An Enantioselective Route to Paeonilactone A via Palladium- and Copper-Catalyzed Reactions

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We herein report on a formal total synthesis of paeonilactone A involving palladium-, copper-, and enzyme-catalyzed reactions starting from 1,3-cyclohexadiene. The key step in the synthesis, a palladium(II)-catalyzed 1,4-oxylactonization of a conjugated diene, simultaneously introduces two of the oxygen substituents required for the target molecule. The synthesis also includes our recently developed copper(I)-catalyzed cross-coupling reaction between dienyltriflates with Grignard reagents, introducing one of the methyl groups present in the target molecule. This new approach toward paeonilactone A allows complete control of all four stereogenic centers and is the first enantioselective route toward paeonilactone A starting from an achiral substrate.

Introduction

Paeonilactone A (**1**), B (**2**), and C (**3**) (Figure 1) are some of the compounds isolated from paeony root, the root of *Paeonia Albiflora* Pallas.[1] This root has been extensively used in Chinese and Japanese herbal medicine for treatment of abdominal pain and syndromes such as stiffness of abdominal muscles.[2] Moreover, paeonilactone C has been proven to suppress both directly and indirectly stimulated muscle twitching of sciatic nerve−sartorius muscle preparations from frogs.[3] Several synthetic approaches toward paeonilactones have been published in racemic[3] as well as enantioselective[2,4,5] forms. However, all of the enantioselective routes used a chiral pool approach. Thus, an enantioselective route toward paeonilactones starting from achiral substrates would therefore be a novel contribution in this area of research.

The 1,4-oxidation of 1,3-dienes developed in our laboratories has proven to be an efficient process for the synthesis of substituted alkenes.[6] These 1,4-additions are usually highly regio- and stereoselective, and we have previously described the use of these reactions in the synthesis of heterocyclic natural products.[7,8] Recently, we described an application of the Pd(II)-catalyzed lactonization in the formal total synthesis of paeonilactone A (**1**) and B (**2**) using the chiral pool approach starting from commercially available *S*-(+)-carvone.[5]

R=Me, Paeonilactone A (**1**)
R=CH_2OCOPh, Paeonilactone C (**3**)

Paeonilactone B (**2**)

Figure 1. Paeonilactone A−C, isolated from paeony root.

We now report a novel route toward paeonilactone A (**1**), which is based on readily available (1*R*,4*S*)-4-bis-(carbomethoxy)-2-cyclohexenol (**4**) as starting material. This substrate is obtained in an enantioselective manner from 1,3-cyclohexadiene via a combination of palladium- and enzyme-catalyzed reactions (Scheme 1) and has earlier been used in the synthesis of chiral lactones.[9] A similar approach has also been employed for the synthesis of chiral amino alcohols.[10]

Our retrosynthetic analysis (Scheme 2) denotes the usefulness of **4** as starting material in the synthesis of paeonilactone A. Oxidation of **4**, MeLi addition to the resulting enone, acylation of the tertiary alcohol, and subsequent Pd(0)-catalyzed allylic elimination yielding **5** would be a possible reaction sequence to introduce the C-10 methyl group[11] and the 1,3-diene necessary for the

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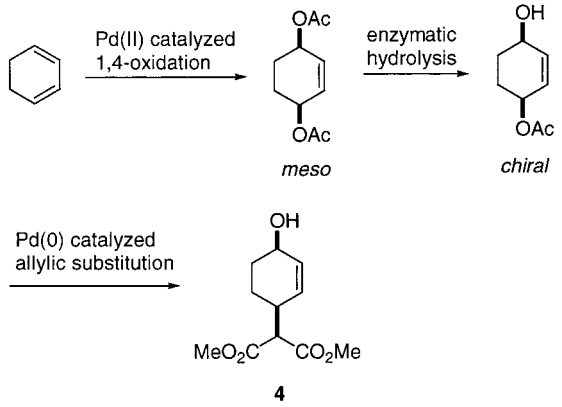
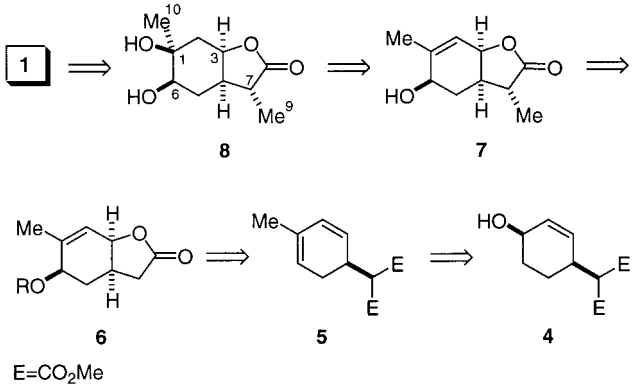
Scheme 1



