Synthesis of (+)- and (-)-dihydromenisdaurilide and (+)- and (-)-dihydroaquilegiolide

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Dedicated to Professor Joan Bosch on his 60th birthday

Abstract

The natural products (-)-dihydromenisdaurilide, (-)-**3**, and (+)-dihydroaquilegiolide, (+)-**4**, were isolated in 1993, but synthetic reports related to these compounds are quite scarce. Only a synthesis of both natural isomers in enantioenriched form and a synthesis in enantiopure form of unnatural **3** and natural **4** have been reported. Starting from an enantiopure monoketal of *p*-benzoquinone, we have investigated several synthetic approaches to both lactones in enantiomerically pure form, but each of them resulted in racemization. Finally, partial hydrogenation of (+)- and (-)-menisdaurilide allowed the preparation of (+)- and (-)-dihydromenisdaurilide, respectively, and a Mitsunobu reaction applied to **3** afforded (+)- and (-)-dihydroaquilegiolide.

Keywords: Dihydromenisdaurilide, dihydroaquilegiolide, *p*-benzoquinone monoketals, Mitsunobu reaction

Introduction

A large number of products containing a highly functionalized cyclohexane subunit have been isolated from nature. (-)-Menisdaurilide, (-)-**1**, (-)-aquilegiolide, (-)-**2**, (-)-dihydromenisdaurilide, (-)-**3**, and (+)-dihydroaquilegiolide, (+)-**4**, are four examples of this kind of natural products (Chart 1). Menisdaurilide was first reported in the literature in 1978 as a product of the acid hydrolysis of the nitrile glucoside menisdaurin,[1] but it was isolated not until 1984, along with aquilegiolide, from *Aquilegia atrata*.[2] Later on, lactone **1** has been isolated from several plants[3-8] and it is also the aglycon of phyllanthurinolactone, a bioactive substance related to the leaf-closing movement of several nyctinastic plants.[9,10] Both enantiomers of aquilegiolide have also been isolated from natural sources.[3-8] (-)-Dihydromenisdaurilide and (+)-dihydroaquilegiolide have been reported as components of the extracts from *Sinomenium acutum*.[5] Two new

glucosides, named trochocarposide and epitrochocarposide, were isolated from *Trochocarpa laurina* in 1995.[11] Hydrolysis of both compounds yielded (-)-dihydroaquilegiolide and (-)-dihydromenisdaurilide, respectively.

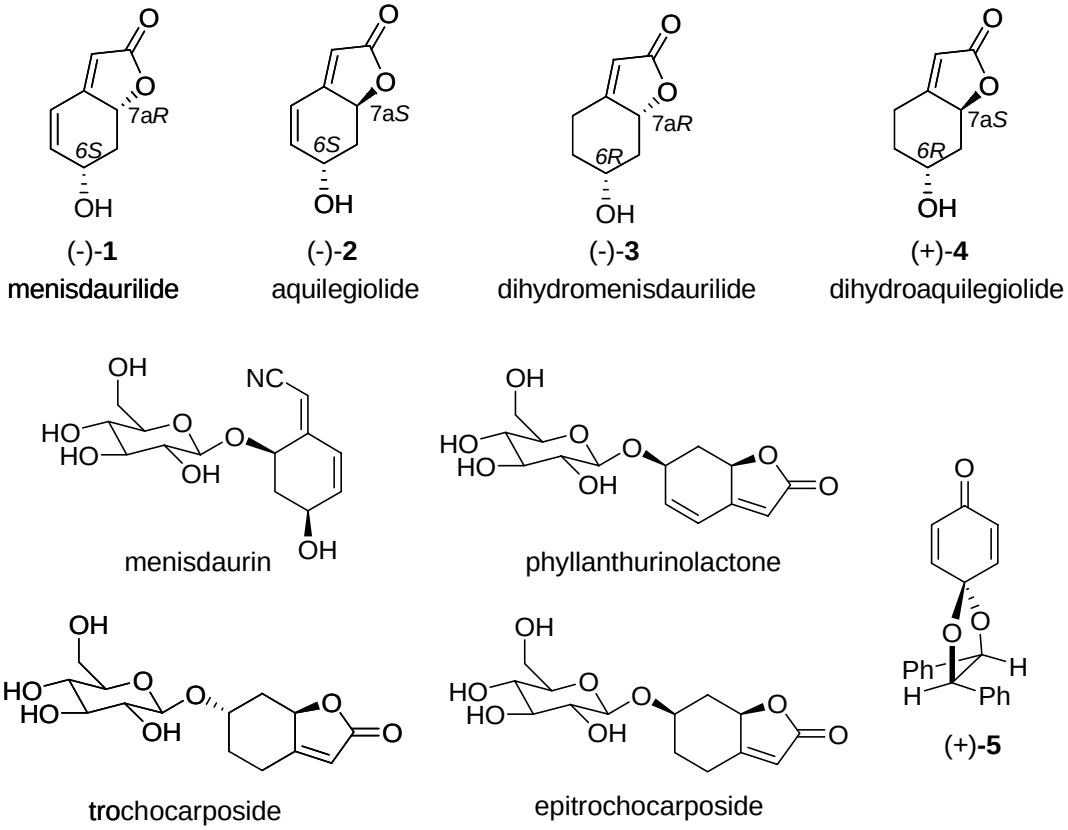


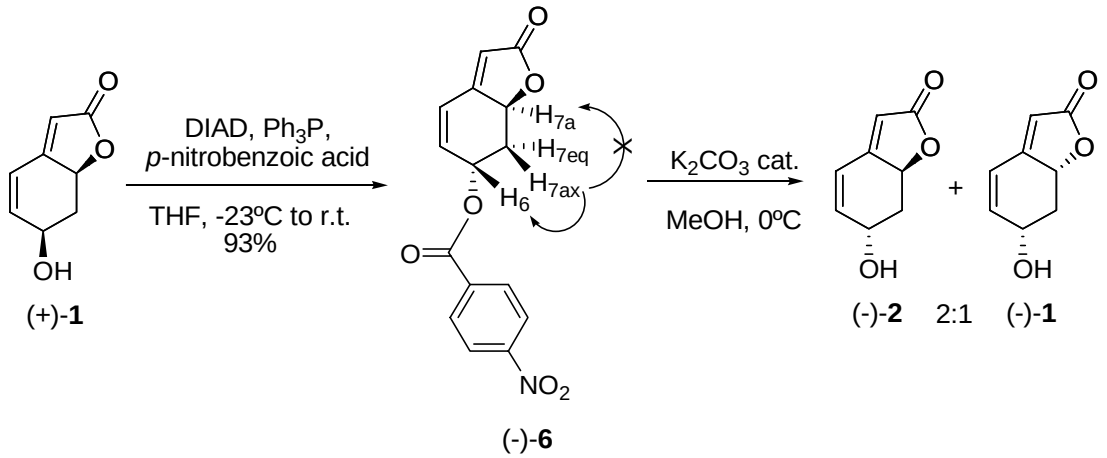
Chart 1. Natural products containing a highly functionalized cyclohexane subunit.

