmol) and *p*-benzoquinone (191 mg, 1.8 mmol) in HOAc (4 ml) was added **4** (145 mg, 8.8 mmol) over a period of 15 h. After an additional reaction time of 10 h, brine (5 ml) was added and the mixture was extracted with Et_2O (3 × 10 ml). The combined organic layers were washed with aqueous 2 M

NaOH (2 × 5 ml) and brine (1 × 5 ml), and dried ($MgSO_4$). Evaporation and flash chromatography of the residue using pentane–Et_2O 70:30 as the eluent gave the lactone acetate **8** (131 mg, 66%, 1:1 C-7 epimeric mixture). ^1H NMR (400 MHz; $CDCl_3$): δ 5.91 (1 H, m), 5.73 (1 H, m), 5.33 (1 H, m), 5.25 (1 H, app. t, J= 3.0 Hz), 4.91 (1 H, m), 4.68 (1 H, m), 2.94 (1 H, app. quintet, J=7.3 Hz), 2.68 (1 H, m), 2.42 (2 H, m), 2.09 (3 H, s), 2.08 (3 H, s), 2.03 (1 H, m), 1.89 (2 H, m), 1.82 (3 H, app. t, J=1.5 Hz), 1.76 (3 H, m), 1.42 (1 H, app. dt, J=14.1, 3.8 Hz), 1.30 (3 H, d, J=6.9 Hz), 1.17 (3 H, d, J=7.3 Hz). ^{13}C NMR (100 MHz; $CDCl_3$): δ 178.8, 178.2, 170.6, 170.5, 139.5, 138.7, 122.9, 122.3, 74.0, 73.4, 67.81, 67.77, 39.6, 38.8, 38.6, 28.7, 25.1, 21.3, 21.1, 21.0, 20.0, 14.3, 9.3.

Lactone alcohol ***9***. Performed as for **11a** (see below) using **8** as substrate. This afforded **9** (88% yield, 1:1 C-7 epimeric mixture) after flash chromatography with pentane–Et_2O 20:80 as the eluent. ^1H NMR (400 MHz; $CDCl_3$): δ 5.79 (1 H, m), 5.64 (1 H, m), 4.89 (1 H, m), 4.64 (1 H, m), 4.15 (1 H, m), 4.10 (1 H, m), 2.96 (1 H, app. quintet, J=7.2 Hz), 2.78 (1 H, m), 2.48 (1 H, m), 2.40 (1 H, app. quintet, J=7.4 Hz), 2.03 (1 H, m), 1.92 (3 H, app. t, J=1.5 Hz), 1.87 (3 H, m), 1.83 (1 H, m), 1.38 (1 H, app. dt, J=13.9, 3.5 Hz), 1.30 (3 H, d, J= 7.3 Hz), 1.20 (3 H, d, J=7.3 Hz).

Lactone acetate ***10***. To $Pd(OAc)_2$ (47 mg, 0.21 mmol) in dry DMSO (8 ml) was added $LiOAc \cdot 2H_2O$ (1.7 g, 17 mmol). The atmosphere was changed to oxygen, by evacuating the vessel and filling it with oxygen from a balloon. This procedure was repeated. After 5 min the acid **4** (350 mg, 2.1 mmol) as a 1:1 mixture of isomers, was introduced by means of a syringe and the temperature was raised to 40 °C. After 48 h the solvent was removed under reduced pressure and EtOAc (50 ml) was added to the residue and the mixture was stirred for 30 min. The solution was filtered and the salts were washed with additional EtOAc (50 ml). The solvent was evaporated off and the crude mixture was purified by flash chromatography using pentane–Et_2O 50:50 as the eluent giving **10** (110 mg, 23%). Spectral data were in accordance with those reported.[4] ^1H NMR (400 MHz; $CDCl_3$): δ 5.70 (1 H, m), 5.27 (1 H, m), 4.87 (1 H, m), 2.75 (1 H, m), 2.32 (1 H, m), 2.07 (3 H, s), 2.06 (1 H, m), 1.88 (1 H, ddd, J=14.8, 6.5, 4.6 Hz), 1.75 (3 H, app. dt, J=1.5, 0.8 Hz), 1.26 (3 H, d, J=7.2 Hz). ^{13}C NMR (100 MHz; $CDCl_3$): δ 178.9, 170.4, 138.1, 122.7, 74.0, 68.2, 39.2, 38.7, 27.9, 21.0, 20.0, 13.6. IR: 1765, 1734 cm^{-1}.

Lactone alcohol ***11a***. To **10** (75 mg 0.33 mmol) in MeOH (2 ml) was added a catalytic amount of K_2CO_3 (5 mg). After 10 h the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using pentane–Et_2O 20:80 as the eluent to give the alcohol **11a** (55 mg, 91%). Conversion into the corresponding Mosher ester and subsequent ^1H NMR analysis showed that **11a** was >99% ee by comparison with a racemic sample. $[\alpha]_D^{25} = +62$ (c=0.64, MeOH). ^1H NMR (400 MHz; $CDCl_3$): δ 5.60 (1 H, m), 4.83 (1 H, m), 4.11 (1 H, m), 2.82 (1 H, app. quintet, J=7.2 Hz), 2.26 (1 H, m), 2.02 (1 H, app. dt, J=14.0, 4.8 Hz), 1.86 (3 H, app. dt, J=1.5, 0.8 Hz), 1.76 (1 H, ddd, J=14.0, 7.9, 5.9), 1.62 (1 H, br), 1.27 (3 H, d, J=7.3 Hz). ^{13}C NMR (100 MHz; $CDCl_3$): δ 179.8, 142.6, 119.9, 74.7, 66.9, 40.3, 39.2, 31.7, 19.9, 14.0. IR: 3615, 1757 cm^{-1}.

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