Scheme 2. Retrosynthetic Analysis of Paeonilactone A

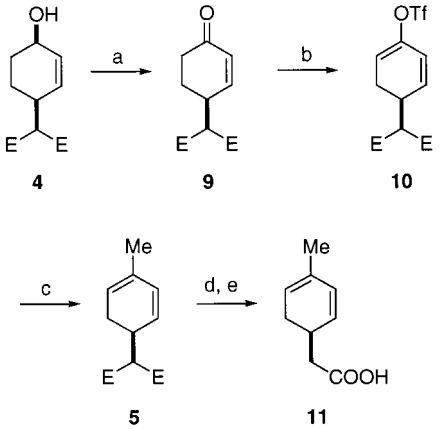


key lactonization step. After Krapcho decarboxylation and saponification, a Pd(II)-catalyzed 1,4-oxylactonization could be carried out providing lactone **6**, which would serve as the key step in this synthesis. In this step, the C-3 and C-6 oxygens are simultaneously introduced, of which the latter will serve as a directing group for the introduction of the C-1 oxygen. We envisioned introducing the second (C-9) of the two methyl groups absent in **4** by deprotonation of the lactone **6** followed by alkylation of the corresponding enolate using MeI. Alcohol **7** (as a 7-Me epimeric mixture) has earlier been used as an intermediate in a route toward paeonilactone A.[4a] To introduce the C-1 oxygen, Kikuchi and co-workers treated **7** with Cl_3CCHO and I_2 to form a trichloroacetal. Subsequent reduction of the iodide, followed by hydrolysis of the acetal, gave diol **8** as an epimeric mixture of 7*R*- and 7*S*-methyl isomers. However, the introduction of the C1 oxygen in that procedure was only performed in 50% yield, which substantially lowered the overall yield. We visualized replacing this somewhat low-yielding pathway by a hydroxyl-directed epoxidation of the allylic alcohol **7**, followed by selective opening of the epoxide by a nucleophile (e.g., I^-). Subsequent reduction of the nucleophile and oxidation of the secondary alcohol would provide paeonilactone A.

Results and Discussion

Allylic alcohol **4** was oxidized to the corresponding unsaturated ketone **9** in 84% yield employing CrO_3/pyridine (Scheme 3).[12] Although the MeLi addition to **9** and acetylation of the corresponding tertiary alcohol was successful, the subsequent Pd(0)-catalyzed allylic elimination gave a mixture of three different dienes with the desired isomer **5** only in low yield.[13] Optimization of this reaction was unsuccessful, and instead a new method for the synthesis of 2-substituted 1,3-dienes was developed.[14] Transformation of **9** to the triflate **10** was done using standard procedures,[15] and subsequent application of our newly developed copper-catalyzed Grignard coupling between **10** and MeMgBr smoothly furnished the desired 2-methyl-1,3-diene **5** in excellent yield. The 1,3-diene acid **11** needed for the key lactonization step was then obtained from **5** in 71% overall yield via a Krapcho decarboxylation[16] and subsequent hydrolysis.

Scheme 3[a]



[a] E = CO_2Me. (a) CrO_3/pyridine, CH_2Cl_2, 84%; (b) (*i*) 2.3 equiv of LDA, THF, (*ii*) 1.4 equiv of Tf_2NPh, THF, 70%; (c) CuI (cat.), MeMgBr, THF, 96%; (d) NaCN, wet DMSO; (e) KOH, MeOH, 71% from **5**.

The lactonization of diene acid **11** was initially performed using the recently developed palladium-catalyzed *cis*-1,4-oxylactonization employing oxygen as a reoxidant and *o*-chlorobenzoic acid as an external nucleophile.[17] Unfortunately, this *cis*-oxylactonization did not perform consistently using **11** as substrate, and instead we had to revert to the *trans*-oxylactonization developed in our group.[18] Using this method, we were able to isolate lactone **12a** in 70% yield (Scheme 4). For the introduction of the C-1 oxygen (vide infra), however, we now had to invert the C-6 oxygen. This was done by hydrolysis of the ester in **12a** (95% yield) and subsequent Mitsunobu reaction[19] (80% yield) providing ester **6a**. Stereoselective introduction of a methyl group in the α-position of a lactone via trapping of the enolate is well-known,[20] and in this way **6a** was alkylated using 1.2 equiv of LDA followed by alkylation with MeI. Alkylation of **6a** proceeded with complete stereoselectivity; however, **7** was isolated as a mixture of 7*R*- and 7*S*-isomers due to epimerization of the methyl group during the hydrolysis