The first synthesis of racemic menisdaurilide and aquilegiolide was reported by the group of Mori.[12] The isomers (-)-**3** and (+)-**4** were obtained only in enantioenriched forms by Majewski and co-workers.[13] Ogasawara *et al*.[14] published another synthesis of racemic menisdaurilide, as well as the only known preparation of (+)-dihydromenisdaurilide and (+)-dihydroaquilegiolide. Recently, we described the first asymmetric synthesis of (+)- and (-)-menisdaurilide, (+)- and (-)-**1**, starting from the easily available enantiopure monoketal of *p*-benzoquinone (+)-**5**.[15] In this paper, we report the results of our investigations directed to the synthesis of the structurally related natural lactones **2**, **3**, and **4** in enantiopure form.

Results and Discussion

With both enantiomers of **1** in our hands, we approached the synthesis of enantiopure epimeric lactone **2** through an inversion of the configuration at C-6 by means of a Mitsunobu reaction. We

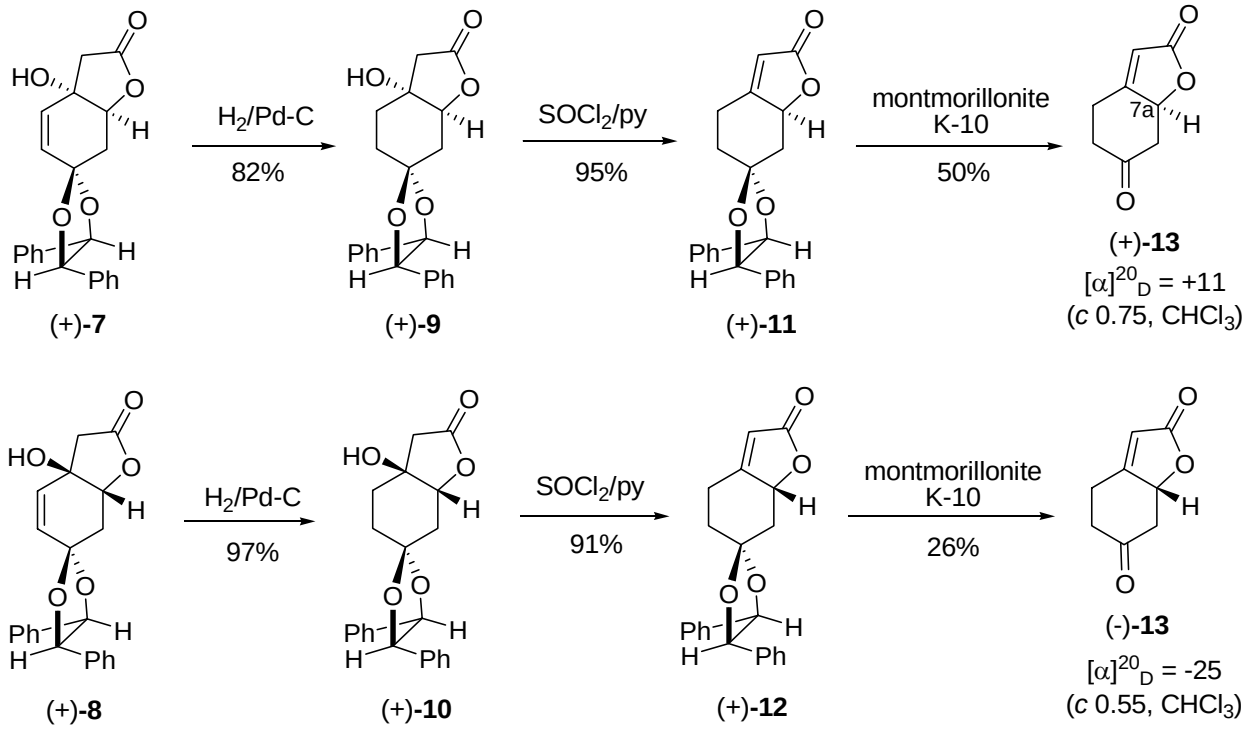
decided to use the experimental conditions described by Coleman's group[16] and therefore, we prepared the new *p*-nitrobenzoates (-)- and (+)-**6** in yields over 90% starting from (+)- and (-)-**1**, respectively (Scheme 1). The formation of the ester is observed in the ^{1}H NMR spectra by the presence of two doublets at δ 8.29 and 8.19 corresponding to the aromatic protons, as well as the downfield shifted absorption of H-6 from δ 4.62 in **1** to δ 5.84 in **6**. The inversion of the configuration at C-6 was established by NOE experiments. Irradiation of the labeled proton H-7ax results in a high enhancement of the signal of H-6 and has no effect on H-7a, while presaturation of H-7eq produces NOE on H-7a and only a small effect on H-6. Unfortunately, treatment of **6** with a stoichiometric amount of potassium carbonate in methanol, the usual conditions for hydrolysis of *p*-nitrobenzoic esters, furnished a mixture of both epimers **2** and **1** in a 1:2 ratio. The configurational instability at the C-7a stereocenter of menisdaurilide and some of its derivatives has already been described in the literature.[2,12,14] Nevertheless, Mori and co-workers[12] reported the use of catalytic amounts of potassium carbonate in methanol in the last step of their synthetic procedure of racemic aquilegiolide and epimerization was not observed. When we performed the hydrolysis of esters **6** under these conditions we still obtained a mixture of aquilegiolide and menisdaurilide, albeit with minor isomerization, since the ratio was now 2:1. In view of this result, we discarded other alternative methodologies for the alcohol inversion, assuming that the epimerization process could not be avoided, thus, we abandoned the synthesis of aquilegiolide in enantiopure form.



Scheme 1. Attempted synthesis of (-)-aquilegiolide.

For the enantiopure synthesis of the dihydro derivatives **3** and **4**, we believed that we could benefit from our synthetic sequence of menisdaurilide, that uses chiron (+)-**5** as the starting material. This ketal was transformed into the diastereoisomeric hydroxylactones (+)-**7** and (+)-**8**, that were easily separated (Scheme 2). The conversion of **7** or **8** into menisdaurilide continued with the dehydration of the secondary alcohol,[15] but with dihydromenisdaurilide being our new target, the reduction of the olefin was undertaken first.

