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From *p*-benzoquinone to cyclohexane chirons: first asymmetric synthesis of (+)-rengyolone and (+)- and (−)-menisdaurilide

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Abstract—Starting from a common, easily available, enantiopure monoketal of *p*-benzoquinone, the synthesis of a large number of cyclohexane chirons has been achieved. The first synthesis of (+)-rengyolone and (+)- and (−)-menisdaurilide has been performed from one of these new building blocks. The wide variety of functional groups of this series of chirons makes them useful for subsequent synthetic processes.

1. Introduction

Nature synthesizes a large number of products which contain a densely functionalized cyclohexane subunit that accommodates several stereocenters in its structure. Rengyolone, (±)-**1**, and menisdaurilide, (−)-**2**, are two representative examples of such natural products (Fig. 1). The benzofuranone **1** was simultaneously isolated in 1984 by two research groups. Endo and Hikino[1] named it rengyolone, because they isolated it from the fruit of the plant *Forsythia suspensa*, named

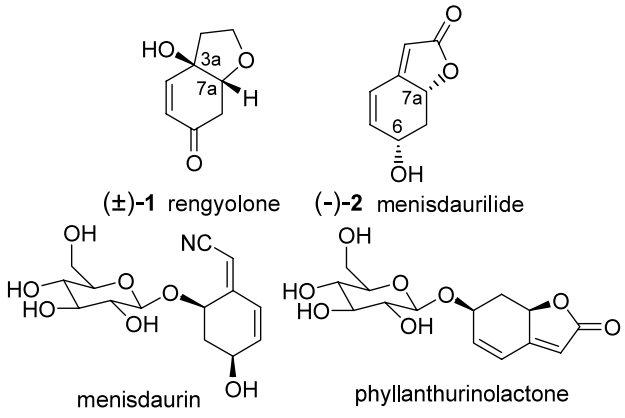

Figure 1.

'rengyo' in oriental medicine and used for its anti-inflammatory, diuretic and antidotal properties. Simultaneously, Italian researchers[2] isolated compound **1** from the leaves of *Halleria lucida*, a plant used for magical purposes and in folk medicine in Southern Africa, and gave it the name halleridone. Afterwards, rengyolone, the name that first appeared in the literature and which will be used in this paper, has been extracted also from other plants[3] and three Japanese patents claim the anticancer activity of **1** and its esters.[4] Benzofuranone **2** was first reported in the literature in 1978 as a product of the acid hydrolysis of menisdaurin, a nitrile glucoside isolated from *Menispermum dauricum*.[5] Later on, lactone **2** has been also isolated from several other plants[6] and its absolute configuration has been unequivocally established.[6c,d] Menisdaurilide is also the aglycon of phyllanthurinolactone, a bioactive substance that folds together the leaves of the plant *Phyllanthus urinaria* in the daytime, a phenomenon called nyctinasty.[7]

Nature also biosynthesizes a series of polyoxygenated cyclohexanes like phyllostine,[8] a phytotoxic compound, or bromoxone,[9] aranorosin,[10] the manumycins,[11] and fumagillin and its analogues,[12] all of them presenting interesting antitumor activity (Fig. 2).

Therefore, it is not surprising that many methodologies for the synthesis of cyclohexane chirons had been developed during the last decade. Some of these efforts include the work by Hudlicky's group,[13] who have described the successful preparation of a large number

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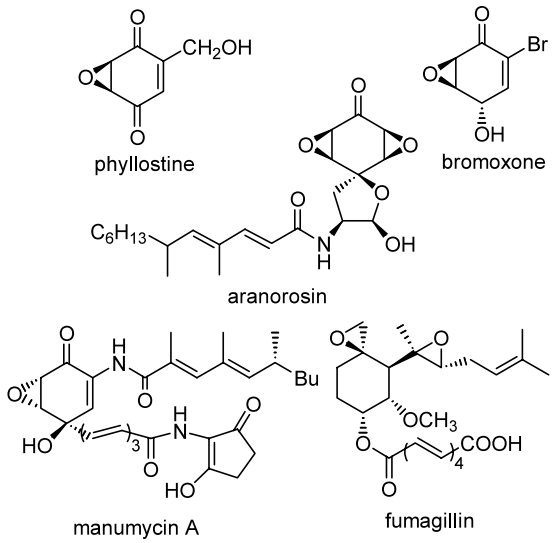


Figure 2.

of enantiopure cyclohexadiene-1,2-diols, **3**, (Fig. 3) by enzymatic oxidation of the aromatic compounds. Ogasawara[14] has synthesized several non racemic Diels–Alder cycloadducts, **4**, derived from *p*-benzoquinone. The cyclohexenone **5** has been described by Sato.[15] Enders[16] has achieved the asymmetric synthesis of several substituted 1,4-cyclohexanedione derivatives, **6**, and Taber has described the cyclohexenone **7**,[17] and used it as an intermediate in a synthesis of fumagillin.[12c] Most of these authors have demonstrated the versatility of these cyclohexanes as chiral building blocks by performing also the syntheses of other natural products in enantiopure form.

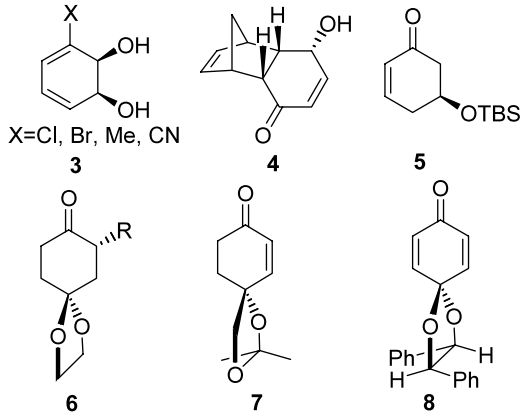


Figure 3.

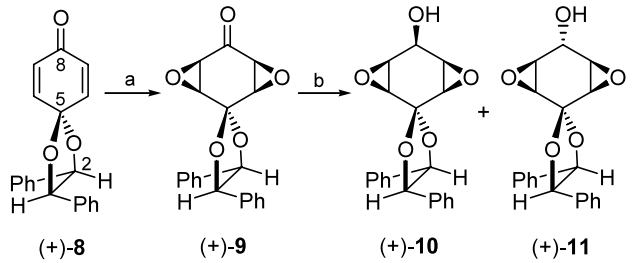
A few years ago, we started a research project, focused on the development of a new class of cyclohexane chirons. As other authors,[9c,14] we visualized the inexpensive *p*-benzoquinone as an appropriate starting material and we conceived a new approach in order to convert this achiral, highly symmetric molecule, presenting two pairs of equivalent functional groups, into a useful chiron. The formation of enantiopure monoketals of *p*-benzoquinone derived from C_2-symmetric 1,2-diols, e.g. **8**, was considered a suitable approach for our purpose.[18] The usefulness of C_2-symmetric diols as chiral auxiliaries for asymmetric induction has been demonstrated during the last years by a substantial number of publications.[9c,19] Chiral auxiliaries with C_2-symmetry usually provide higher levels of stereochemical control than those lacking symmetry as they present the main advantage of reducing the number of possible competing transition states. Owing to their C_2-symmetry, in monoketal **8** both faces of the remaining carbonyl group and both carbon–carbon double bonds are equivalent. Another important feature is that all six carbon atoms of the cyclohexane ring are functionalised. Monoketal (+)-**8** can be prepared in gram-scale from *p*-benzoquinone and (*R*,*R*)-hydrobenzoin in a single step.[18a] In recent papers, we have already described the utility of these enantiopure monoketals in several diastereoselective transformations,[20] including an efficient synthesis of (*S*)-4-hydroxy-2-cyclohexen-1-one. We report now the straightforward synthesis of several new enantiopure polyfunctionalised cyclohexanes with the structure of 1,4-dioxa[4.5]decane, starting from monoketal **8**. The value of these new chirons for bioactive product synthesis is demonstrated by completing the first synthesis of (+)-rengyolone and (+)- and (−)-menisdaurilide.[21]

2. Results and discussion

2.1. Synthesis of new cyclohexane chirons

With the aim of preparing a new set of cyclohexane chirons, we have systematically explored the modification of the C–C double bonds and the carbonyl group of **8**. Epoxidation, bromination, and iodination reactions have been performed, because many cyclohexane natural products present the oxygen or halogen atoms as substituents. Considering that the cyclohexane ring may present different degrees of unsaturation, several reduction processes of **8** have also been studied. Finally, we have investigated the formation of new C–C bonds at the carbonyl carbon atom and its α-position, since several interesting natural products present side chains at these positions.

Reaction of ketal **8** with an excess of hydrogen peroxide in the presence of a catalytic amount of sodium hydroxide at room temperature afforded the *cis*-bisepoxide (+)-**9** as a white solid in 95% yield (Scheme 1).

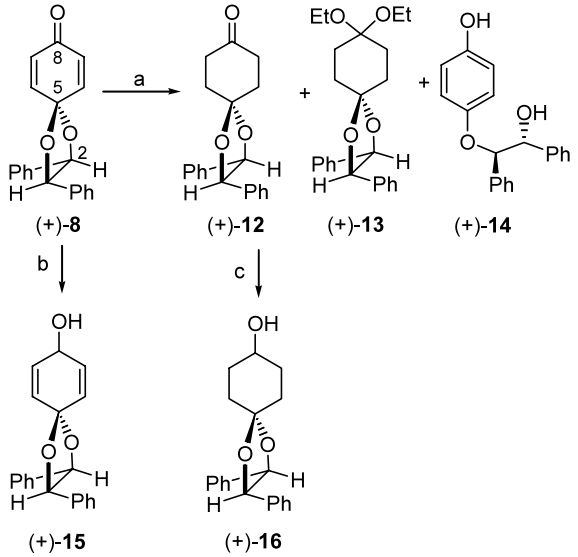


Scheme 1. *Reagents and conditions*: (a) exc. H_2O_2, NaOH cat., MeOH, rt, 1 day, 95%; (b) $NaBH_4$, MeOH, 0°C, 10 min, 81%.

The presence in the ^{13}C NMR spectrum of eight non-aromatic signals reveals the loss of symmetry in the molecule and hence evidences that the epoxides are in a *cis*-relationship. The ^{1}H NMR spectrum of **9** displays four different signals for the oxirane protons, all of them showing a multiplicity of double doublet. This pattern discloses the existence of long range coupling constants between the pairs of protons H-7/H-9 and H-6/H-10, indicative of a boat conformation for the cyclohexane ring with the oxirane oxygen atoms occupying axial positions, as in the case of the natural product aranorosin.[10b] The exclusive formation of *cis* bisepoxides in the oxidation of *p*-benzoquinone ketals was already documented in the literature.[22] The advantage of using a C_2-symmetric chiral auxiliary becomes apparent here, where a unique diastereoisomer of the *cis*-bisepoxide is possible.