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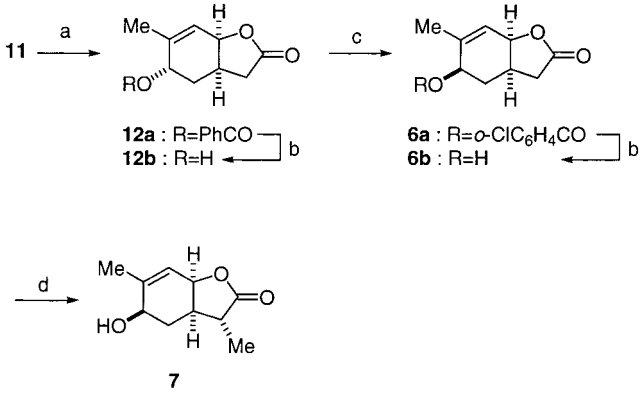
Scheme 4[a]

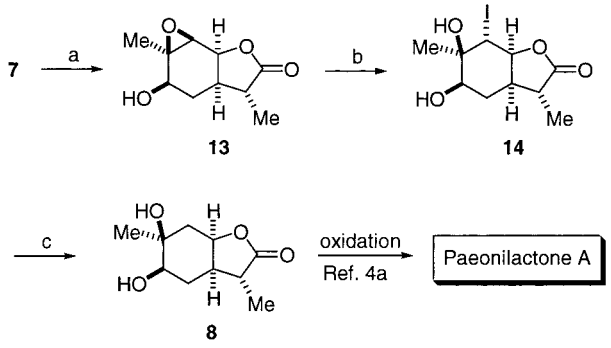


[a] (a) $Pd(OAc)_2$ (cat.), *p*-benzoquinone, $PhCO_2H$, acetone, 70%; (b) MeOH, K_2CO_3, 95%; (c) PPh_3, DEAD, *o*-$ClC_6H_4CO_2H$, 80%; (d) (*i*) 2.2 equiv of LDA, (*ii*) MeI, THF, 82%.

of the ester group. Unfortunately, attempts to suppress this isomerization by modifying the conditions for the hydrolysis proved to be unsuccessful. Because of the problem with eperimization during the hydrolysis of the ester group, we decided to reverse the introduction of the α-methyl and the hydrolysis step. Thus, hydrolysis of **6a** to **6b** (95% yield) followed by treatment of **6b** with 2.2 equiv of LDA and subsequent alkylation of the enolate with MeI led to the formation of methyl lactone **7** in 82% yield (>95% of the desired isomer).

Epoxidation of **7** was more complicated than initially anticipated. Employing ^{t}BuOOH in combination with both catalytic and stoichiometric amounts of Ti(O-*i*-Pr)$_4$,[21] or using CF_3CO_3H,[22] gave no or very low amounts of the desired epoxide. The use of $VO(acac)_2$ in combination with ^{t}BuOOH[23] gave mainly the unsaturated ketone as a product. Using 1.5 equiv of *m*-CPBA in CH_2Cl_2 at 0 °C gave 60% isolated yield of the desired epoxide **13** with the remainder of the mass balance being the *anti* epoxide. Increasing the amount of *m*-CPBA or changing the solvent to benzene or CCl_4 gave no improvement. Performing the reaction at −15 °C resulted in a much improved ratio between the *syn*- and *anti*-epoxide, but the reaction was not complete after 72 h. Finally, a reasonable reaction time in combination with good selectivity could be achieved by using 1.3 equiv of *m*-CPBA and performing the reaction at −6 °C (Scheme 5). This protocol made it possible to isolate the desired epoxide **13** in 70% yield after 48 h. Opening of the epoxide was equally intricate. Most of the attempts made use of I^- as the nucleophile, which renders a group that is easy to remove after the reaction. Iodine in combination with Ti(O-*i*-Pr)$_4$ as the Lewis acid[24] gave low yield of the desired iodohydrin **14** as did MgI_2.[25] Iodine and PPh_3 in CH_2Cl_2[26] gave approximately a 40% yield of **14** and even better results were achieved using ammonium iodide in acetonitrile in the presence of $LiClO_4$.[27] This procedure afforded iodohydrin **14** in 78% yield. The final steps include a tributyltin hydride reduction of **14** giving the diol **8**.[28] The ee of **8** was determined to be 98% by ^{1}H NMR analysis of the corresponding Mosher ester.[29] The transformation of diol **8** to paeonilactone A in more than 74%[30] yield has been previously described in the literature.[2]

Scheme 5[a]



[a] (a) *m*-CPBA, CH_2Cl_2, −6 °C, 70%; (b) NH_4I, $LiClO_4$, CH_3CN, 78%; (c) Bu_3SnH, PhH, rflx, 97%.