Conventional hydrogenation of (+)-**7** and (+)-**8** afforded the new saturated lactones (+)-**9** and (+)-**10** in 82% and 97% yield, respectively, considering the recovered starting material. In both cases the reaction was stopped before a complete olefin consumption was reached, due to the observed formation of several decomposition compounds when the reaction was conducted until disappearance of **7** or **8**. In the ^{1}H NMR spectra of **9** and **10**, no signals corresponding to olefinic protons are observed. Using bidimensional NMR experiments most of the absorptions of the protons and carbon atoms of both isomers could be assigned. Dehydration of each alcohol was carried out by treatment with thionyl chloride and pyridine. The unknown butenolides (+)-**11** and (+)-**12** were isolated in over 90% yield and they were also characterized by their spectroscopic data. The presence of a singlet at δ 5.84 in the ^{1}H NMR spectra of both isomers confirms the formation of the double bond in each compound.

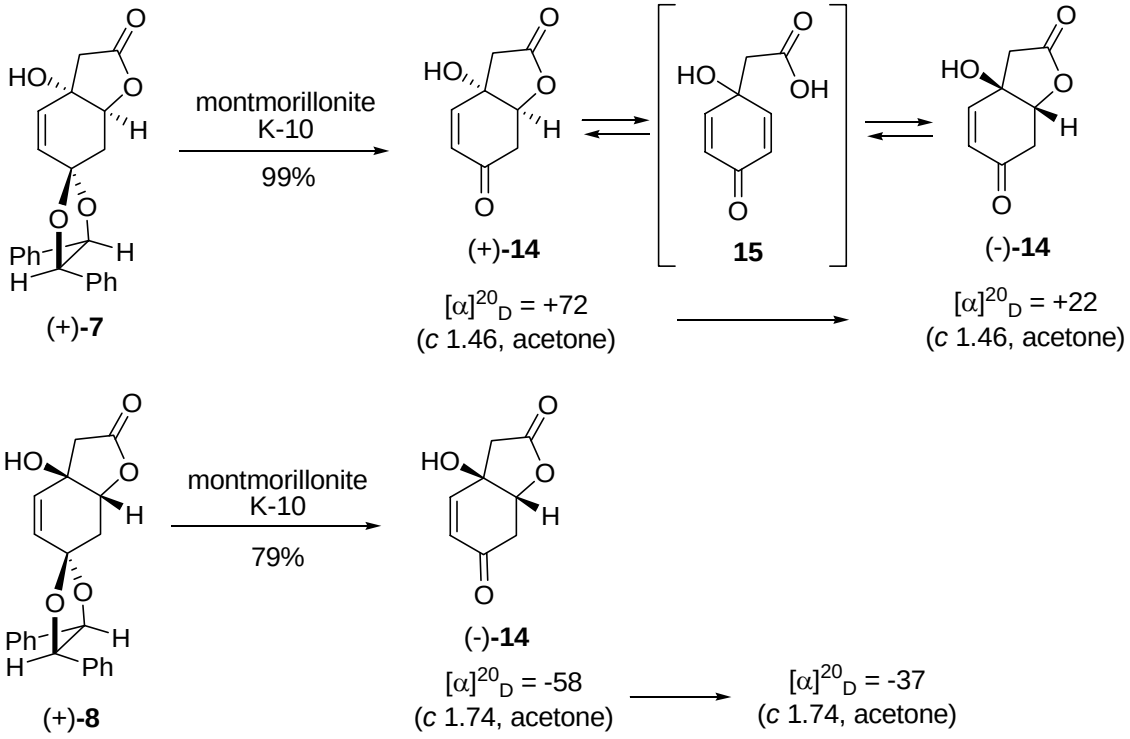


Scheme 2. Transformation of ketals (+)-**7** and (+)-**8** into **13** in enantioenriched form.

Hydrolysis of ketals **11** and **12** proved to be problematic. Treatment with montmorillonite K-10 under the same conditions previously used in our group for the hydrolysis of structurally similar ketals resulted in no deprotection. The use of *p*-toluenesulfonic acid in acetone or cerium ammonium nitrate in an acetonitrile/water mixture[17,18] did not yield the desired ketone **13** either. After several attempts, reproducible hydrolyses were achieved using larger amounts of montmorillonite K-10 and solvent than those reported before. Unfortunately, the new compound **13** could not be obtained in pure form and was contaminated with *ca.* 5% of an unidentified

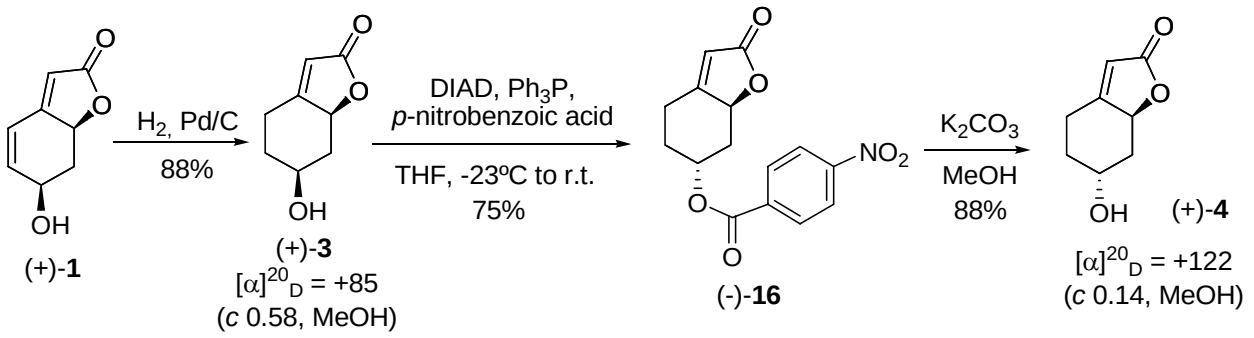
product according to its ^{1}H NMR spectrum. Since the specific rotation values determined for the isolated samples of (+)-**13** and (-)-**13,** obtained starting from **11** and **12**, respectively, were significantly different ($[\alpha]^{20}_D$ = +11 (*c* 0.75, $CHCl_3$) and $[\alpha]^{20}_D$ = -25 (*c* 0.55, $CHCl_3$)), we concluded that partial racemization had taken place again, most probably due to the acidic character of the proton H-7a. This circumstance renders this synthetic sequence ineffective for the preparation of enantiopure samples of dihydromenisdaurilide and/or dihydroaquilegiolide and therefore, we searched for a second approach toward the synthesis of the enantiopure lactones **3** and **4**.