Treatment of **9** with sodium borohydride gave the diastereoisomeric alcohols (+)-**10** and (+)-**11** in 54% and 27% yield, respectively, as solids. Besides the four oxirane protons, the ^{1}H NMR spectra of both alcohols show two doublets at $\delta \approx 4.5$ and 2.7, assignable to the H-8 and the hydroxyl proton, respectively. The stereochemical assignment of the less polar and major isomer **10** relies on the NOE observed on two of the oxirane protons upon irradiation of H-8. The same experiment was negative for its diastereoisomer **11**.

Next, we studied the reduction processes of the dienone system of **8**. The hydrogenation of **8** using Pd over charcoal in ethanol was very fast, the starting substrate being consumed in 15 min, and purification of the crude material afforded three new compounds identified as (+)-**12**, (+)-**13**, and (+)-**14** in 15, 36 and 39% yield, respectively (Scheme 2). The same reaction performed in ethyl acetate to avoid the incorporation of the solvent furnished only compounds **12** (59%) and **14** (16%).



Scheme 2. *Reagents and conditions*: (a) H_2, Pd/C, toluene, 15 min, 95%; (b) $NaBH_4$, $MeOH/CH_2Cl_2$ 1/1, 0°C, 30 min, 87%; (c) $NaBH_4$, MeOH, 0°C, 15 min, 91%.

We reasoned that the formation of phenol **14** could be favored by traces of acid present in the solvents. Thus, a third essay in toluene provided the desired cyclohexanone **12** in 95% yield. A different preparation of **12**, starting from 1,4-cyclohexanediol was recently described by Konopelski[23] in relation with the synthesis of anticancer chemotherapeutic agents, but we believe that our new access to **12** competes advantageously. The structural assignment of bisketal **13** relies on the presence of a quadruplet at δ 3.49 and a triplet at δ 1.18 in the ^{1}H NMR and the two acetal signals at δ 109.5 and 99.2 in its ^{13}C NMR. The ^{1}H NMR spectrum of **14** shows two doublets at δ 6.71 and 6.60, which are characteristic for an electron rich *p*-disubstituted benzene ring.

When ketone **8** was subjected to $NaBH_4$ reduction in methylene chloride–methanol solution (1:1), the new bisallylic alcohol (+)-**15** was isolated in 87% yield as a white solid. The absorptions at δ 99.4 and 62.4 in its ^{13}C NMR spectrum demonstrate the presence of the ketal group and the allylic alcohol, respectively.

Sodium borohydride reduction of the carbonyl group of ketal **12** delivered the alcohol (+)-**16** as a solid in 91% yield. The C_2-symmetry of the chiral auxiliary prevents the formation of a new stereogenic center at C-8 and hence the existence of diastereoisomeric products. Nevertheless, in alcohol (+)-**16** the molecular symmetry is lost causing the appearance of a different doublet at δ 4.75 and 4.71 for each dioxolane proton. Compound **16** is an intermediate in the above mentioned Konopelski's synthesis of **12**.[23]

We also explored the incorporation of chlorine and bromine atoms into the cyclohexane moiety of ketal **8**, which had a double interest. Firstly, some bioactive cyclohexanes present a vinylic halogen atom in their structure and, secondly, a vinylic halide is an appropriate precursor for the introduction of side chains through well established C–C coupling reactions.[24] Treatment of **8** with an excess of bromine in methylene chloride followed by addition of triethylamine afforded the bromo derivatives (+)-**17** and (+)-**18** as white solids in 73 and 24% yield, respectively (Fig. 4). Using 0.53 equivalents of bromine the monoreaction product **17** was the main product, isolated in 86% yield considering the recovered acetal **8**. The NMR spectra of **18** were very simple, according to the high symmetry of the molecule, while the ^{1}H NMR spectrum of **17** showed three olefinic absorptions at δ 7.39, 6.97 and 6.40, corresponding to H-6, H-10 and H-9, respectively. The iodination reaction was performed with an excess of iodine in carbon tetrachloride as solvent and in the presence of pyridine. The mono- and direaction products, (+)-**19** and (+)-**20**, respectively, were isolated as white solids in ca. 50% yield each. The olefinic protons of **19** resonate at δ 7.70, 6.96 and 6.41.

Once the reduction and oxidation reactions of the dienone system of **8** had been thoroughly investigated, our next goal was the attachment of carbon chains to the cyclohexane skeleton. Some natural products con-

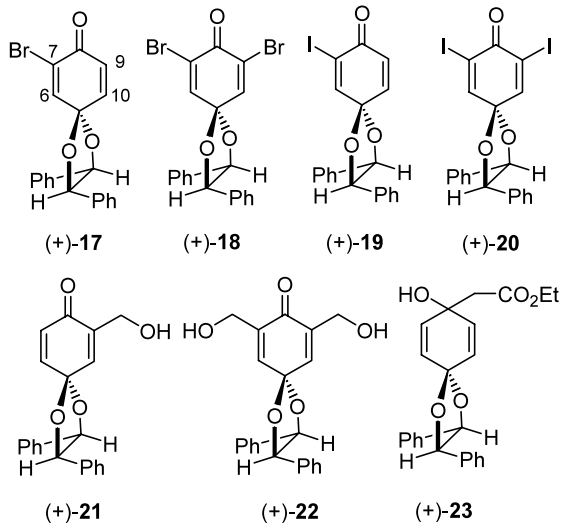


Figure 4.

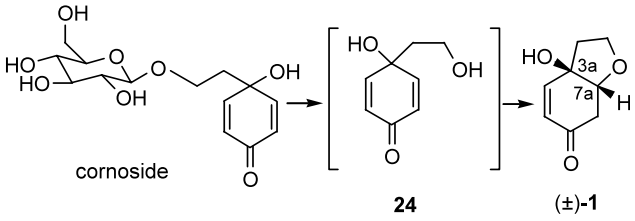
tain a hydroxymethyl group or longer chains at the α-carbonyl position of a cyclohexenone. For this reason we decided to attempt the reaction of ketal **8** with formaldehyde. The incorporation of a hydroxymethyl group would additionally open several synthetic alternatives to enlarge this side chain. The reaction between **8** and an excess of aqueous formaldehyde in the presence of 4-dimethylaminopyridine (DMAP)[25] afforded the mono- and dihydroxymethyl derivatives, (+)-**21** and (+)-**22**, in 25 and 51% isolated yield, respectively. The ^{1}H NMR spectrum of **21** discloses two deshielded protons at δ 7.00–6.90 (H-6 and H-10) and a third one at δ 6.26 (H-9). That of **22**, according to the symmetry of the molecule, shows only three singlets at δ 6.95, 4.94 and 4.45 due to the olefinic, benzylic and methylene protons, respectively, along with the aromatic signals. In the ^{13}C NMR spectra of **21** and **22** the hydroxymethyl groups display resonances at δ 60.2 and 57.1, respectively.

Compounds **17**, **19** and **21** are *p*-benzoquinone derivatives in which both pairs of functional groups initially equivalent have been differentiated, and hence may be particularly useful for further synthetic transformations.

Considering the structure of rengyolone and menisdaurilide, we then directed our efforts to link a C_2-chain to the carbonyl group of **8**. Wittig-type reactions were originally attempted, but all our trials to condense **8** with phosphonates derived from ethyl acetate or acetic acid failed. However, treatment of **8** with ethyl iodoacetate in the presence of indium powder[26] led to the isolation of the new ester (+)-**23** in 94% yield as a colorless oil. Both olefinic protons of compound **23** resonate at δ 6.3–6.1, according to the loss of conjugation, and the incorporation of the acetate unit is confirmed by the presence of the ethoxy group (δ 4.17 and 1.26) and a singlet at δ 2.63 in the ^{1}H NMR spectrum and the absorption at 1731 cm^{-1} in the IR spectrum.

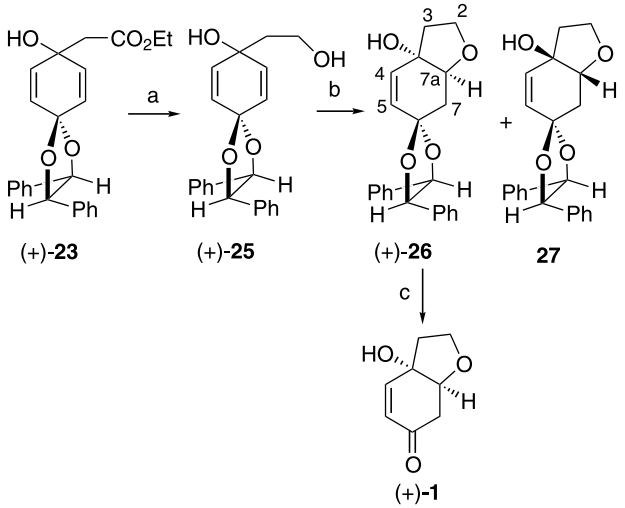
2.2. Synthesis of (+)-rengyolone

None of the samples of rengyolone isolated from natural sources present a significant value of specific rotation and it is therefore accepted that the natural compound occurs as a racemate. The proposed biosynthetic pathway involves spontaneous closure of the achiral quinol **24** (Scheme 3) formed by the enzymatic hydrolysis of the glucoside cornoside.[3d,27] Nevertheless, in 1997 a Chinese group published the isolation of six new compounds from *Clerodendrum indicum*, one of them with identical structure and relative stereochemistry to rengyolone.[28] This compound was named cleroindicin F and the authors reported a specific rotation of $[\alpha]_D^{20}$ −2.74 (*c* 0.016, MeOH). Moreover, since rengyolone had only been synthesized in racemic form,[27,29] the actual specific rotation of the pure enantiomers was unknown.



Scheme 3.

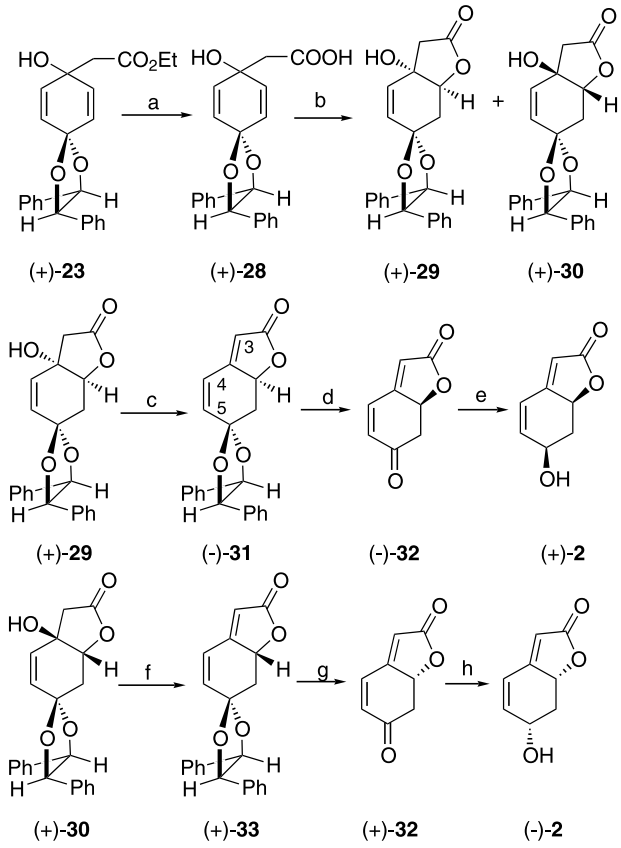
We envisaged hydroxyester **23** as a suitable precursor to intend an asymmetric synthesis of rengyolone, through a biomimetic strategy consisting in the preparation of a chiral equivalent of the postulated biogenetic intermediate **24** (Scheme 4). The reduction of **23** with lithium aluminum hydride furnished a complex mixture of ketone **8**, unreacted **23**, phenol **14**, and the desired diol (+)-**25** in a ratio 1:3:1:5. Fortunately, a second attempt with lithium borohydride afforded the diol **25** as a solid in 94% yield.