Conclusions

We have developed an efficient enantioselective route toward paeonilactone A starting from commercially available 1,3-cyclohexadiene. The synthesis utilizes a combination of palladium-, enzyme-, and copper-catalyzed reactions. The key step is the highly stereo- and regioselective palladium (II)-catalyzed oxylactonization reaction demonstrating its utility in the total synthesis of natural products. Although a large body of enantioselective synthetic routes toward paeonilactones is present in the literature, all utilize the chiral pool approach. To our knowledge an enantioselective approach based on achiral material has not yet been reported, thus making our organotransition metal approach both competitive and attractive.

Experimental Section

General Procedures. ^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded on a Varian Mercury spectrometer. IR spectra were obtained using a Perkin-Elmer 1600 FT-IR instrument, and the samples were examined as thin films or $CDCl_3$ solutions. Only the strongest/structurally most important peaks (cm^{-1}) are listed. Merck silica gel 60 (240−400 mesh) was used for flash chromatography, and analytical thin-layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Melting points (mp) are uncorrected. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany. Analytical high-pressure liquid chromatoghraphy (HPLC) was performed on a Waters liquid chromatograph using a Daicel Chiracel OD-H column. Unless otherwise noted, all material was obtained from commercial suppliers and used without further purification. All reactions were performed at room temperature unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. *cis*-(1*R*,4*S*)-4-[Bis(methoxycarbonyl)methyl]-2-cyclohexanol (**4**)[9] was prepared according

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(28) Kuivila, H. G. *Synthesis* **1970**, 499.

(29) A sample with 80% ee resulting from incomplete enzyme hydrolysis was used as a comparison.

(30) The 75% yield also includes hydrolysis of an acetal.

to literature procedures and had spectral data in accordance with those previously reported.

***cis*-(1*R*,4*S*)-4-[Bis(methoxycarbonyl)methyl]-2-cyclohexanol (4).** The ee for **4** was determined to 95% by HPLC analysis (hexane/^{i}PrOH 95:5; retention times 33.9, 38.5 min); $[\alpha]^{24}_{D}$ +23 (c = 0.6, $CHCl_3$).

(*S*)-4-[Bis(methoxycarbonyl)methyl]-2-cyclohexen-1-one (9). Chromium trioxide (36.7 g, 0.36 mol) was added at 0 °C to a stirred solution of dry pyridine (57.9 g, 0.74 mol) in dry CH_2Cl_2 (600 mL) under argon. After 30 min of stirring at room temperature, a solution of the alcohol **4** (14.0 g, 0.061 mol) in dry CH_2Cl_2 (22 mL) was added to the dark red-brown solution. A black tarry substance precipitated after a few minutes. The flask was equipped with a drying tube, and the mixture was stirred for 24 h at room temperature. The CH_2Cl_2 solution was decanted, and the residue was extracted with alternating portions of ethyl ether and saturated aqueous $NaHCO_3$ (3 × 300 mL and 2 × 250 mL respectively). All extracts were combined with the CH_2Cl_2 solution and shaken. The aqueous phase was removed and extracted twice with ethyl ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, 2% aqueous sulfuric acid, saturated aqueous sodium bicarbonate, and brine. The resulting organic phase was dried over $MgSO_4$ and concentrated, yielding 11.6 g (84%) of a colorless oil. The ee was determined by HPLC analysis (hexane/^{i}PrOH 98.5:1.5; retention times 120.7 and 127.3 min) to be 95%; $[\alpha]^{24}_{D}$ −52 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (ddd, J = 10.4, 2.6, 1.7 Hz, 1H), 6.02 (ddd, J = 10.4, 2.7, 0.8 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.49 (d, J = 7.8 Hz, 1H), 3.22 (m, 1H), 2.52 (dt, J = 17.0, 4.7 Hz, 1H), 2.41 (ddd, J = 17.0, 12.6, 4.9 Hz, 1H), 2.11 (m, 1H), 1.84 (ddt, J = 12.6, 10.2, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 168.0, 167.9, 150.2, 130.1, 55.0, 52.8, 52.7, 36.8, 36.0, 27.0. IR ($CDCl_3$): 1734, 1681 cm^{-1}.