We visualized that the same saturated butyrolactones **7** and **8** could serve as possible intermediates for a new synthetic path. The corresponding deprotected ketone **14** might be configurationally more stable and could hopefully be transformed into the target molecules by several routes. Ketals **7** and **8** were easily hydrolyzed in comparision to **11** and **12** using also montmorillonite K-10 and enantioenriched compounds (+)-**14** and (-)-**14** were isolated in 99% and 79% yield, respectively (Scheme 3). Although product **14** was first synthesized by photooxidation of *p*-hydroxyphenylpyruvic acid[19] and was afterwards isolated from several plants,[20,21] no data on its specific rotation had been reported. The spectroscopic data of our samples were identical to those published, but their specific rotation values diminished over longer time periods without observing any decomposition by NMR analysis. This fact reveals that in this case a partial racemization also occurs, most probably through the achiral conjugated enone **15**, which is an intermediate in the mentioned photooxidation process.[19]



Scheme 3. Hydrolysis of ketals (+)-**7** and (+)-**8**.

This result forced us to look for a third alternative approach. We decided to investigate the selective reduction of menisdaurilide. Fortunately, when (+)- and (-)-**1** were submitted to catalytic hydrogenation in the presence of palladium over charcoal we isolated the desired (+)- and (-)-dihydromenisdaurilide, **3**, in high yield, respectively (Scheme 4). The spectroscopic data of our samples matched with those previously reported.[5] However, the specific rotation values of our synthetic materials, $[\alpha]^{20}_D$ = +85 (*c* 0.58, methanol) and $[\alpha]^{20}_D$ = -88 (*c* 0.38, $CHCl_3$), were considerably lower than the reported data of $[\alpha]^{20}_D$ = +123 (*c* 0.2, methanol) for the enantiopure unnatural isomer[14] and of $[\alpha]^{20}_D$ = -112 (*c* 2.0, methanol) for the natural isomer with 90% ee.[13] Nevertheless, a chiral GC analysis of our samples revealed an ee≥95%, and their enantiopurity was further proven by their conversion to dihydroaquilegiolide (*vide infra*). This synthesis of enantiopure dihydromenisdaurilide competes favourably with the previously reported route.[14]



Scheme 4. Synthesis of (+)-dihydromenisdaurilide, (+)-**3**, and (+)-dihydroaquilegiolide (+)-**4**.

Finally, we focused our attention towards the synthesis of dihydroaquilegiolide through a Mitsunobu reaction. Starting from (+)- and (-)-dihydromenisdaurilide we prepared *p*-nitrobenzoates (-)- and (+)-**16** by conventional methodology in 75% and 97% yield, respectively. These new esters were spectroscopically characterized and their specific rotation values were $[\alpha]^{20}_D$ = -33 (*c* 1.24, acetone) and $[\alpha]^{20}_D$ = +32 (*c* 0.42, acetone). As in the case of derivatives **6**, the presence of two doublets at δ 8.29 and 8.18, along with the chemical absorption of H-6 at δ 5.61, demonstrate the formation of the ester. With the aid of two dimensional NMR experiments we were able to assign all the proton and carbon atom signals. Confirmation of the expected inversion of configuration at C-6 resulted from the hydrolysis of (-)- and (+)-**16** using stoichiometric amounts of potassium carbonate in methanol, which afforded (+)- and (-)-dihydroaquilegiolide in 88% and 71% yield, respectively. The spectroscopic data of the synthesized samples of **4** matched with those of the literature.[5] The specific rotation values measured for our samples, $[\alpha]^{20}_D$ = +122 (*c* 0.14, methanol) and $[\alpha]^{20}_D$ = -124 (*c* 0.11, methanol), were in good agreement with those previously reported of $[\alpha]^{20}_D$ = +125 (*c* 0.9, methanol)[14] and $[\alpha]^{20}_D$ = +113 (*c* 1.0, methanol)[13] with 90% ee. Therefore, this synthesis of dihydroaquilegiolide in enantiopure form corroborates the enantiomeric purity of our samples of

dihydromenisdaurilide. Consequently, the hydrolysis of esters **16** resulted in no racemization. This new synthesis of enantiopure dihydroaquilegiolide is also shorter than the one previously reported.[14]

In conclusion, we described herein an attempt to prepare aquilegiolide in enantiopure form along with a short access to each enantiomer of dihydromenisdaurilide and dihydroaquilegiolide.

Experimental Section

General Procedures. Reaction mixtures were magnetically stirred. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 5-10 Torr. Flash chromatography was performed using Merck silica gel (230-400 mesh). Infrared spectra were recorded on a Bruker Tensor 2000 (ATR) spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250-WB or a Bruker ARX-400 instrument at 250 or 400 MHz and 62.5 or 100 MHz, respectively, in $CDCl_3$ solutions, unless otherwise indicated. Combustion elemental analysis were performed at the *Servei d'Anàlisi Química* at the *Universitat Autònoma de Barcelona*. Mass spectra were performed on a Hewlett-Packard 5989 instrument using the electrospray technique. HRMS spectra were recorded with a Micromass Autospec instrument. Chiral GC were performed using a capillary column of FS-Lipodex B (20 m x 0.25 mm) from Macherey-Nagel. Both enantiomers of menisdaurilide and compounds (+)-**7** and (+)-**8** were prepared following literature procedures.[15]