Scheme 4. *Reagents and conditions*: (a) $LiBH_4$, THF, 0°C, 4 days, 94%; (b) $Hg(CF_3COO)_2$, DME, rt, 2 h, then $NaBH_4$, 1.2 M NaOH, rt, 5 min, 78%; (c) montmorillonite K-10, CH_2Cl_2, rt, 1 day, 45%.

The next transformation consisted in the cyclization to the benzofuran skeleton through an intramolecular addition of the primary alcohol to the olefin. In principle, this process could give rise to up to four diastereoisomers, but we expected only the formation of the *cis* fused isomers according to reported precedents in related ring closing reactions leading to the formation of benzofurans.[27,29] Thus, treatment of **25** with mercuric trifluoroacetate followed by reduction with sodium borohydride[30] afforded a ca. 2:1 mixture of cyclic ethers **26** and **27** in 78% yield. Repeated column chromatography led to the isolation of the less polar and major isomer **26** as a solid in 52% yield. Its ^{1}H NMR spectrum shows two olefin protons at δ 6.05 (d) and 5.91 (dd). The last signal attributed to H-5 because of the long range coupling constant with one H-7. The formation of the furan ring is also evidenced by the signal of H-7a at δ 4.26 (dd). The NOESY spectrum of **26** was not conclusive to determine its stereochemistry, but an X-ray crystallographic analysis confirmed the *cis* stereochemistry of the ring fusion and also revealed that the absolute configuration of the new stereogenic centers (3a and 7a) was *S*.[21b]

The minor isomer **27** was obtained with a 92% purity and was characterized by its NMR data. Removal of the chiral auxiliary from compound **26** using montmorillonite K-10[11b,22b] yielded 45% of (+)-**1** as a colorless oil that crystallized on standing, whose NMR data match those reported for (±)-**1**.[1,2,3c,29a] This synthetic (+)-rengyolone showed a specific rotation $[\alpha]_D^{20}$ +48.6 (*c* 0.3 MeOH) and an enantiomeric excess of 85%, determined by CGC and NMR analysis assisted by the perdeuterated Pirkle alcohol[31] as chiral shift reagent. Since the value of the specific rotation measured for our sample of (+)-**1** with 85% ee is much higher than that reported for cleroindicin F ($[\alpha]_D^{20}$ −2.74),[28] it is clear that the last compound should be identified as racemic rengyolone.



Scheme 5. *Reagents and conditions*: (a) KOH, H_2O/EtOH, rt, 5 h, 84%; (b) CF_3COOH, $CHCl_3$, rt, 2 days, 60% of **29** and 28% of **30** or $Hg(CF_3COO)_2$, CH_2Cl_2, rt, 1 day, 30% of **29** and 45% of **30**; (c) $SOCl_2$, py, rt, 30 min, 84%; (d) montmorillonite K-10, CH_2Cl_2, reflux, 6 days, 49%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 0°C, 30 min, 74%; (f) $SOCl_2$, py, rt, 15 min, 89%; (g) montmorillonite K-10, CH_2Cl_2, reflux, 1 day, 65%; (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 0°C, 30 min, 63%.

2.3. Synthesis of (+)- and (−)-menisdaurilide

To the best of our knowledge, there is only one reported synthesis of **2** and it is prepared as the racemate.[32] Our synthesis of (+)- and (−)-**2** is depicted in Scheme 5. Potassium hydroxide mediated saponification of **23** provided the hydroxy acid (+)-**28** as a white solid in 84% yield.

γ-Lactonisation was achieved by intramolecular addition of the carboxylic acid to the olefin promoted either by trifluoroacetic acid or mercuric trifluoroacetate.[33] Under both conditions, the *cis* fused, crystalline lactones (+)-**29** and (+)-**30** were exclusively produced in 60 and 28 or 30 and 45% yields, respectively. The formation of the lactone is secured by the presence of signals at 1774 and 1785 cm^{-1} in the IR spectrum of **29** and **30**, respectively. The less polar diastereoisomer **29** could be isolated in pure form, while **30** was contaminated with ca. 7% of **29**, according to NMR analysis. Although the configuration of the new stereocenters could not be determined by spectroscopic analysis, it was established by chemical correlation (vide infra).

The synthesis of menisdaurilide was continued independently from each diastereoisomer. Dehydration of the tertiary alcohol of **29** was unsuccessful in both acid and basic media, but treatment with thionyl chloride,[34] afforded (−)-**31** as a white solid in 84% yield. Its ^{1}H NMR spectrum shows three signals in the olefin region at δ 6.74 (d), 6.31 (dd) and 5.92 (dd) that correspond to H-5, H-4, and H-3, respectively. The IR spectrum shows the characteristic absorptions of an α,β-butenolide at 1785 and 1758 cm^{-1}. Removal of the acetal was performed as above by treatment of **31** with montmorillonite K-10. This reaction furnished 49% yield of the benzofuranone (−)-**32**, which spectroscopic data are identical to those reported for racemic **32**.[32b] Finally, (+)-menisdaurilide ($[\alpha]_D^{20}$ = +27.6 (*c* 0.6, MeOH)) was prepared in 74% yield by reduction of the ketone function of (−)-**32** using Luche's reagent, as previously described for the synthesis of (±)-**2**.[32] In a similar way, the levorotatory natural isomer of **2** was synthesized from lactone **30**. Dehydration of **30** afforded (+)-**33** as a solid in 89% yield. Removal of the chiral auxiliary provided a 65% yield of the solid benzofuranone (+)-**32** which upon reduction afforded a sample of crystalline

(−)-**2** in 63% yield ($[\alpha]_D^{20}$ −20.0 (*c* 0.4, MeOH)). The specific rotation values previously reported for (−)-**2**, isolated from natural sources oscilate in the range between −27.3 and −31.4.[5,6]

The spectral data of both (+)-**2** and (−)-**2** matched exactly those of (±)-**2**.[6b–d,32b] The enantiomeric purity of our synthetic samples was determined by NMR analysis assisted by the perdeuterated Pirkle alcohol.[31] The measured ee of (+)-**2** was >98% and that of (−)-**2** 80%, values in accordance with the specific rotations experimentally observed.

3. Conclusions

In conclusion we have described a straightforward and efficient access to the first enantiopure bisepoxide of a *p*-benzoquinone monoketal and the preparation of several new cyclohexane chirons with a wide variety of functional groups which are useful for further synthetic elaborations. Considering the low cost and easy accessibility of the starting materials, *p*-benzoquinone and enantiopure hydrobenzoin, this set of enantiopure cyclohexanes can become valuable chirons for bioactive product synthesis. As an application, we have accomplished the first synthesis of (+)-rengyolone, and (+)- and (−)-menisdaurilide from the common cyclohexane building block (+)-**23** in 22, 15 and 14% overall yields, respectively. Enantioselective syntheses of other natural products from chiral building blocks derived from *p*-benzoquinone monoketals are currently under development.

4. Experimental

4.1. General

Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 5–10 Torr. Flash chromatographies were performed using Merck silica gel (230–400 mesh). (*R*,*R*)-Hydrobenzoin was prepared according to a previously described method.[35] Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250-WB instrument at 250 and 62.5 MHz, respectively, in $CDCl_3$ solutions. Mass spectra were performed on a Hewlett-Packard 5985B instrument using electron impact at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments. Alternatively, chemical ionization with ammonia has been used. CGC was performed using a capillary column of FS-Lipodex B (25 m×0.25 μm) from Macherey-Nagel.

4.2. (2*R*,3*R*,6*R*,7*S*,9*R*,10*S*)-6,7:9,10-Diepoxy-2,3-diphenyl-1,4-dioxaspiro-[4.5]decan-8-one, (+)-9

To a solution of (+)-**8** (201 mg, 0.66 mmol) in methanol (35 mL), a 30% aqueous solution of hydrogen peroxide (2.4 mL, 23.3 mmol) was added. A 0.06 M aqueous solution of NaOH (1.6 mL, 0.10 mmol) was added dropwise and the resulting solution was left at room temperature for 1 day. Water was added (5 mL) and the solution was extracted with methylene chloride. Flash chromatography of the oily crude material (304 mg) using hexane/ethyl acetate (4:1) as eluent afforded (+)-**9** as a white solid (210 mg, 0.62 mmol, 95%): mp 116–117°C (ether/pentane); $[\alpha]_D^{20}$ = +44.1 (*c* 1.2, $CHCl_3$); IR (KBr) 3037, 2924, 1715, 1455, 1138, 998, 934, 766, 702 cm^{-1}; ^{1}H NMR δ 7.50–7.20 (m, 10H), 5.08 (d, *J* = 8.8 Hz, 1H), 4.95 (d, *J* = 8.8 Hz, 1H), 3.83 (t, *J* = 3.7 Hz, 1H), 3.74 (t, *J* = 3.7 Hz, 1H), 3.58 (dd, *J* = 3.7, 2.6 Hz, 1H), 3.50 (dd, *J* = 3.7, 2.6 Hz, 1H); ^{13}C NMR δ 197.4, 134.5, 134.3, 129.2, 129.0, 128.8, 128.7, 126.6, 126.5, 101.4, 86.8, 86.0, 60.8, 60.0, 55.3, 55.2; MS *m*/*z* 337 (M^++1, 1), 173 (21), 167 (34), 165 (22), 156 (26), 145 (26), 131 (39), 105 (100), 96 (21), 91 (53), 89 (23), 79 (30), 77 (50), 68 (22). Anal. calcd for $C_{20}H_{16}O_5$: C, 71.00; H, 5.36. Found: C, 71.04; H, 5.05.