(*S*)-5-Dimethylmalonate-1,3-cyclohexadiene-2-yl Triflate (10). A solution of LDA (77.9 mmol) was prepared by adding *n*-butyllithium (48.6 mL of a 1.6 M solution in hexane, 77.9 mmol) to diisopropylamine (10.8 mL, 82.4 mmol) in THF (94 mL) at 0 °C under argon. The resulting solution was cooled to −78 °C, and ketone **9** (8.10 g, 35.8 mmol) in THF (10 mL) was added dropwise. The resulting suspension was rapidly stirred for 3 h at −78 °C, and then Tf_2NPh (17.9 g, 50.2 mmol) in THF (60 mL) was added. The mixture was allowed to warm to 0 °C over 2 h, and the reaction was completed after stirring at 4 °C for 16 h. The solvent was evaporated, and the crude material was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (pentane:Et_2O 4:1) to give 9.06 g (71%) of **10** as a pale yellow unstable oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (ddd, J = 10.2, 4.1, 0.8 Hz, 1H), 5.90 (app dt, J = 10.2, 2.0 Hz, 1H), 5.68 (ddt, J = 4.8, 2.0, 0.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.52, (d, J = 8.7 Hz, 1H), 3.15 (dddt, J = 9.7, 8.7, 4.1, 1.7, 1 H), 2.56 (ddd, J = 17.7, 8.7, 4.8 Hz, 1H), 2.34 (ddd, J = 17.7, 9.7, 4.8 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 168.0, 167.9, 145.2, 132.0, 122.0, 118.5 (q, J (^{13}C,^{19}F) = 320 Hz), 114.0, 53.6, 52.8, 52.7, 32.1, 25.6.

(*S*)-5-Dimethylmalonate-2-methyl-1,3-cyclohexadiene (5). To a stirred solution of CuI (0.033 g, 0.17 mmol) and **10** (2.5 g, 6.98 mmol) in THF (23 mL) at 0 °C was added MeMgBr in Et_2O (6.98 mL 20.9 mmol). After 20 min, the reaction was quenched by addition of saturated aqueous NH_4Cl. Et_2O was added, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were subsequently washed with brine, dried ($MgSO_4$), and evaporated. The crude mixture was purified by flash chromatography using pentane:Et_2O 4:1 as eluent to give 1.51 g (96%) of **5** as a colorless oil. Spectral data are consistent with those previously reported.[14] $[\alpha]^{24}_{D}$ −150 (c = 0.64, $CHCl_3$).

((*R*)-4-Methylcyclohexa-2,4-dienyl)acetic Acid (11). A mixture of **5** (1.8 g, 8.0 mmol), NaCN (1.97 g, 40 mmol), and H_2O (0.72 g, 40 mmol) in DMSO (25 mL) was heated to 60 °C for 48 h. The solution was cooled, water (150 mL) was added, and the aqueous layer was extracted with pentane:Et_2O 7:3. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 1.06 g (80%) of the monoester which was used without further purification.

The product from the Krapcho reduction (1.0 g, 6.0 mmol) was dissolved in MeOH:H_2O 5:1 (25 mL). KOH (1.0 g, 18 mmol) was added, and the mixture was stirred for 4 h. The solvent was evaporated, and H_2O (25 mL) was added. The basic layer was subsequently extracted with pentane:Et_2O 1:1, acidified to pH = 1 (concentrated HCl), and extracted with EtOAc. The combined organic layers were washed with H_2O, dried ($MgSO_4$), and evaporated to give 0.86 g (95%) of **11** as a colorless oil. $[\alpha]^{22}_{D}$ −185 (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (br s, COOH), 5.82 (app dt, J = 9.7, 1.6 Hz, 1H), 5.74 (dd, J = 9.7, 4.0 Hz, 1H), 5.44 (m, 1H), 2.70 (m, 1H), 2.44 (dd, J = 15.6, 7.2 Hz, 1H), 2.38 (dd, J = 15.6, 7.8 Hz, 1H), 2.31 (m, 1H), 2.00 (m, 1H), 1.73 (app q, J = 1.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 131.2, 129.1, 128.6, 119.3, 38.1, 29.6, 28.5, 21.0. IR ($CHCl_3$): 1703 cm^{-1}.