(6*S*,7a*S*)-2-Oxo-2,6,7,7a-tetrahydrobenzofuran-6-yl *p*-nitrobenzoate ((-)-6). To a stirred solution of (+)-menisdaurilide, (+)-**1**, (26 mg, 0.17 mmol), triphenylphosphine (134 mg, 0.51 mmol), and *p*-nitrobenzoic acid (85 mg, 0.51 mmol) in dry THF (2 mL) under a nitrogen atmosphere at -23ºC, diisopropyl azodicarboxylate (DIAD, 101 μL, 0.51 mmol) was added dropwise during 5 min. The mixture was stirred at the same temperature for 4 h and then 16 h at room temperature. The solvent was removed and the remaining yellow oil was purified by flash chromatography using hexane/ethyl acetate (from 9:1 to 7:3) as eluent, affording 48 mg of (-)-**6** (0.16 mmol, 93%) as a white solid: mp. 203-205ºC (ethyl acetate/hexane); $[\alpha]^{20}_{D}$ = -575 (*c* 1.61, $CHCl_3$); ^{1}H NMR (400 MHz): δ 8.29 (d, J = 9.1 Hz, 2H, H-Ar), 8.19 (d, J = 9.1 Hz, 2H, H-Ar), 6.80 (d, $J_{4,5}$ = 9.7 Hz, 1H, H-4), 6.42 (br dd, $J_{5,4}$ = 9.7 Hz, $J_{5,6}$ = 5.3 Hz, 1H, H-5), 5.93 (m, 1H, H-3), 5.84 (ddd, $J_{6,7ax} \approx J_{6,5} \approx$ 4.7 Hz, $J_{6,7eq}$ = 2.1 Hz, 1H, H-6), 5.31 (ddd, $J_{7a,7ax}$ = 12.6 Hz, $J_{7a,7eq}$ = 5.3 Hz, $J_{7a,3}$ = 1.8 Hz, 1H, H-7a), 2.81 (dddt, $J_{7eq,7ax}$ = 13.5 Hz, $J_{7eq,7a}$ = 5.3 Hz, $J_{7eq,6}$ = 2.1 Hz, $J_{7eq,5} \approx J_{7eq,3} \approx$ 1.2 Hz, 1H, H-7eq), 2.01 (td, $J_{7ax,7eq} \approx J_{7ax,7a} \approx$ 13.5 Hz, $J_{7ax,6}$ = 4.4 Hz, 1H, H-7ax); ^{13}C NMR (100 MHz): δ 172.5 (C-2), 163.8 (COO), 161.1 (C-3a), 150.8/134.8 (C-Ar), 132.8 (C-5), 130.9 (C-Ar), 124.8 (C-4), 123.7 (C-Ar), 114.0 (C-3), 75.8 (C-7a), 68.0 (C-6), 34.6 (C-7); IR (ATR): 3115, 3072, 3049, 2923, 2853, 1743, 1718, 1648, 1605, 1521, 1335, 1270, 1101, 1023, 1009, 848, 715 cm^{-1}; MS (ESI+, *m/z*): 340 (M^++K, 51), 324 (M^++Na, 100); HRMS (CI/CH_4, *m/z*): calcd for (M^++1) $C_{15}H_{11}NO_6$: 302.0665. Found: 302.0664.

(6*R*,7a*R*)-2-Oxo-2,6,7,7a-tetrahydrobenzofuran-6-yl *p*-nitrobenzoate ((+)-6). The same procedure described previously applied to (-)-menisdaurilide afforded (+)-**6** (92%) as a white solid: mp 202-205ºC (ethyl acetate/hexane); $[\alpha]^{20}_D$ = +566 (*c* 1.52, $CHCl_3$).

Hydrolysis of (-)-6. A suspension of (-)-**6** (9.5 mg, 0.032 mmol) and potassium carbonate (0.4 mg, 0.003 mmol) in methanol (0.8 mL) under argon atmosphere at 0ºC was stirred for 1 h. The mixture was filtered through a short path of silica gel and the solvent was removed. Flash chromatography of the crude solid using hexane/ethyl acetate (2:1) as eluent yielded the following fractions: (i) 6 mg of a 1:1.7 mixture of (-)-**6** and methyl *p*-nitrobenzoate; and (ii) 2.3 mg of a colorless oil identified as a 2:1 mixture of (-)-aquilegiolide, (-)-**2**, and (-)-menisdaurilide, (-)-**1**.

(3a*R*,7a*S*,4'*R*,5'*R*)-4',5'-Diphenyl-3a-hydroxyperhydrospiro[benzofuro-6(2*H*),2'-[1,3]dioxolan]-2-one ((+)-9). A suspension of (+)-**7** (1.07 g, 2.93 mmol) and 10% palladium over charcoal (316 mg, 0.30 mmol) in ethyl acetate (60 mL) was stirred under a hydrogen atmosphere at room temperature for 4 h. The mixture was filtered through celite® and the solvent was removed. Flash chromatography of the crude material using hexane/ether (1:1) as eluent yielded the following fractions: (i) 152 mg (14%) of starting material; and (ii) 753 mg (2.06 mmol, 82% yield considering the recovered material) of (+)-**9** as a white solid: mp 131-133ºC (methylene chloride/pentane); $[\alpha]^{20}_D$ = +7.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (250 MHz): δ 7.40-7.10 (m, 10H, H-Ar), 4.75 (s, 2H, H-4', H-5'), 4.55 (dd, $J_{7a,7}$ = 9.0 Hz, $J_{7a,7}$= 6.5 Hz, 1H, H-7a), 2.77 (d, $J_{3,3}$ = 17.2 Hz, 1H, H-3), 2.63 (ddd, $J_{7,7}$ = 14.0 Hz, $J_{7,7a}$ = 6.5 Hz, $J_{7,5}$ = 2.2 Hz, 1H, H-7), 2.50 (d, $J_{3,3}$ = 17.2 Hz, 1H, H-3), 2.35-2.05 (m, 3H, 2H-4, H-5), 2.00-1.80 (m, 3H, H-7, H-5, OH); ^{13}C NMR (62.5 MHz): δ 175.0 (C-2), 136.2/129.03/128.97/127.2/126.9 (C-Ar), 108.0 (C-6), 86.1/85.8 (C-4'/C-5), 84.8 (C-7a), 75.4 (C-3a), 40.2 (C-3), 39.8 (C-7), 33.0 (C-5), 31.3 (C-4); IR (ATR): 3438, 3032, 2952, 1779, 1496, 1453, 1359, 1229, 1187, 1107, 1022, 799, 764 cm^{-1}; MS (ESI+, *m/z*): 389 (M^++Na, 100). Anal. calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 71.84; H, 6.11.

(3a*S*,7a*R*,4'*R*,5'*R*)-4',5'-Diphenyl-3a-hydroxyperhydrospiro[benzofuro-6(2*H*),2'-[1,3]dioxolan]-2-one ((+)-10). The same procedure described previously applied to (+)-**8** for 2.5 h afforded (+)-**10** (97%) as a white solid: mp 138-140ºC (methylene chloride/pentane); $[\alpha]^{20}_D$ = +49 (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz): δ 7.40-7.10 (m, 10H, H-Ar), 4.79 (d, $J_{4',5'}$ = 8.6 Hz, 1H, H-4'/H-5'), 4.71 (d, $J_{4',5'}$ = 8.6 Hz, 1H, H-4'/H-5'), 4.64 (dd, $J_{7a,7}$ = 9.3 Hz, $J_{7a,7}$= 6.6 Hz, 1H, H-7a), 2.77 (d, $J_{3,3}$ = 17.3 Hz, 1H, H-3), 2.65 (ddd, $J_{7,7}$ = 13.8 Hz, $J_{7,7a}$ = 6.6 Hz, $J_{7,5}$ = 2.2 Hz, 1H, H-7), 2.52 (d, $J_{3,3}$ = 17.3 Hz, 1H, H-3), 2.30-1.80 (m, 6H, 2H-4, 2H-5, H-7, OH); ^{13}C NMR (62.5 MHz): δ 174.6 (C-2), 135.83/135.76/128.7/128.6/128.5/126.7/126.6 (C-Ar), 107.7 (C-6), 85.4 (C-4'+C-5'), 84.1 (C-7a), 74.8 (C-3a), 40.0 (C-3), 39.5 (C-7), 32.1/31.0 (C-4/C-5); IR (ATR): 3412, 3032, 2931, 1779, 1496, 1454, 1358, 1271, 1185, 1109, 1021, 764, 698 cm^{-1}.