4.3. (2*R*,3*R*,6*R*,7*R*,8*R*,9*S*,10*S*)-6,7:9,10-Diepoxy-2,3-diphenyl-1,4-dioxaspiro[4.5]decan-8-ol, (+)-10, and its (2*R*,3*R*,6*R*,7*R*,8*S*,9*S*,10*S*)-isomer, (+)-11

To a solution of (+)-**9** (86 mg, 0.26 mmol) in methanol (3 mL) at 0°C, $NaBH_4$ (8 mg, 0.21 mmol) was added in small portions. The mixture was allowed to react for 10 min. The solvent was removed and water was added (2 mL); the mixture was neutralized with saturated aqueous NH_4Cl and was extracted with methylene chloride. Flash chromatography of the oily crude material (109 mg) using CH_2Cl_2/ether (25:1) as eluent afforded the following fractions: (i) 48 mg (0.14 mmol, 54%) of (+)-**10** as a white solid; and (ii) 23 mg (0.07 mmol, 27%) of (+)-**11** as a white solid. (+)-**10**: mp 215–217°C (CH_2Cl_2/pentane); $[\alpha]_D^{20}$ = +20.4 (*c* 0.8, $CHCl_3$); IR (KBr) 3543, 3473, 3065, 3037, 2994, 2896, 1497, 1455, 1258, 1145, 1124, 1072, 1008, 970, 878, 766, 702 cm^{-1}; ^{1}H NMR δ 7.40–7.10 (m, 10H), 5.04 (d, *J* = 8.8 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.58 (d, *J* = 9.5 Hz, 1H), 3.47 (m, 2H), 3.34 (m, 1H), 3.25 (m, 1H), 2.85 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR δ 134.9, 129.1, 128.73, 128.68, 128.5, 126.7, 126.5, 102.0, 86.7, 85.6, 60.8, 55.8, 55.6, 53.9, 53.4; MS *m*/*z* (CI/NH_3) 356 (M^++18, 100), 214 (30), 197 (38). Anal. calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 71.22; H, 5.30. (+)-**11**: mp 213–215°C (CH_2Cl_2/pentane); $[\alpha]_D^{20}$ = +8.9 (*c* 0.9, $CHCl_3$); IR (KBr) 3431, 3194, 3030, 2891, 1494, 1453, 1391, 1261, 1151, 1128, 1066, 1021, 996, 941, 770, 702 cm^{-1}; ^{1}H NMR δ 7.40–7.20 (m, 10H), 5.06 (d, *J* = 8.6 Hz, 1H), 4.90 (d, *J* = 8.6 Hz, 1H), 4.36 (br d, *J* = 10.2 Hz, 1H), 3.63 (m, 1H), 3.58 (m, 1H), 3.50 (m, 2H), 2.50 (br d, *J* = 10.2 Hz, 1H); ^{13}C NMR δ 135.0, 134.7, 129.1, 128.8, 128.7, 128.6, 126.8, 126.5, 101.8, 86.8, 85.7, 63.9, 58.0, 57.4, 56.3, 56.1; MS *m*/*z* (CI/NH_3) 356 (M^++18, 100), 339 (M^++1, 6).

4.4. (2*R*,3*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]decan-8-one, (+)-12

(a) A suspension of (+)-**8** (101 mg, 0.33 mmol) and palladium (10%) on activated carbon (32 mg) in ethanol

(10 mL) and ethyl acetate (2 mL) was reduced with hydrogen at room temperature and atmospheric pressure for 15 min. The mixture was filtered through Celite and the solvent was removed. Flash chromatography of the oily crude material (110 mg) using hexane/ether (5:1) as eluent afforded the following fractions: (i) 47 mg (0.12 mmol, 36%) of (2*R*,3*R*)-8,8-diethoxy-2,3-diphenyl-1,4-dioxaspiro[4.5]decane, (+)-**13**, as a colorless oil; (ii) 15 mg (0.05 mmol, 15%) of (+)-**12**,[23] as a colorless oil; and (iii) 40 mg (0.13 mmol, 39%) of 4-[(1*R*,2*R*)-2-hydroxy-1,2-diphenylethoxy]phenol, (+)-**14**, as a white solid. (b) A suspension of (+)-**8** (100 mg, 0.33 mmol) and palladium (10%) on activated carbon (32 mg) in ethyl acetate (2 mL) was reduced with hydrogen at room temperature and atmospheric pressure for 15 min. The mixture was filtered through Celite and the solvent was removed. Flash chromatography of the oily crude material (76 mg) using hexane/ether (2:1) as eluent afforded the following fractions: (i) 60 mg (0.19 mmol, 59%) of (+)-**12**[23] as a colorless oil; and (ii) 16 mg (0.05 mmol, 16%) of (+)-**14** as a white solid. (c) A suspension of (+)-**8** (200 mg, 0.66 mmol) and palladium (10%) on activated carbon (66 mg) in toluene (5 mL) was reduced with hydrogen at room temperature and atmospheric pressure for 15 min. The mixture was filtered through Celite and the solvent was removed. Flash chromatography of the oily crude material (222 mg) using hexane/ether (2:1) as eluent afforded the following fractions: (i) 194 mg (0.63 mmol, 95%) of (+)-**12**;[23] and (ii) 10 mg (0.03 mmol, 5%) of (+)-**14**. (+)-**12**: $[\alpha]_D^{20}=+38.4$ (*c* 1.3, $CHCl_3$); IR (KBr) 3066, 3033, 2959, 2898, 1718, 1452, 1266, 1131, 1098, 1026, 934, 759, 702 cm^{-1}; ^1H NMR δ 7.25–7.10 (m, 10H), 4.81 (s, 2H), 2.62 (br t, $J=6.9$ Hz, 4H), 2.29 (m, 4H); ^{13}C NMR δ 209.9, 136.1, 128.5, 126.6, 107.8, 85.4, 38.0, 35.2; MS *m*/*z* (CI/NH_3) 326 (M^++18, 100), 309 (M^++1, 13), 103 (31), 86 (25). Anal. calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.19; H, 6.61. (+)-**13**: $[\alpha]_D^{20}=+18.5$ (*c* 0.3, $CHCl_3$); IR (film) 3066, 3036, 2971, 2930, 2883, 1451, 1374, 1261, 1126, 1054, 982, 700 cm^{-1}; ^1H NMR δ 7.35–7.12 (m, 10H), 4.73 (s, 2H), 3.49 (q, $J=7.3$ Hz, 4H), 1.99 (s, 8H), 1.18 (t, $J=7.3$ Hz, 6H); ^{13}C NMR δ 136.9, 128.4, 128.2, 126.6, 109.5, 99.2, 85.1, 55.4, 32.9, 30.6, 15.5; MS *m*/*z* (CI/NH_3) 337 (M^+–EtO, 76), 141 (100). Anal. calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.29; H, 8.01. (+)-**14**: mp 154–155°C (CH_2Cl_2); $[\alpha]_D^{20}=+13.3$ (*c* 0.5, acetone); IR (KBr) 3571, 3522, 3058, 3030, 2889, 1511, 1230, 1166, 1026, 780, 702 cm^{-1}; ^1H NMR δ 7.30–6.93 (m, 10H), 6.71 (d, $J=8.8$ Hz, 2H), 6.60 (d, $J=8.8$ Hz, 2H), 4.95 (d, $J=7.9$ Hz, 1H), 4.86 (d, $J=7.9$ Hz, 1H), 4.62 (s, 1H), 3.40 (s, 1H); ^{13}C NMR δ 151.7, 150.1, 138.6, 137.3, 128.1, 128.0, 127.9, 127.4, 126.9, 117.6, 116.0, 86.6, 78.7; MS *m*/*z* (CI/NH_3) 324 (M^++18, 42), 306 (M^+, 2), 289 (26), 214 (100), 197 (45). Anal. calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.37; H, 6.01.

4.5. (2*R*,3*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-ol, (+)-15

To a solution of (+)-**8** (300 mg, 0.99 mmol) in methanol (2.5 mL) and CH_2Cl_2 (2.5 mL) at 0°C, $NaBH_4$ (38 mg, 0.97 mmol) was added in small portions. The mixture was allowed to react at the same temperature for 30 min. The solvent was removed, water (10 mL) was added and the mixture was acidified with aqueous 5% HCl. Extraction with CH_2Cl_2 afforded an oily crude material (303 mg) that was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent to yield 263 mg (0.86 mmol, 87%) of (+)-**15** as a white solid: mp 104–106°C (ether/pentane); $[\alpha]_D^{20}=+24.4$ (*c* 2.1, $CHCl_3$); IR (KBr) 3472, 3036, 2894, 1496, 1458, 1399, 1251, 1196, 1112, 1032, 1006, 960, 775, 703 cm^{-1}; ^1H NMR δ 7.45–7.25 (m, 6H), 7.25–7.10 (m, 4H), 6.28 (m, 2H), 6.17 (m, 2H), 4.85 (s, 2H), 4.49 (br d, $J=9.5$ Hz, 1H), 2.21 (d, $J=9.5$ Hz, 1H); ^{13}C NMR δ 136.0, 133.4, 128.5, 128.2, 126.7, 126.6, 99.4, 85.6, 85.5, 62.4; MS *m*/*z* (CI/NH_3) 324 (M^++18, 21), 214 (100), 197 (76). Anal. calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.41; H, 6.05.

4.6. (2*R*,3*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]decan-8-ol, (+)-16

To a solution of (+)-**12** (134 mg, 0.43 mmol) in methanol (10 mL) at 0°C, $NaBH_4$ (17 mg, 0.43 mmol) was added in small portions. The mixture was allowed to react at 0°C for 15 min. The solvent was removed, water (2 mL) was added and the mixture was acidified with aqueous 5% HCl. Extraction with CH_2Cl_2 afforded an oily crude material (134 mg) that was purified by flash chromatography using hexane/ether (1:1) as eluent to yield 122 mg (0.39 mmol, 91%) of (+)-**16**[23] as a white solid: mp 80–83°C (ether/pentane); $[\alpha]_D^{20}=+44.4$ (*c* 1.2, $CHCl_3$); IR (KBr) 3286, 2954, 2932, 2876, 1453, 1368, 1127, 1034, 938, 764, 702 cm^{-1}; ^1H NMR δ 7.40–7.10 (m, 10H), 4.75 (d, $J=8.6$ Hz, 1H), 4.71 (d, $J=8.6$ Hz, 1H), 3.87 (br s, 1H), 2.25–1.70 (m, 9H); ^{13}C NMR δ 136.8, 128.4, 128.3, 126.7, 126.7, 109.1, 85.2, 68.1, 33.1, 32.9, 32.0, 31.8; MS *m*/*z* (CI/NH_3) 311 (M^++1, 6), 214 (100). Anal. calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.20; H, 7.21.