Benzoic Acid (3a*R*,5*S*,7a*R*)-6-Methyl-2-oxo-2,3,3a,4,5,-7a-hexahydrobenzofuran-5-yl Ester (12a). Diene **11** (2.0 g, 13.2 mmol) was added over a 16 h period to a stirred solution of $Pd(OAc)_2$ (0.21 g 0.92 mmol), *p*-benzoquinone (3.12 g, 28.9 mmol), and benzoic acid (2.84 g, 105.2 mmol) in acetone (83 mL). After an additional reaction time of 24 h, the solvent was evaporated and Et_2O (150 mL) was added. The organic fraction was washed with 2 M NaOH (5 × 50 mL) (until the organic phase was light yellow) and brine. Evaporation of the solvent and flash chromatography using Et_2O/pentane (3:1) as eluent afforded lactone **12a** (2.51 g, 70%) as white crystals. The ee was determined by HPLC analysis (hexane/^{i}PrOH 75:25; retention times 24.6, 28.4 min) to be 92%. Recrystallization from EtOAc/ hexane gave 99% ee. $[\alpha]^{22}_{D}$ −213 (c = 0.53, $CHCl_3$). mp 90−92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 5.92 (dq, J = 4.2, 1.5 Hz, 1H), 5.52 (t, J = 3.9 Hz, 1H), 4.90 (m, 1H), 2.90−2.76 (m, 2H), 2.34 (m, 1H), 2.07 (dt, J = 14.4, 3.9 Hz, 1H), 1.79−1.90 (m, 1H), 1.88 (app t, J = 1.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 165.9, 139.4, 133.2, 129.8, 129.5, 128.4, 122.5, 75.5, 68.6, 35.3, 29.8, 29.4, 21.2. IR ($CHCl_3$): 1771, 1716 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93; Found: C, 70.40; H, 5.84.

(3a*R*,5*S*,7a*R*)-5-Hydroxy-6-methyl-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (12b). To **12a** (1.41 g, 5.18 mmol) in MeOH (32 mL) was added a catalytic amount of K_2CO_3 (0.073 g, 0.53 mmol). After 12 h, the solvent was removed in vacuo, and the crude product was purified by flash chromatography using Et_2O/MeOH (gradient 100:0 to 95:5). The product was isolated as white crystals (0.83 g, 95%). $[\alpha]^{22}_{D}$ −51 (c = 1.0, $CHCl_3$); mp 70.5−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (app dq J = 5.8, 1.5 Hz, 1H), 4.79 (m, 1 H), 4.10 (t, J = 3.9 Hz, 1 H), 2.76−2.90 (m, 2H), 2.29 (m, 1H), 2.0 (br s OH), 1.91 (app t, J = 1,5 Hz, 3 H), 1.85 (dt, J = 13.9, 3.9 Hz, 1H), 1.69 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 176.3, 142.6, 119.9, 75.8, 66.3, 35.5, 32.8, 28.8, 21.2. IR ($CHCl_3$): 3478, 1770 cm^{-1}. Anal. Calcd for $C_9H_{12}O_3$: C, 64.25; H, 7.19; Found: C,64.01; H, 7.03.

2-Chlorobenzoic Acid (3a*R*,5*R*,7a*R*)-6-Methyl-2-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-5-yl Ester (6a). To a solution of **12b** (0.38 g, 2.27 mmol), triphenylphosphine (1.19 g, 4.55 mmol), and *o*-chlorobenzoic acid (0.71 g, 4.55 mmol) in THF (4.2 mL) under argon was added DEAD (0.79 g, 4.55 mmol) over a period of 30 min. The reaction mixture was then stirred for 12 h and concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and washed with water and aqueous $NaHCO_3$. Drying ($MgSO_4$) and evaporation gave an oily residue. Purification by flash chromatography (1:4 pentane/ EtOAc) gave **6a** as white crystals (0.55 g, 80%). The ee was determined by HPLC analysis (hexane/*i*-PrOH 98:2; retention times 164.0, 170.9 min) to be 99%. $[\alpha]^{22}_{D}$ +25.2 (c = 0.76, MeOH). mp 64.5−67.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (ddd, J = 7.8, 1.5, 0.6 Hz, 1H), 7.46 (m, 2H), 7.33 (ddd, J = 7.8, 6.7, 2.0 Hz, 1H), 5.81 (dq, J = 3.9, 1.5 Hz, 1H), 5.62 (m, 1H), 4.83 (m, 1H), 2.77 (m, 2H), 2.51 (m, 1H), 2.22 (ddd, J = 13.2, 5.1, 4.3 Hz, 1H), 1.87 (app q, J = 1.5 Hz, 3,H,), 1.82 (ddd, J = 13.2, 10.7, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 165.2, 141.0, 133.8, 132.8, 131.21, 131.22, 129.6, 126.7, 121.5, 75.3, 70.3, 35.6, 31.7, 29.5, 19.5. IR ($CHCl_3$): 1774,