(7a*S*,4'*R*,5'*R*)-4',5'-Diphenyl-4,5,7,7a-tetrahydrospiro[benzofuro-6(2*H*),2'-[1,3]dioxolan]-2-one ((+)-11). A solution of (+)-**9** (201 mg, 0.55 mmol) and thionyl chloride (395 μL, 5.45 mmol) in pyridine (7 mL) under a nitrogen atmosphere was stirred at room temperature for 18 h. A few mL of ethyl acetate were added and the organic solution was successively washed with water,

saturated sodium bicarbonate solution, and twice with water. The solvent was removed and flash chromatography of the remaining orange oil (252 mg) using hexane/ethyl acetate (4:1) as eluent yielded 182 mg (0.52 mmol, 95%) of (+)-**11** as a white solid: mp 146-148ºC (ether); $[\alpha]^{20}_D$ = +41 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz): δ 7.40-7.30 (m, 6H, H-Ar), 7.25-7.10 (m, 4H, H-Ar), 5.84 (br s, 1H, H-3), 5.06 (dd, $J_{7a,7}$ = 11.7 Hz, $J_{7a,7}$ = 6.7 Hz, 1H, H-7a), 4.84 (d, $J_{4',5'}$ = 8.8 Hz, 1H, H-4'/H-5'), 4.78 (d, $J_{4',5'}$ = 8.8 Hz, 1H, H-4'/H-5'), 2.95 (ddd, $J_{4,4}$ = 14.1 Hz, $J_{4,5}$ = 5.4 Hz, $J_{4,5}$ = 2.2 Hz, 1H, H-4), 2.90 (ddd, $J_{7,7}$ = 12.3 Hz, $J_{7,7a}$ = 6.7 Hz, $J_{7,5}$ = 2.6 Hz, 1H, H-7), 2.80 (br td, $J_{4,4} \approx J_{4,5} \approx$ 14.1 Hz, $J_{4,5}$ = 5.7 Hz, 1H, H-4), 2.36 (ddt, $J_{5,5}$ = 13.5 Hz, $J_{5,4}$ = 5.7 Hz, $J_{5,4} \approx J_{5,7} \approx$ 2.2 Hz, 1H, H-5), 1.92 (td, $J_{5,5} \approx J_{5,4} \approx$ 13.5 Hz, $J_{5,4}$ = 5.4 Hz, 1H, H-5), 1.88 (t, $J_{7,7} \approx J_{7,7a} \approx$ 12.0 Hz, 1H, H-7); ^{13}C NMR (62.5 MHz): δ 173.2 (C-2), 169.7 (C-3a), 135.62/135.57/128.7/128.60/128.55/126.7/126.5 (C-Ar), 113.7 (C-3), 108.2 (C-6), 85.8/85.5 (C-4'/C-5'), 79.9 (C-7a), 42.6 (C-7), 35.9 (C-5), 23.5 (C-4); IR (ATR): 3098, 2952, 2929, 2894, 1742, 1650, 1497, 1454, 1435, 1277, 1191, 1126, 1043, 881, 766, 752, 705 cm^{-1}; MS (ESI+, *m/z*): 371 (M^++Na, 100). Anal. calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.92; H, 5.69.

(7a*R*,4'*R*,5'*R*)-4',5'-Diphenyl-4,5,7,7a-tetrahydrospiro[benzofuro-6(2*H*),2'-[1,3]dioxolan]-2-one ((+)-12). The same procedure described previously applied to (+)-**10** for 2 h afforded (+)-**12** (91%) as a white solid: mp 146-148ºC (ether); $[\alpha]^{20}_D$ = +75 (*c* 0.12, $CHCl_3$); ^{1}H NMR (250 MHz): δ 7.40-7.27 (m, 6H, H-Ar), 7.26-7.10 (m, 4H, H-Ar), 5.84 (s, 1H, H-3), 5.16 (dd, $J_{7a,7}$ = 11.2 Hz, $J_{7a,7}$ = 6.5 Hz, 1H, H-7a), 4.83 (d, $J_{4',5'}$ = 8.5 Hz, 1H, H-4'/H-5'), 4.77 (d, $J_{4',5'}$ = 8.5 Hz, 1H, H-4'/H-5'), 2.98-2.85 (m, 2H, H-7, H-4), 2.72 (td, $J_{4,4} = J_{4,5}$ = 13.2 Hz, $J_{4,5}$ = 5.9 Hz, 1H, H-4), 2.32 (ddt, $J_{5,5}$ = 13.4 Hz, $J_{5,4}$ = 5.9 Hz, $J_{5,4} \approx J_{5,7} \approx$ 2.1 Hz, 1H, H-5), 1.97 (td, $J_{5,5} = J_{5,4}$ = 13.5 Hz, $J_{5,4}$ = 5.6 Hz, 1H, H-5), 1.82 (t, $J_{7,7} \approx J_{7,7a} \approx$ 12.0 Hz, 1H, H-7); ^{13}C NMR (62.5 MHz): δ 173.2 (C-2), 169.7 (C-3a), 135.6/135.5/128.8/128.7/128.62/128.55/126.7/126.6 (C-Ar), 113.7 (C-3), 108.4 (C-6), 85.7/85.4 (C-4'/C-5'), 79.6 (C-7a), 43.5 (C-7), 35.0 (C-5), 23.9 (C-4); IR (ATR): 3027, 2961, 2883, 1785, 1754, 1658, 1455, 1274, 1253, 1236, 1214, 1034, 884, 854, 767, 725, 697 cm^{-1}.