4.7. Bromination reaction of (+)-8

(a) To a solution of (+)-**8** (100 mg, 0.33 mmol) at 0°C, a 0.1 M solution of bromine in CH_2Cl_2 (5 mL, 0.50 mmol) was added. The mixture was allowed to react at 0°C for 15 min and triethylamine (95 μL, 0.66 mmol) was added. After 1 h at room temperature, ether was added and the mixture was washed successively with water, 1 M HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. Flash chromatography of the oily crude material (129 mg) using hexane/CH_2Cl_2 (3:2) as eluent afforded the following fractions: (i) 35 mg (0.08 mmol, 24%) of (2*R*,3*R*)-7,9-dibromo-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, (+)-**18**, as a white solid; and (ii) 93 mg (0.24 mmol, 73%) of (2*R*,3*R*)-7-bromo-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, (+)-**17**, as a white solid. (b) To a solution of (+)-**8** (298 mg, 0.98 mmol) in CH_2Cl_2 (2 mL) at 0°C, a 0.089 M solution of bromine in CH_2Cl_2 (6 mL, 0.54 mmol) was added. The mixture was allowed to

react at 0°C for 15 min and triethylamine (102 μL, 0.75 mmol) was added. After 1 h at room temperature, ether was added and the mixture was washed successively with water, 1 M HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. Flash chromatography of the oily crude material (329 mg) using hexane/CH_2Cl_2 (3:2) as eluent afforded the following fractions: (i) 12 mg (0.026 mmol, 3%) of (+)-**18** as a white solid; (ii) 182 mg (0.47 mmol, 49%) of (+)-**17** as a white solid; and (iii) 129 mg (43%) of starting (+)-**8**. Considering the recovered material, the yield of (+)-**17** is 86%. (+)-**17**: mp 119–121°C (CH_2Cl_2/pentane); $[\alpha]_D^{20}=+49.2$ (*c* 1.0, CH_2Cl_2); IR (KBr) 3034, 2923, 2854, 1683, 1610, 1454, 1327, 1274, 1208, 1127, 1011, 987, 951, 816, 767, 699 cm^{-1}; ^1H NMR δ 7.39 (d, $J=2.9$ Hz, 1H), 7.37–7.30 (m, 6H), 7.27–7.15 (m, 4H), 6.97 (dd, $J=10.0$, 2.9 Hz, 1H), 6.40 (d, $J=10.0$ Hz, 1H), 4.93 (s, 2H); ^{13}C NMR δ 177.8, 144.2, 144.0, 134.6, 129.0, 128.8, 127.6, 126.6, 125.6, 100.1, 86.1, 86.0; MS *m*/*z* (CI/NH_3) 402–400 (M^++18, 43, 44), 214 (100). Anal. calcd for $C_{20}H_{15}BrO_3$: C, 62.68; H, 3.95. Found: C, 62.83; H, 3.92. (+)-**18**: mp 192–195°C (CH_2Cl_2/pentane); $[\alpha]_D^{20}=+36.0$ (*c* 1.3, CH_2Cl_2); IR (KBr) 3056, 3037, 2922, 1694, 1604, 1452, 1310, 1261, 1126, 1003, 758, 700 cm^{-1}; ^1H NMR δ 7.38 (s, 2H), 7.37–7.30 (m, 6H), 7.25–7.15 (m, 4H), 4.91 (s, 2H); ^{13}C NMR δ 171.7, 144.6, 134.1, 129.2, 128.8, 126.6, 123.2, 101.0, 86.1; MS *m*/*z* (CI/NH_3) 482-480-478 (M^++18, 2, 3, 2), 214 (100). Anal. calcd for $C_{20}H_{14}Br_2O_3$: C, 51.98; H, 3.05. Found: C, 51.82; H, 3.13.

4.8. Iodination reaction of (+)-8

To a solution of (+)-**8** (101 mg, 0.33 mmol) in CCl_4 (2 mL) and pyridine (1 mL) at 0°C, iodine (200 mg, 0.78 mmol) was added. The mixture was allowed to react at room temperature for 3 h. Ether (10 mL) was added and the mixture was washed successively with water, 1 M HCl, water (twice), and 20% aqueous $Na_2S_2O_3$. Flash chromatography of the solid crude material (188 mg) using hexane/ether (15:1) as eluent afforded the following fractions: (i) 77 mg (0.14 mmol, 42%) of (2*R*,3*R*)-7,9-diiodo-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, (+)-**20**, as a white solid; (ii) 64 mg (0.15 mmol, 45%) of (2*R*,3*R*)-7-iodo-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, (+)-**19**, as a white solid; and (iii) 13 mg (13%) of starting (+)-**8**. Considering the recovered material, the yield of (+)-**20** is 48% and that of (+)-**19** is 52%. (+)-**19**: mp 130–131°C; $[\alpha]_D^{20}=+45.0$ (*c* 1.7, $CHCl_3$); IR (KBr) 3037, 2917, 1680, 1602, 1455, 1321, 1279, 1124, 1029, 1005, 815, 759, 695 cm^{-1}; ^1H NMR δ 7.70 (d, $J=2.9$ Hz, 1H), 7.40–7.27 (m, 6H), 7.25–7.15 (m, 4H), 6.96 (dd, $J=9.9$, 2.9 Hz, 1H), 6.41 (d, $J=9.9$ Hz, 1H), 4.93 (d, $J=8.8$ Hz, 1H), 4.89 (d, $J=8.8$ Hz, 1H); ^{13}C NMR δ 178.6, 152.2, 144.0, 134.5, 129.0, 128.7, 126.6, 126.3, 105.5, 99.8, 86.0, 85.9; MS *m*/*z* (CI/NH_3) 448 (M^++18, 7), 431 (M^++1, 4), 324 (74), 214 (100), 200 (46), 197 (98), 169 (40), 141 (45). Anal. calcd for $C_{20}H_{15}IO_3$: C, 55.83; H, 3.51. Found: C, 55.87; H, 3.55. (+)-**20**: mp 233–236°C (CH_2Cl_2/pentane); $[\alpha]_D^{20}=+28.3$ (*c* 0.6, $CHCl_3$); IR (KBr) 3037, 2924, 1680, 1314, 1124, 998, 752, 702 cm^{-1}; ^1H NMR δ 7.78 (s, 2H), 7.40–7.30 (m, 6H), 7.25–7.10 (m, 4H), 4.91 (s, 2H); ^{13}C NMR δ 152.7, 134.2, 129.2, 128.8, 126.6, 101.4, 99.6, 86.0; MS *m*/*z* (CI/NH_3) 574 (M^++18, 0.2), 557 (M^++1, 0.6), 214 (100), 197 (47), 196 (47). Anal. calcd for $C_{20}H_{14}I_2O_3$: C, 43.19; H, 2.54. Found: C, 43.29; H, 2.51.

4.9. Reaction between (+)-8 and formaldehyde

A solution of (+)-**8** (207 mg, 0.68 mmol), 4-dimethylaminopyridine (29 mg, 0.24 mmol) and 35–40% aqueous formaldehyde (175 μL, 2.3 mmol) in THF (4 mL) was heated at the reflux temperature for 7 days in a vessel under nitrogen atmosphere provided with a balloon. The solvent was removed and the oily crude material (354 mg) was purified by flash chromatography using CH_2Cl_2/ether (9:1) as eluent affording the following fractions: (i) 14 mg (7%) of starting (+)-**8**; (ii) 54 mg (0.16 mmol, 24%) of (2*R*,3*R*)-7-hydroxymethyl-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, (+)-**21**, as a colorless oil; and (iii) 117 mg (0.32 mmol, 47%) of (2*R*,3*R*)-7,9-di(hydroxymethyl)-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, (+)-**22**, as a white solid. Considering the recovered starting material, the yields of (+)-**21** and (+)-**22** are 25% and 51%, respectively. (+)-**21**: $[\alpha]_D^{20}=+56.0$ (*c* 2.0, $CHCl_3$); ^1H NMR δ 7.40–7.28 (m, 6H:H_{ar}), 7.27–7.17 (m, 4H), 7.00–6.90 (m, 2H), 6.26 (d, $J=9.7$ Hz, 1H), 4.96 (d, $J=8.7$ Hz, 1H), 4.92 (d, $J=8.7$ Hz, 1H), 4.44 (d, $J=1.3$ Hz, 2H); ^{13}C NMR δ 185.8, 144.1, 138.4, 138.0, 135.0, 134.9, 129.0, 128.9, 128.87, 128.83, 128.6, 126.7, 126.6, 99.0, 86.0, 85.8, 60.2; MS *m*/*z* (CI/NH_3) 352 (M^++18, 1), 335 (M^++1, 13), 317 (60), 228 (100), 214 (38), 197 (45), 91 (28); HRMS (FAB) calcd for $(M+1)^+$ $C_{21}H_{19}O_4$: 335.1282. Found: 335.1274. (+)-**22**: mp 204–206°C (THF/pentane); $[\alpha]_D^{20}=+65.2$ (*c* 0.7, THF); IR (KBr) 3347 (br), 3067, 3041, 2907, 2880, 1691, 1654, 1454, 1308, 1186, 1088, 1024, 994, 977, 910, 751, 697 cm^{-1}; ^1H NMR δ 7.40–7.30 (m, 6H), 7.25–7.15 (m, 4H), 6.95 (s, 2H), 4.94 (s, 2H), 4.45 (br s, 4H); ^1H NMR (d_6-DMSO) δ 7.40 (br s, 10H), 7.08 (s, 2H), 5.21 (t, $J=5.5$ Hz, 2H), 5.18 (s, 2H), 4.25 (d, $J=5.5$ Hz, 4H); ^{13}C NMR δ 186.4, 139.1, 138.0, 134.9, 128.9, 128.7, 126.7, 99.2, 85.9, 60.3; ^{13}C NMR (d_6-DMSO) δ 185.0, 138.8, 138.0, 135.1, 128.8, 128.5, 127.3, 99.1, 84.5, 57.1; MS *m*/*z* (CI/NH_3) 382 (M^++18, 1), 365 (M^++1, 3), 317 (44), 258 (22), 214 (100), 197 (20). Anal. calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.30; H, 5.51.

4.10. Ethyl 2-[(2*R*,3*R*)-8-hydroxy-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-yl]acetate, (+)-23

To a suspension of recently opened 99.99% indium powder (0.57 g, 4.93 mmol) in freshly distilled DMF (6 mL) under nitrogen atmosphere, ethyl iodoacetate (0.78 mL, 6.57 mmol) was added dropwise over 5 min. The resulting hot solution was allowed to cool down to room temperature and stirred for 30 min. Ketal (+)-**8** (1.00 g, 3.29 mmol) was added in portions over 5 min and the solution stirred at the same temperature for 5 h. Then it was added to a stirred mixture of ethyl acetate (100 mL) and water (10 mL) and stirring was maintained for 15 min. The supernatant liquid was decanted and the remaining gelatinous solid was

washed with ethyl acetate (2×20 mL). The joined organic phases were mixed with water (30 mL) and stirred vigorously for 20 min. The aqueous phase was again washed with ethyl acetate (25 mL). Flash chromatography of the oily crude material (1.93 g) using hexane/ethyl acetate (4:1) as eluent afforded (+)-**23** (1.21 g, 3.08 mmol, 94%) as a colorless oil: $[\alpha]_D^{20}=+11.8$ (*c* 3.7, $CHCl_3$); IR (film) 3452 (br), 3034, 2981, 1731, 1454, 1412, 1202, 1162, 1117, 1015, 699 cm^{-1}; ^1H NMR δ 7.40–7.27 (m, 6H), 7.25–7.15 (m, 4H), 6.26 (d, $J=$ 10.2 Hz, 2H), 6.13 (m, 2H), 4.86 (d, $J=8.0$ Hz, 1H), 4.81 (d, $J=8.0$ Hz, 1H), 4.17 (q, $J=7.3$ Hz, 2H), 3.62 (br s, 1H), 2.63 (s, 2H), 1.26 (t, $J=7.3$ Hz, 3H); ^{13}C NMR δ 171.3, 136.0, 135.32, 135.26, 128.5, 128.4, 128.1, 128.0, 127.8, 127.35, 127.29, 126.8, 126.5, 99.3, 85.6, 85.5, 66.1, 60.9, 44.8, 14.1; MS *m*/*z* (CI/NH_3) 393 (M^++1, 4), 214 (100), 199 (27), 197 (78). Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 72.97; H, 6.45.