1728.cm^{-1}. Anal. Calcd for $C_{16}ClH_{15}O_4$: C, 62.63; H, 4.933. Found: C, 62.50; H, 4.93.

(3a*R*,5*R*,7a*R*)-5-Hydroxy-6-methyl-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (6b). To **6a** (0.21 g, 0.69 mmol) in MeOH (1.32 mL) was added a catalytic amount of K_2CO_3 (9.5 mg, 0.069 mmol). After stirring 12 h at room temperature, the solvent was removed and the crude product was purified by flash chromatography using Et_2O/MeOH (gradient 100:0 to 95:5). The product was isolated as white crystals (0.10 g, 88%). $[\alpha]^{22}_D$ +7.9 (*c* = 1.0, MeOH). mp 143.5−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (dq, *J* = 4.2, 1.5 Hz, 1H), 4.73 (m, 1H), 4.13 (m, 1H), 2.78 (dd, *J* = 17.4, 8.2 Hz, 1H), 2.61 (m, 1H), 2.45 (dd, *J* = 17.4, 2.5 Hz, 1H), 2.03 (d, *J* = 7.05 Hz, 1H), 2.02 (app dt, *J* = 12.7, 4.8 Hz, 1H) 1.89 (app q, *J* = 1.5 Hz, 3H), 1.52 (dt, *J* = 12.7, 9.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 145.6, 118.6, 76.0, 67.8, 36.4, 33.7, 32.4, 19.2. IR ($CHCl_3$): 3474, 1770 cm^{-1}. Anal. Calcd for $C_9H_{12}O_3$: C, 64.25; H, 7.19. Found: C, 64.04; H, 7.20.

(3*R*,3a*R*,5*R*,7a*R*)-5-Hydroxy-3,6-dimethyl-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (7). A solution of LDA (0.92 mmol) was prepared by adding *n*-butyllithium (0.57 mL of a 1.6 M solution in hexanes, 0.92 mmol) to diisopropylamine (96.9 mg, 0.96 mmol) in THF (5.3 mL) at 0 °C under argon. The resulting solution was cooled to −78 °C, and lactone **6b** (70.0 mg, 0.41 mmol) in THF (3 mL) was added dropwise. The resulting suspension was rapidly stirred for 1.5 h. Freshly distilled MeI (70.9 mg, 0.50 mmol) was added, and the solution was stirred at −78 °C for 5 h. TsOH (95.1 mg, 0.50 mmol) was then added, and the solution was allowed to warm to −30 °C. Water was added, the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation followed by flash chromatography (pentane:Et_2O, 1:5) gave **7** (61.6 mg, 82%) as white crystals. Conversion to the corresponding Mosher ester and subsequent ^{1}H NMR analysis showed that **7** was >98% ee by comparison with a racemic sample. No traces of the other isomer could be seen. Spectral data are consistent with those previously reported.[5] $[\alpha]^{27}_D$ +58 (*c* = 0.69, MeOH).

(1a*R*,2*R*,3a*R*,4*R*,6a*S*)-2-Hydroxy-1α,4-dimethylhexahydro-1,6-dioxacyclopropa[*e*]inden-5-one (13). To a stirred solution of **7** (100 mg, 0.55 mmol) in CH_2Cl_2 (1.45 mL) at −6 °C was added *m*-CPBA (123.2 mg, 0.71 mmol) in small portions. The reaction was stirred for 48 h at −6 °C. The solvent was evaporated, and the crude mixture was purified by flash chromatography using EtOAc:pentane (gradient 3:1 to 1:0) to give **13** (74.8 mg, 70%) as white crystals. $[\alpha]^{21}_D$ +33.6 (*c* = 0.45, $CHCl_3$). mp 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (dd, *J* = 7.6, 3.3 Hz, 1H), 3.94 (ddd, *J* = 10.1, 8.8, 4.9 Hz, 1H), 3.38 (d, *J* = 3.3 Hz, 1H), 2.46 (dq, *J* = 7.5, 4.2 Hz, 1H), 2.16 (m, 1H), 1.83 (ddd, *J* = 13.0, 6.2, 4.9 Hz, 1H), 1.66 (ddd, *J* = 13.0, 11.4, 10.1 Hz, 1H), 1.63 (br d, *J* = 8.8 Hz, OH), 1.48 (s, 3H), 1.26 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 74.4, 69.2, 61.9, 59.8, 41.8, 40.1, 31.9, 18.5, 15.9. IR ($CHCl_3$): 3578, 1772 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.11. Found: C, 60.34; H, 6.97.