(*S*)-4,5,7,7a-Tetrahydrobenzofuran-2,6-dione ((+)-13). A mixture of (+)-**11** (128 mg, 0.37 mmol) and montmorillonite K-10 (3.0 g) in methylene chloride (60 mL) and water (0.2 mL) was heated at reflux temperature for 3 days. The mixture was filtered, the montmorillonite was washed several times with hot ethyl acetate, and the solvent was removed. Flash chromatography of the remaining yellow oil (172 mg) using hexane/ethyl acetate (from 5:1 to 2:1) as eluent afforded the following fractions: (i) 63 mg of 2-benzyl-2,4,5-triphenyl-1,3-dioxolane and diphenylacetaldehyde, both compounds derived from hydrobenzoin; (ii) 24 mg (19%) of starting material; and (iii) 28 mg (0.18 mmol, 50%) of (+)-**13** as a colorless oil (although contaminated with *ca*. 5% by an unidentified compound): $[\alpha]^{20}_D$ = +10.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz): δ 5.98 (s, 1H, H-3), 5.03 (dd, $J_{7a,7}$ = 11.7 Hz, $J_{7a,7}$= 7.1 Hz, 1H, H-7a), 3.21 (ddd, $J_{7,7}$ = 14.1 Hz, $J_{7,7a}$ = 7.1 Hz, $J_{7,5}$ = 1.5 Hz, 1H, H-7), 3.11 (m, 1H, H-4), 2.76-2.60 (m, 2H, H-4, H-5), 2.49 (m, 1H, H-5), 2.43 (dd, $J_{7,7}$ = 14.1 Hz, $J_{7,7a}$ = 11.7 Hz, 1H, H-7); ^{13}C NMR (100 MHz): δ 203.8 (C-6), 172.2 (C-2), 166.6 (C-3a), 115.3 (C-3), 78.8 (C-7a), 47.8 (C-7), 38.8 (C-5), 23.4 (C-4).

(*R*)-4,5,7,7a-Tetrahydrobenzofuran-2,6-dione ((-)-13). The same procedure described previously applied to (+)-**12** for 1 day afforded (-)-**13** (26%): $[\alpha]^{20}_D$ = -25 (*c* 0.55, $CHCl_3$).

(3a*S*,7a*S*)-3a-Hydroxy-3,3a,7,7a-tetrahydrobenzofuran-2,6-dione ((+)-14). A mixture of (+)-**7** (139 mg, 0.38 mmol) and montmorillonite K-10 (287 mg) in methylene chloride (14 mL) was heated at reflux temperature for 22 h. The mixture was filtered, the montmorillonite was washed several times with hot ethyl acetate, and the solvent was removed. Flash chromatography of the remaining yellow oil (129 mg) using hexane/ethyl acetate (5:4) as eluent afforded the following fractions: (i) 60 mg of 2-benzyl-2,4,5-triphenyl-1,3-dioxolane and diphenylacetaldehyde, both compounds derived from hydrobenzoin; (ii) 32 mg (23%) of starting material; and (iii) 49 mg (0.29 mmol, 99% yield considering the recovered material) of (+)-**14** as a white solid: mp 95-97ºC (ethyl acetate/hexane); $[\alpha]^{20}_D$ = +72 (*c* 1.46, acetone); ^{1}H NMR (250 MHz): δ 6.71 (dd, $J_{4,5}$ = 10.2 Hz, $J_{4,7a}$ = 1.3 Hz, 1H, H-4), 6.11 (d, $J_{5,4}$ = 10.2 Hz, 1H, H-5), 4.82 (td, $J_{7a,7} \approx J_{7a,7} \approx$ 5.5 Hz, $J_{7a,4}$ = 1.3 Hz, 1H, H-7a), 2.98 (d, $J_{3,3}$ = 17.4 Hz, 1H, H-3), 2.96 (dd, $J_{7,7}$ = 17.2 Hz, $J_{7,7a}$ = 4.8 Hz, 1H, H-7), 2.79 (d, $J_{3,3}$ = 17.4 Hz, 1H, H-3), 2.72 (dd, $J_{7,7}$ = 17.2 Hz, $J_{7,7a}$ = 5.9 Hz, 1H, H-7); ^{13}C NMR (62.5 MHz): δ 193.7 (C-6), 172.4 (C-2), 145.3 (C-4), 129.8 (C-5), 82.1 (C-7a), 71.9 (C-3a), 42.5 (C-3), 38.7 (C-7).

(3a*R*,7a*R*)-3a-Hydroxy-3,3a,7,7a-tetrahydrobenzofuran-2,6-dione ((-)-14). The same procedure described previously applied to (+)-**8** afforded (-)-**14** (79%): $[\alpha]^{20}_D$ = -58 (*c* 1.74, acetone).

(6*S*,7a*S*)-6-Hydroxy-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, (+)-dihydromenisdaurilide, ((+)-3). A suspension of (+)-**1** (37 mg, 0.24 mmol) and 10% palladium over charcoal (26 mg, 0.024 mmol) in ethyl acetate (7.5 mL) was stirred under a hydrogen atmosphere at room temperature for 30 min. The mixture was filtered through celite® and the solvent was removed. Flash chromatography of the crude material (55 mg) using hexane/ethyl acetate (1:1) as eluent yielded 33 mg (0.21 mmol, 88%) of (+)-**3** as a colorless oil: $[\alpha]^{20}_D$ = +85 (*c* 0.58, methanol) with ee ≥ 95%, lit.[14] $[\alpha]^{20}_D$ = +123 (*c* 0.2, methanol); ^{1}H NMR (250 MHz, CD_3OD): δ 5.84 (br s, 1H, H-3), 4.95 (dd, $J_{7a,7ax}$ = 11.8 Hz, $J_{7a,7eq}$ = 6.3 Hz, 1H, H-7a), 3.92 (tt, $J_{6,7ax} \approx J_{6,5ax} \approx$ 11.3 Hz, $J_{6,7eq} \approx J_{6,5eq} \approx$ 3.9 Hz, 1H, H-6), 2.90 (ddd, $J_{4eq,4ax}$ = 14.3 Hz, $J_{4eq,5ax}$ = 4.8 Hz, $J_{4eq,5eq}$ = 2.2 Hz, 1H, H-4eq), 2.71 (m, 1H, H-7eq), 2.45 (tdd, $J_{4ax,5ax} \approx J_{4ax,4eq} \approx$ 13.8 Hz, $J_{4ax,5eq}$ = 5.7 Hz, $J_{4ax,3}$ = 2.0 Hz, 1H, H-4ax), 2.22 (m, 1H, H-5eq), 1.40 (dddd, $J_{5ax,4ax}$ = 13.8 Hz, $J_{5ax,5eq}$ = 12.6 Hz, $J_{5ax,6}$ = 11.3 Hz, $J_{5ax,4eq}$ = 4.8 Hz, 1H, H-5ax), 1.27 (q, $J_{7ax,7a} \approx J_{7ax,7eq} \approx J_{7ax,6} \approx$ 11.5 Hz, 1H, H-7ax); ^{13}C NMR (62.5 MHz, CD_3OD): δ 176.9 (C-2), 174.9 (C-3a), 114.3 (C-3), 82.5 (C-7a), 68.2 (C-6), 44.2 (C-7), 36.7 (C-5), 25.9 (C-4). ^{13}C NMR (62.5 MHz): δ 173.4 (C-2), 170.2 (C-3a), 113.3 (C-3), 79.6 (C-7a), 66.8 (C-6), 42.1 (C-7), 34.7 (C-5), 24.1 (C-4).