4.11. (2*R*,3*R*)-8-(2-Hydroxy)ethyl-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-ol, (+)-25

To a solution of (+)-**23** (200 mg, 0.51 mmol) in anhydrous THF (2 mL) at 0°C, a 2 M solution of $LiBH_4$ in THF (250 μL, 0.50 mmol) was added. The mixture was allowed to react at the same temperature for 4 d. A few drops of water were added, the mixture was filtered through Celite and the solvent was removed. Flash chromatography of the solid crude material (179 mg) using hexane/ethyl acetate (2:1) as eluent afforded the following fractions: (i) 10 mg (0.03 mmol, 6%) of (+)-**15**; and (ii) 167 mg (0.48 mmol, 94%) of (+)-**25** as a white solid: mp 41–43°C (ethyl acetate/hexane); $[\alpha]_D^{20}=$ +14.2 (*c* 2.5, $CHCl_3$); IR (KBr) 3386 (br), 3033, 2888, 1496, 1454, 1411, 1201, 1119, 1076, 1040, 1015, 965, 699 cm^{-1}; ^1H NMR δ 7.40–7.25 (m, 6H), 7.25–7.10 (m, 4H), 6.24 (d, $J=10.2$ Hz, 2H), 6.19–6.08 (m, 2H), 4.86 (d, $J=8.5$ Hz, 1H), 4.81 (d, $J=8.5$ Hz, 1H), 3.80 (q, $J\approx5.7$ Hz, 2H), 2.34 (t, $J=5.7$ Hz, 1H), 2.28 (br s, 1H), 1.94 (t, $J=5.8$ Hz, 2H); ^{13}C NMR δ 136.8, 136.7, 135.9, 128.5, 127.5, 127.4, 126.7, 126.6, 99.5, 85.7, 85.5, 68.2, 59.3, 42.0; MS *m*/*z* (CI/NH_3) 351 (M^++1, 1), 315 (11), 199 (84), 155 (20), 137 (100); HRMS (FAB) calcd for $(M+1)^+$ $C_{22}H_{23}O_4$: 351.1596. Found: 351.1593.

4.12. (3a*S*,7a*S*,4′*R*,5′*R*)-4′,5′-Diphenyl-3,3a,7,7a-tetrahydrospiro[benzofuro-6(2*H*),2′-[1,3]dioxolan]-3a-ol, (+)-26, and its (3a*R*,7a*R*,4′*R*,5′*R*)-isomer, 27

To a solution of (+)-**25** (116 mg, 0.33 mmol) in dry DME (6.5 mL) at room temperature, mercuric trifluoroacetate (176 mg, 0.40 mmol) in dry DME (2.5 mL) was added. The mixture was allowed to react at the same temperature for 2 h. A solution of $NaBH_4$ (41 mg, 1.05 mmol) in 1.2 M aqueous NaOH (2.6 mL) was added and the reaction mixture was stirred at room temperature for 5 min. The mixture was filtered, the solid was washed with ether and the organic solution was washed with water. Flash chromatography of the oily crude material (118 mg) using hexane/ether (1:1) as eluent yielded the following fractions: (i) 13 mg (0.04 mmol, 12%) of (+)-**26** as a white solid; (ii) 77 mg (0.22 mmol, 66%) of a *ca* 1.5:1 mixture of (+)-**26** and **27** as a white solid; and (iii) 23 mg of an unidentified solid material. Repeated chromatography allowed the isolation of 60 mg (0.17 mmol, 52%) of (+)-**26**: mp 64–66°C (ether/pentane); $[\alpha]_D^{20}=+2.4$ (*c* 1.7, $CHCl_3$); IR (KBr) 3403 (br), 3033, 2957, 2929, 2886, 1453, 1396, 1190, 1140, 1092, 1049, 1019, 980, 760, 698 cm^{-1}; ^1H NMR δ 7.30–7.26 (m, 6H), 7.23–7.15 (m, 4H), 6.05 (d, $J=10.0$ Hz, 1H), 5.91 (dd, $J=10.0$, 1.5 Hz, 1H), 4.77 (d, $J=8.4$ Hz, 1H:H), 4.68 (d, $J=8.4$ Hz, 1H), 4.26 (dd, $J=11.3$, 5.5 Hz, 1H), 4.19–4.08 (m, 2H), 2.46 (ddd, $J=13.2$, 5.5, 1.5 Hz, 1H), 2.25 (s, 1H), 2.15–1.97 (m, 3H); ^{13}C NMR δ 135.9, 133.1, 129.0, 128.54, 128.51, 128.45, 126.9, 126.63, 126.57, 106.4, 85.42, 85.36, 83.4, 78.0, 67.7, 40.4, 38.2; MS *m*/*z* (CI/NH_3) 368 (M^++18, 12), 351 (M^++1, 20), 214 (100), 172 (66). **27** (ca. 92:8 mixture of **27** and **26**): ^1H NMR δ 7.35–7.26 (m, 6H), 7.23–7.15 (m, 4H), 6.00 (s, 2H), 4.81 (d, $J=8.5$ Hz, 1H), 4.75 (d, $J=8.5$ Hz, 1H), 4.32 (dd, $J=9.5$, 5.0 Hz, 1H), 4.11 (dd, $J=8.5$, 6.7 Hz, 1H), 4.09 (dd, $J=8.5$, 4.7 Hz, 1H), 2.51 (dd, $J=13.6$, 5.0 Hz, 1H), 2.18–2.04 (m, 3H), 1.87 (s, 1H); ^{13}C NMR δ 136.2, 136.1, 133.4, 129.8, 128.54, 128.47, 128.43, 126.7, 105.8, 85.5, 85.4, 82.6, 77.2, 67.4, 40.0, 38.7; MS *m*/*z* (CI/NH_3) 368 (M^++18, 6), 351 (M^++1, 20), 214 (100), 172 (58). Mixture of **26** and **27**. Anal. calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.34; H, 6.38.

4.13. (3a*S*,7a*S*)-3a-Hydroxy-3,3a,7,7a-tetrahydrobenzofuran-6(2*H*)-one, (+)-rengyolone, (+)-1

A mixture of (+)-**26** (40 mg, 0.11 mmol) and montmorillonite K-10 (200 mg) in CH_2Cl_2 (1 mL) was stirred at room temperature for 22 h. The mixture was filtered and the solvent was removed. Flash chromatography of the crude material (30 mg) using hexane/ethyl acetate (1:1) as eluent yielded the following fractions: (i) 16 mg (0.07 mmol, 65%) of (*R*,*R*)-hydrobenzoin; and (ii) 8 mg (0.05 mmol, 45%) of (+)-rengyolone, (+)-**1**, as a white solid with ee (CGC and NMR) = 85%: mp 60–62°C; $[\alpha]_D^{20}=+48.6$ (*c* 0.3, MeOH); ^1H NMR δ 6.74 (dd, $J=10.2$, 1.3 Hz, 1H), 6.00 (d, $J=10.2$ Hz, 1H), 4.22 (ddd, $J=5.7$, 4.7, 1.3 Hz, 1H), 4.06 (td, $J\approx8.5$, 6.5 Hz, 1H), 3.93 (td, $J\approx8.5$, 6.5 Hz, 1H), 2.76 (dd, $J=16.9$, 4.7 Hz, 1H), 2.58 (dd, $J=16.9$, 5.7 Hz, 1H), 2.32 (s, 1H), 2.31 (ddd, $J=13.0$, 8.5, 6.5 Hz, 1H), 2.18 (ddd, $J=13.0$, 8.5, 6.5 Hz, 1H); ^{13}C NMR δ 196.5, 147.6, 128.9, 81.7, 75.8, 66.2, 40.2, 39.6.

4.14. 2-[(2*R*,3*R*)-8-Hydroxy-2,3-diphenyl-1,4-dioxaspiro-[4.5]deca-6,9-dien-8-yl]acetic acid, (+)-28

To a solution of (+)-**23** (97 mg, 0.25 mmol) in ethanol (1 mL), a 2.6 M aqueous solution of KOH (0.7 mL, 1.8 mmol) was added. The mixture was allowed to react at room temperature for 5 h and 5% HCl was added until pH = 2. The solution was extracted with chloroform and the organic phase was washed with water. Flash chromatography of the oily crude material (82 mg) using hexane/ethyl acetate (2:1) as eluent yielded 76 mg (0.21 mmol, 84%) of (+)-**28** as a white solid: mp 121–123°C (ethyl acetate/hexane); $[\alpha]_D^{20}=+14.8$ (*c* 1.2, $CHCl_3$); IR (KBr) 3370, 3062, 3033, 1709, 1687, 1420, 1274, 1171, 1119, 1075, 1020, 994, 971, 697 cm^{-1}; ^1H

NMR δ 7.40–7.26 (m, 6H), 7.23–7.15 (m, 4H), 6.25 (d, $J=10.4$ Hz, 2H), 6.15 (m, 2H), 4.85 (d, $J=8.7$ Hz, 1H), 4.81 (d, $J=10.4$ Hz, 1H), 2.67 (s, 2H); ^{13}C NMR δ 174.7, 135.8, 134.9, 134.8, 128.6, 128.5, 128.4, 128.3, 126.8, 126.6, 99.1, 85.7, 85.5, 66.0, 44.6; MS m/z (CI/NH_3) 382 (M^++18, 11), 214 (67), 199 (21), 198 (56), 197 (100). Anal. calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.33; H, 5.54.