(3*R*,3a*R*,5*R*,6*R*,7*R*,7a*S*)-5,6-Dihydroxy-7-iodo-3,6-dimethylhexahydrobenzofuran-2-one (14). A solution of epoxide **13** (15 mg, 0.076 mmol) in acetonitrile (75 μL) was treated with $LiClO_4$ (12.1 mg, 0.11 mmol) and NH_4I (16.4 mg, 0.11 mmol), and the resulting reaction mixture was stirred at 65 °C for 48 h under argon. The solution was bubbled with argon a few times during the reaction time to get rid of NH_3 that formed during the reaction. The solvent was evaporated, and the crude material was purified by flash chromatography using EtOAc:pentane (3:1) as eluent yielding **14** as a white solid in 78% yield (19.2 mg). $[\alpha]^{21}_D$ +42.6 (*c* = 0.38, MeOH). mp 152−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + drops of CD_3OD): δ 4.68 (dd, *J* = 10.7, 7.6 Hz, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 3.93 (app t, *J* = 3.3 Hz, 1H), 3.19 (dq, *J* = 12.6, 7.1 Hz, 1H), 2.07−2.17 (m, 2H), 1.88 (ddd, *J* = 15.9, 6.8, 3.3 Hz, 1H), 1.27 (s, 3H), 1.19 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + drops of CD_3OD): δ 178.2, 82.7, 73.8, 71.9, 43.4, 41.7, 37.9, 26.3, 23.8, 13.1. IR ($CDCl_3$): 3557, 1776 cm^{-1}. Anal. Calcd for $C_{10}H_{15}IO_4$: C, 36.83 H, 4.63. Found: C, 36.75; H, 4.47.

(3*R*,3aR,5R,6*S*,7a*R*)-5,6-Dihydroxy-3,6-dimethylhexahydrobenzofuran-2-one (8). A solution of iodohydrin **14** (28 mg, 0.086 mmol), AIBN (0.5 mg, 3 ìmol) and tributyltin hydride (0.030 mL, 0.11 mmol) in degassed benzene (1.5 mL) was heated at reflux under argon for 4 h. The solvent was evaporated and the crude material was purified by flash chromatography (EtOAc:hexane, gradient 1:1 to 4:1) to give compound **8** (16.7 mg, 97%) as white crystals. About 4% of an isomeric byproduct contaminated the product. An analytical pure sample was obtained after an additional flash chromatography (CH_2Cl_2:EtOH, 98:2). $[\alpha]^{21}_D$ +44 (*c* = 0.22, $CHCl_3$). mp 144−148 °C (amorphous material). ^{1}H NMR spectral data are consistent with those previously reported.[4a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (ddd, *J* = 7.8, 6.1, 5.6 Hz, 1H), 3.57 (app q, *J* = 4.9 Hz, 1H), 2.88 (app quintet, *J* = 7.3 Hz, 1H), 2.32 (d, *J* = 4.9, OH), 2.20 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.17 (ddd, *J* = 12.3, 7.8, 6.1 Hz, 1H), 2.02 (br s, OH), 1.86 (m, 3H), 1.28 (s, 3H), 1.26 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 76.0, 72.8, 71.5, 40.6, 40.5, 37.1, 29.0, 25.3, 13.7.

Conversion to the corresponding Mosher ester and subsequent ^{1}H NMR analysis showed that **8** was 98% ee by comparison with a sample that was ca. 80% ee. The ^{1}H NMR for the enantiopure ester revealed a triplet at 4.99, a broad quartet at 3.52, and a quintet at 2.46 ppm whereas the ca. 80% ee ester had these signals and in addition a triplet at 5.02, a broad quartet at 3.56, and a quintet at 2.35 ppm.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **9** to **11**. ^{1}H NMR for pertinent regions of the spectra for the Mosher ester of enantiopure and 80% ee diol **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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