(6*R*,7a*R*)-6-Hydroxy-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, (-)-dihydromenisdaurilide, ((-)-3). The same procedure described previously applied to (-)-**1** afforded (-)-**3** (77%): $[\alpha]^{20}_D$ = -88 (*c* 0.38, $CHCl_3$) with ee ≥ 95%, lit.[13] $[\alpha]^{20}_D$ = -112 (*c* 2.0, methanol) with 90% ee.

(6*S*,7a*S*)-2-Oxo-2,4,5,6,7,7a-hexahydrobenzofuran-6-yl *p*-nitrobenzoate ((-)-16). To a stirred solution of (+)-**3** (17 mg, 0.11 mmol), triphenylphosphine (104 mg, 0.40 mmol), and *p*-nitrobenzoic acid (71 mg, 0.42 mmol) in dry THF (1 mL) under a nitrogen atmosphere at -23ºC,

DIAD (87 μL, 0.44 mmol) was added dropwise during 5 min. The mixture was stirred at the same temperature for 4 h and then 15 h at room temperature. The solvent was removed and flash chromatography of the remaining yellow oil using hexane/ethyl acetate (from 9:1 to 7:3) as eluent afforded 25 mg (0.082 mmol, 75%) of (-)-**16** as a white solid: mp 164-166ºC (ethyl acetate/hexane); $[\alpha]^{20}_D$ = -33 (*c* 1.24, acetone); ^{1}H NMR (400 MHz): δ 8.29 (d, *J* = 9.1 Hz, 2H, H-Ar), 8.18 (d, *J* = 9.1 Hz, 2H, H-Ar), 5.85 (s, 1H, H-3), 5.61 (br s, 1H, H-6), 5.09 (dd, $J_{7a,7ax}$ = 11.4 Hz, $J_{7a,7eq}$ = 6.2 Hz, 1H, H-7a), 2.98-2.85 (m, 2H, H-7eq, H-4eq), 2.69 (td, $J_{4ax,4eq} = J_{4ax,5ax}$ = 13.8 Hz, $J_{4ax,5eq}$ = 5.6 Hz, 1H, H-4ax), 2.41 (br d, *J* ≈ 14.4 Hz, 1H, H-5eq), 1.77 (ddd, $J_{5ax,5eq}$ = 14.7 Hz, $J_{5ax,4ax}$ = 13.8 Hz, $J_{5ax,4eq}$ = 5.3 Hz, 1H, H-5ax), 1.65 (ddd, $J_{7ax,7eq}$ = 13.7 Hz, $J_{7ax,7a}$ = 11.4 Hz, $J_{7ax,6}$ = 2.6 Hz, 1H, H-7ax); ^{13}C NMR (100 MHz): δ 172.8 (C-2), 169.7 (C-3a), 163.5 (COO), 150.8/135.1/130.7/123.7 (C-Ar), 113.5 (C-3), 78.0 (C-7a), 70.2 (C-6), 37.8 (C-7), 30.2 (C-5), 23.3 (C-4); IR (ATR): 3115, 2954, 1733, 1717, 1689, 1606, 1524, 1349, 1276, 1102, 1070, 716 cm^{-1}; MS (ESI+, *m/z*): 326 (M^++Na, 100). Anal. calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.10; H, 4.15; N, 4.52.

(6*R*,7a*R*)-2-Oxo-2,4,5,6,7,7a-hexahydrobenzofuran-6-yl *p*-nitrobenzoate ((+)-16). The same procedure described previously applied to (-)-**3** afforded (+)-**16** (97%): $[\alpha]^{20}_D$ = +32 (*c* 0.42, acetone).

(6*R*,7a*S*)-6-Hydroxy-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, (+)-dihydroaquilegiolide, ((+)-4). A mixture of (-)-**16** (24 mg, 0.08 mmol) and potassium carbonate (13 mg, 0.09 mmol) in methanol (3 mL) was stirred at room temperature for 10 min. The suspension was filtered through a short path of silica gel and the solvent was removed. Flash chromatography of the remaining yellow oil (40 mg) using hexane/ethyl acetate (1:1) as eluent afforded the following fractions: (i) 13 mg of methyl *p*-nitrobenzoate as a yellow solid; and (ii) 11 mg (0.07 mmol, 88%) of (+)-**4** as a colorless oil: $[\alpha]^{20}_D$ = +122 (*c* 0.14, methanol) lit.[14] $[\alpha]^{20}_D$ = +125 (*c* 0.9, methanol), lit.[13] $[\alpha]^{20}_D$ = +113 (*c* 1.0, methanol) with 90% ee; ^{1}H NMR (400 MHz, CD_3OD): δ 5.82 (s, 1H, H-3), 5.17 (dd, $J_{7a,7ax}$ = 11.4 Hz, $J_{7a,7eq}$ = 6.5 Hz, 1H, H-7a), 4.29 (m, 1H, H-6), 2.75 (dd, $J_{4,5}$ = 8.8 Hz, $J_{4,5}$ = 3.2 Hz, 2H, H-4), 2.76 (m, 1H, H-7eq), 2.15 (m, 1H, H-5eq), 1.62 (m, 1H, H-5ax), 1.44 (ddd, $J_{7ax,7eq}$ = 12.6 Hz, $J_{7ax,7a}$ = 11.4 Hz, $J_{7ax,6}$ = 2.4 Hz, 1H, H-7ax); ^{13}C NMR (100 MHz, CD_3OD): δ 177.1 (C-2), 176.2 (C-3a), 113.5 (C-3), 81.7 (C-7a), 67.2 (C-6), 42.4 (C-7), 34.9 (C-5), 24.6 (C-4).

(6*S*,7a*R*)-6-Hydroxy-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one, (-)-dihydroaquilegiolide, ((-)-4). The same procedure described previously applied to (+)-**16** afforded (-)-**4** (71%): $[\alpha]^{20}_D$ = -124 (*c* 0.11, methanol).

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