4.15. (3a*S*,7a*S*,4′*R*,5′*R*)-3a-Hydroxy-4′,5′-diphenyl-3,3a,7,7a-tetrahydrospiro[benzofuro-6(2*H*),2′-[1,3]dioxolan]-2-one, (+)-29, and its (3a*R*,7a*R*,4′*R*,5′*R*)-isomer, (+)-30

(a) A solution of (+)-**28** (271 mg, 0.74 mmol) and trifluoroacetic acid (13 μL, 0.17 mmol) in chloroform (14 mL) was allowed to react at room temperature for 2 days. The mixture was washed with water and extracted with chloroform. Flash chromatography of the oily crude material (280 mg) using hexane/ether (1:1) as eluent yielded the following fractions: (i) 163 mg (0.45 mmol, 60%) of (+)-**29** as a white solid; and (ii) 77 mg (0.21 mmol, 28%) of (+)-**30** as a white solid contaminated with ca. 7% of (+)-**29** by NMR analysis. (b) A solution of (+)-**28** (40 mg, 0.11 mmol) and mercuric trifluoroacetate (12 mg, 0.03 mmol) in CH_2Cl_2 (0.7 mL) was allowed to react at room temperature for 1 day. Saturated aqueous $NaHCO_3$ (1 mL) was added and after 5 min of stirring the mixture was extracted with CH_2Cl_2. Flash chromatography of the crude material (43 mg) using hexane/ether (1:1) as eluent yielded the following fractions: (i) 12 mg (0.03 mmol, 30%) of (+)-**29** as a white solid; and (ii) 18 mg (0.05 mmol, 45%) of (+)-**30** as a white solid contaminated with ca. 7% of (+)-**29** by NMR analysis. (+)-**29**: mp 155–156°C (ether/pentane); $[\alpha]_D^{20}=+15.6$ (c 1.0, $CHCl_3$); IR (KBr) 3514 (br), 3036, 2978, 2902, 1774, 1295, 1174, 1092, 1053, 1014, 700 cm^{-1}; ^{1}H NMR δ 7.40–7.26 (m, 6H), 7.24–7.08 (m, 4H), 6.04 (dd, $J=10.0$, 1.2 Hz, 1H), 5.98 (d, $J=10.0$ Hz, 1H), 4.80 (d, $J=8.5$ Hz, 1H), 4.73 (dd, $J=11.9$, 5.4 Hz, 1H), 4.69 (d, $J=8.5$ Hz, 1H), 2.75 (d, $J=17.8$ Hz, 1H), 2.69 (ddd, $J=13.2$, 5.4, 1.2 Hz, 1H), 2.66 (d, $J=17.8$ Hz, 1H), 2.51 (br s, 1H), 2.09 (dd, $J=13.2$, 11.9 Hz, 1H); ^{13}C NMR δ 174.2, 135.4, 135.3, 131.2, 130.5, 128.8, 128.7, 128.6, 126.9, 126.5, 104.9, 85.64, 85.56, 83.9, 74.0, 40.9, 39.6; MS m/z (CI/NH_3) 382 (M^++18, 100), 214 (29), 197 (28). Anal. calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.10; H, 5.43. (+)-**30** (ca. 93:7 mixture of **30** and **29**): mp 103–106°C (ether/pentane); $[\alpha]_D^{20}=+18.0$ (c 1.0, $CHCl_3$); IR (KBr) 3428 (br), 3034, 2926, 1785, 1178, 1130, 1057, 1025, 699 cm^{-1}; ^{1}H NMR δ 7.40–7.26 (m, 6H), 7.23–7.10 (m, 4H), 6.04 (dd, $J=10.0$, 1.0 Hz, 1H), 5.89 (d, $J=10.0$ Hz, 1H), 4.81 (d, $J=8.5$ Hz, 1H), 4.79 (dd, $J=10.5$, 5.2 Hz, 1H), 4.73 (d, $J=8.5$ Hz, 1H), 3.20 (br s, 1H), 2.75 (d, $J=17.8$ Hz, 1H), 2.68 (ddd, $J=13.4$, 5.2, 1.0 Hz, 1H), 2.64 (d, $J=17.8$ Hz, 1H), 2.13 (dd, $J=13.4$, 10.5 Hz, 1H); ^{13}C NMR δ 174.2, 135.5, 131.6, 130.8, 128.7, 128.62, 128.57, 128.51, 126.6, 126.5, 104.4, 85.6, 85.4, 83.2, 73.3, 41.3, 39.0; MS m/z (CI/NH_3) 382 (M^++18, 6), 364 (M^+, 25), 214 (100), 172 (64), 112 (21), 78 (24), 74 (64). Anal. calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.21; H, 5.45.

4.16. (7a*S*,4′*R*,5′*R*)-4′,5′-Diphenyl-7,7a-dihydrospiro-[benzofuro-6(2*H*),2′-[1,3]dioxolan]-2-one, (−)-31

A solution of (+)-**29** (176 mg, 0.48 mmol) and freshly distilled thionyl chloride (98 μL, 1.35 mmol) in pyridine (2 mL) was allowed to react at room temperature for 30 min. Ethyl acetate was added and the mixture was washed successively with water, saturated aqueous $NaHCO_3$ and twice with water. Flash chromatography of the oily crude material (167 mg) using hexane/ethyl acetate (4:1) as eluent yielded 141 mg (0.41 mmol, 84%) of (−)-**31** as a white solid: mp 154–156°C (ethyl acetate/hexane); $[\alpha]_D^{20}=-96.6$ (c 4.7, $CHCl_3$); IR (KBr) 3033, 2958, 2924, 2897, 1785, 1758, 1199, 1095, 1058, 1020, 700 cm^{-1}; ^{1}H NMR δ 7.37–7.26 (m, 6H), 7.23–7.10 (m, 4H), 6.74 (d, $J=9.7$ Hz, 1H), 6.31 (dd, $J=9.7$, 1.3 Hz, 1H), 5.92 (dd, $J\approx1.8$, 0.8 Hz, 1H), 5.24 (ddd, $J=12.6$, 5.2, 1.8 Hz, 1H), 4.85 (d, $J=8.5$ Hz, 1H), 4.77 (d, $J=8.5$ Hz, 1H), 2.98 (dddd, $J=12.0$, 5.2, 1.3, 0.8 Hz, 1H), 2.17 (t, $J\approx12.3$ Hz, 1H); ^{13}C NMR δ 172.8, 161.8, 138.0, 135.1, 135.0, 128.8, 128.6, 126.7, 126.6, 121.8, 113.3, 105.6, 85.8, 85.2, 78.1, 41.8; MS m/z (CI/NH_3) 364 (M^++18, 72), 347 (M^++1, 100). Anal. calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.15; H, 5.14.

4.17. (7a*R*,4′*R*,5′*R*)-4′,5′-Diphenyl-7,7a-dihydrospiro-[benzofuro-6(2*H*),2′-[1,3]dioxolan]-2-one, (+)-33

A solution of (+)-**30** (166 mg, 0.46 mmol) and freshly distilled thionyl chloride (94 μL, 1.29 mmol) in pyridine (2 mL) was allowed to react at room temperature for 15 min. Ethyl acetate was added and the mixture was washed successively with water, saturated aqueous $NaHCO_3$ and twice with water. Flash chromatography of the solid crude material (192 mg) using hexane/ethyl acetate (4:1) as eluent yielded 141 mg (0.41 mmol, 89%) of (+)-**33** as a white solid: mp 160–163°C (ethyl acetate/hexane); $[\alpha]_D^{20}=+222.8$ (c 4.3, $CHCl_3$); IR (KBr) 3062, 3031, 2924, 2900, 1784, 1757, 1195, 1031, 701 cm^{-1}; ^{1}H NMR δ 7.37–7.26 (m, 6H), 7.23–7.15 (m, 4H), 6.72 (d, $J=9.9$ Hz, 1H), 6.43 (dd, $J=9.9$, 1.4 Hz, 1H), 5.92 (dd, $J\approx1.8$, 1.0 Hz, 1H), 5.30 (ddd, $J=12.7$, 5.0, 1.8 Hz, 1H), 4.91 (d, $J=8.6$ Hz, 1H), 4.86 (d, $J=8.6$ Hz, 1H), 3.06 (dddd, $J=11.8$, 5.0, 1.4, 0.9 Hz, 1H), 2.16 (dd, $J=12.7$, 11.8 Hz, 1H); ^{13}C NMR δ 172.7, 161.7, 138.5, 135.4, 135.2, 128.8, 128.7, 128.64, 128.58, 126.6, 126.4, 122.0, 113.4, 105.5, 86.1, 85.7, 77.7, 42.6; MS m/z (CI/NH_3) 364 (M^++18, 100), 347 (M^++1, 93). Anal. calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.64; H, 5.09.

4.18. (*S*)-6-Oxo-7,7a-dihydrobenzofuran-2(6*H*)-one, (−)-32

A mixture of (−)-**31** (127 mg, 0.37 mmol) and montmorillonite K-10 (725 mg) in CH_2Cl_2 (3.5 mL) was heated at the reflux temperature for 6 d. The mixture was filtered and the solvent was removed. Flash chromatography of the solid crude material (125 mg) using hexane/ethyl acetate (4:1) as eluent afforded the following fractions: (i) 65 mg of a mixture of 2-benzyl-2,4,5-triphenyl-1,3-dioxolane and diphenylacetaldehyde, both compounds derived from hydrobenzoin; (ii) 14 mg (0.04

mmol, 11%) of starting (−)-**31**; and (iii) 24 mg (0.16 mmol, 44%) of (−)-**32** as a white solid. Considering the recovered (−)-**31** the yield of (−)-**32** is 49%. (−)-**32**: mp 109–111°C (ethyl acetate/hexane) (lit.[32b] (±)-**32**: 104–106°C (MeOH)); $[\alpha]_D^{20}=-207.4$ (*c* 1.2, acetone); ^{1}H NMR δ 7.51 (d, $J=9.9$ Hz, 1H), 6.32 (d, $J=9.9$ Hz, 1H), 6.19 (br s, 1H), 5.28 (ddd, $J=12.2$, 6.4, 2.0 Hz, 1H), 3.35 (dd, $J=15.4$, 6.4 Hz, 1H), 2.58 (dd, $J=15.4$, 12.2 Hz, 1H:H_7).

4.19. (*R*)-6-Oxo-7,7a-dihydrobenzofuran-2(6*H*)-one, (+)-32

A mixture of (+)-**33** (103 mg, 0.30 mmol) and montmorillonite K-10 (592 mg) in CH_2Cl_2 (3 mL) was heated at the reflux temperature for 1 day. The mixture was filtered and the solvent was removed. Flash chromatography of the solid crude material (125 mg) using hexane/ethyl acetate (4:1) as eluent afforded the following fractions: (i) 57 mg of a mixture of 2-benzyl-2,4,5-triphenyl-1,3-dioxolane and diphenylacetaldehyde, both compounds derived from hydrobenzoin; and (ii) 29 mg (0.19 mmol, 65%) of (+)-**32** as a white solid: mp 107–109°C (ethyl acetate/hexane) (lit.[32b] (±)-**32**: 104–106°C (MeOH)); $[\alpha]_D^{20}=+165.6$ (*c* 1.3, acetone).

4.20. (6*R*,7a*S*)-6-Hydroxy-7,7a-dihydrobenzofuran-2(6*H*)-one, (+)-menisdaurilide, (+)-2

Following the method described by Mori et al.,[32b] reduction of (−)-**32** yielded (+)-**2** with ee (NMR)>98%, determined with the assistance of perdeuterated Pirkle alcohol,[31] in 74% yield: mp 107–109°C (CH_2Cl_2/pentane) (lit.[32b] (±)-**2**: 105–107°C; $[\alpha]_D^{20}=+27.6$ (*c* 0.6, MeOH); ^{1}H NMR δ 6.54 (dd, $J=9.9$, 2.5 Hz, 1H), 6.29 (dt, $J=9.9$, 1.7 Hz, 1H:H_4), 5.79 (br s, 1H), 4.85 (ddd, $J=13.4$, 4.9, 1.8 Hz, 1H), 4.62 (m, 1H), 2.89 (m, 1H), 2.23 (br d, $J=6.4$ Hz, 1H), 1.65 (ddd, $J=13.4$, 11.0, 10.4 Hz, 1H); ^{13}C NMR δ 173.5, 163.0, 143.6, 119.9, 111.4, 78.1, 66.7, 39.9.

4.21. (6*S*,7a*R*)-6-Hydroxy-7,7a-dihydrobenzofuran-2(6*H*)-one, (−)-menisdaurilide, (−)-2

Following the method described by Mori et al.,[32b] reduction of (+)-**32** yielded (−)-**2** with ee (NMR) = 80%, determined with the assistance of perdeuterated Pirkle alcohol,[31] in 63% yield: mp 106–108°C (CH_2Cl_2/pentane) (lit.[5] 113°C, lit.[6b] 118–120°C, lit.[6c] 86°C, lit.[6d] 109–111°C); $[\alpha]^{20}{}_D$ −20.0 (*c* 0.4, MeOH) (lit.[5] $[\alpha]_D^{20}$ −31.4 (*c* 1.00, MeOH), lit.[6b] $[\alpha]_D^{20}=-28.9$ (*c* 0.130, MeOH), lit.[6c] $[\alpha]_D^{20}$ −30.6 (*c* 0.041, MeOH), lit.[6d] $[\alpha]_D^{20}$ −27.3 (*c* 0.307, MeOH)).

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References

1. Endo, K.; Hikino, H. *Can. J. Chem.* **1984**, *62*, 2011–2014.
2. Messana, I.; Sperandei, M.; Multari, G.; Galeffi, C.; Marini Bettolo, G. B. *Phytochemistry* **1984**, *23*, 2617–2619.
3. (a) Llera, L. D.; Trujillo, J. M.; Breton, J. L.; Navarro, E. *J. Nat. Prod.* **1987**, *50*, 251–252; (b) Kuwajima, H.; Takahashi, M.; Ito, M.; Wu, H.-X.; Takaishi, K.; Inoue, K. *Phytochemistry* **1993**, *33*, 137–139; (c) Hase, T.; Kawamoto, Y.; Ohtani, K.; Kasai, R.; Yamasaki, K.; Picheansoonthon, C. *Phytochemistry* **1995**, *39*, 235–241; (d) Limiroli, R.; Consonni, R.; Ranalli, A.; Bianchi, G.; Zetta, L. *J. Agric. Food Chem.* **1996**, *44*, 2040–2048; (e) Jensen, S. R. *Biochem. Syst. Ecol.* **2000**, *28*, 45–51.
4. (a) Nishino, C.; Kobayashi, K. (Mitsubishi Kasei Corp.) JP 01,290,627, 1989 [*Chem. Abstr.* **1990**, *112*, 191943y]; (b) Nishino, C.; Kobayashi, K. (Mitsubishi Kasei Corp.) JP 01,290,666, 1989 [*Chem. Abstr.* **1990**, *112*, 235165c]; (c) Nagakura, A.; Sato, M.; Kikuchi, M.; Nakatsu, T. (Takasago Perfumery Co.) JP 02,200,631, 1990 [*Chem. Abstr.* **1991**, *114*, 30162u].
5. Takahashi, K.; Matsuzawa, S.; Takani, M. *Chem. Pharm. Bull.* **1978**, *26*, 1677–1681.
6. (a) Guerriero, A.; Pietra, F. *Phytochemistry* **1984**, *23*, 2394–2396; (b) Yogo, M.; Ishiguro, S.; Murata, H.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 225–226; (c) Bachmann, T. L.; Ghia, F.; Torssell, K. B. G. *Phytochemistry* **1993**, *33*, 189–191; (d) Otsuka, H.; Ito, A.; Fujioka, N.; Kawamata, K. I.; Kasai, R.; Yamasaki, K.; Satoh, T. *Phytochemistry* **1993**, *33*, 389–392.
7. Ueda, M.; Shigemori-Suzuki, T.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 6267–6270.
8. (a) Sakamura, S.; Ito, J.; Sakai, R. *Agr. Biol. Chem.* **1970**, *34*, 153–155; (b) Sakamura, S.; Ito, J.; Sakai, R. *Agr. Biol. Chem.* **1971**, *35*, 105–110; (c) Ichihara, A.; Oda, K.; Sakamura, S. *Agr. Biol. Chem.* **1971**, *35*, 445–446; (d) Ichihara, A.; Kimura, R.; Oda, K.; Moriyasu, K.; Sakamura, S. *Agr. Biol. Chem.* **1982**, *46*, 1879–1883; (e) Yoshida, N.; Konno, H.; Kamikubo, T.; Takahashi, M.; Odasawara, K. *Tetrahedron: Asymmetry* **1999**, *10*, 3849–3857.
9. (a) Higa, T.; Okuda, R. K.; Severns, R. M.; Scheuer, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063–1070; (b) Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759–8760; (c) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674–6675; (d) Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716–721.
10. (a) Roy, K.; Mukhopadhyay, T.; Reddy, G. C. S.; Desikan, K. R.; Rupp, R. H.; Ganguli, B. N. *J. Antibiot.* **1988**, *41*, 1780–1784; (b) Fehlhaber, H. W.; Kogler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Ganguli, B. N. *J. Am. Chem. Soc.* **1988**, *110*, 8242–8244; (c) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 201–203; (d) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385–1393.
11. (a) Buzzetti, F.; Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zähner, H. *Pharm. Acta Helv.* **1963**, *38*, 871–874; (b) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.*

1998, *63*, 3526–3527; (c) Taylor, R. J. K.; Alcaraz, L.; Kapfer-Eyer, I.; Macdonald, G.; Wei, X.; Lewis, N. *Synthesis* **1998**, 775–790; (d) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707–3716.

12. (a) Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 971–974; (b) Wernert, N.; Stanjek, A.; Kiriakidis, S.; Hugel, A.; Jha, H. C.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3228–3231; (c) Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589–5590; (d) Hutchings, M.; Moffat, D.; Simpkins, N. S. *Synlett* **2001**, 661–663; (e) Boiteau, J.-G.; Van de Weghe, P.; Eustache, J. *Org. Lett.* **2001**, *3*, 2737–2740; (f) Baldwin, J. E.; Bulger, P. G.; Marquez, R. *Tetrahedron* **2002**, *58*, 5441–5452.
13. Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35–62 and references cited therein.
14. (a) Konno, H.; Ogasawara, K. *Synthesis* **1999**, 1135–1140; (b) Hiroya, K.; Zhang, H.; Ogasawara, K. *Synlett* **1999**, 529–532 and references cited therein.
15. Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640–3650.
16. Enders, D.; Nühring, A.; Runsink, J. *Chirality* **2000**, *12*, 374–377.
17. Taber, D. F.; Christos, T. E.; Rahimizadeh, M.; Chen, B. *J. Org. Chem.* **2001**, *66*, 5911–5914.
18. (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895–3897; (b) de March, P.; Figueredo, M.; Font, J.; Medrano, J. *Tetrahedron* **1999**, *55*, 7907–7914.
19. (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590; (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511; (c) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045–2055; (d) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 4979–4980; (e) Ramachandran, P. V.; Chen, G.-M.; Lu, Z.-H.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 3795–3798; (f) Takeda, T.; Imamoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 3209–3218; (g) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375–380; (h) Matsumoto, K.; Sato, Y.; Shimojo, M.; Hatanaka, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1965–1973.
20. (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J. *Tetrahedron Lett.* **1995**, *36*, 8665–8688; (b) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1997**, *62*, 7781–7787; (c) de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron* **2000**, *56*, 3603–3609; (d) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; García-García, E.; Rodríguez, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4473–4483.
21. Preliminary results of this work have been published: (a) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron: Asymmetry* **2001**, *12*, 3077–3080; (b) Cantó, M.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S.; Álvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2002**, *13*, 455–459.
22. (a) Keller, R. (Hoechst AG) DE 3045680, 1982 [*Chem. Abstr.* **1983**, *98*, 34904m]; (b) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 1881–1884.
23. Konopelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105–1107.
24. (a) Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327–9328; (b) Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679–1680; (c) Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1087–1089; (d) Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059–2062.
25. Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965–5966.
26. Araki, S.; Katsumura, N.; Kawasaki, K.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499–500.
27. (a) Endo, K.; Seya, K.; Hikino, H. *Tetrahedron* **1989**, *45*, 3673–3682; (b) Bianco, A.; Lo Scalzo, R.; Scarpati, M. L. *Phytochemistry* **1993**, *32*, 455–457.
28. Tian, J.; Zhao, Q.-S.; Zhang, H.-J.; Lin, Z.-W.; Sun, H.-D. *J. Nat. Prod.* **1997**, *60*, 766–769.
29. (a) Saito, I.; Chujo, Y.; Shimazu, H.; Yamane, M.; Matsuura, T.; Cahnmann, H. J. *J. Am. Chem. Soc.* **1975**, *97*, 5272–5277; (b) Schweizer, J.; Lattrell, R.; Hecker, E. *Experientia* **1975**, *31*, 1267–1268; (c) Breton, J. L.; Llera, L. D.; Navarro, E.; Trujillo, J. *Tetrahedron* **1987**, *43*, 4447–4451; (d) Navarro, E.; Alonso, S. J.; Boada, J.; Trujillo, J.; Ayuso, M. J.; Gutierrez Navarro, A. *Fitoterapia* **1992**, *63*, 251–254.
30. Kocovský, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580–5589.
31. Gil, J.; Virgili, A. *J. Org. Chem.* **1999**, *64*, 7274–7276.
32. (a) Mori, K.; Audran, G.; Nakahara, Y.; Bando, M.; Kido, M. *Tetrahedron Lett.* **1997**, *38*, 575–578; (b) Audran, G.; Mori, K. *Eur. J. Org. Chem.* **1998**, 57–62.
33. Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 560–564.
34. Rubottom, G. M.; Juve, H. D., Jr. *J. Org. Chem.* **1983**, *48*, 422–425.
35. Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302–8303.