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TETRAHEDRON: *ASYMMETRY*

First synthesis of (+)-rengyolone and (+)- and (−)-menisdaurilide

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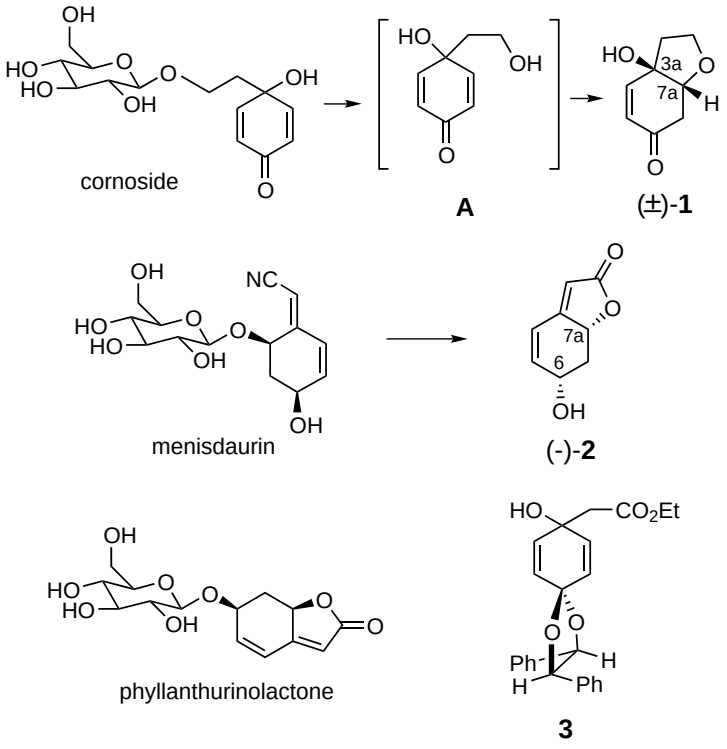
Abstract—The benzofuranone natural products (+)-rengyolone and (+)- and (−)-menisdaurilide have been synthesised for the first time from a common enantiopure cyclohexane building block derived from a monoketal of *p*-benzoquinone.

In 1984 the same benzofuran natural product **1** (Scheme 1) was independently isolated by two research groups from different sources. Endo and Hikino[1] named **1** rengyolone, because they isolated it from the fruit of the plant *Forsythia suspensa*, known as 'rengyo' in oriental medicine and used for its antiinflamatory, diuretic and antidotal properties. Simultaneously, Italian researchers[2] isolated compound **1** from the leaves of



Scheme 1.

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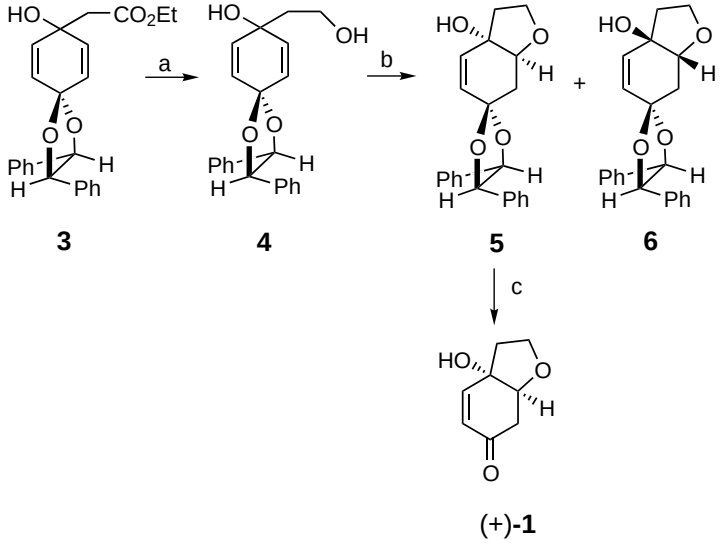
Halleria lucida, a plant used for magical purposes and in folk medicine in Southern Africa, and gave it the name halleridone. Afterwards, rengyolone, the name that first appeared in the literature and which will be used in this paper, was also extracted from other plants[3] and three Japanese patents claim the anticancer activity of **1** and derived esters.[4]

In 1997, a Chinese group published the isolation of six new compounds from *Clerodendrum indicum*, one which had identical structure and relative stereochemistry to rengyolone.[5] The compound was named cleroindicin F by these authors reporting a specific rotation of $[\alpha]_D^{20} = -2.7$ (*c* 0.016, MeOH). The rengyolone samples previously isolated did not present a significant value of optical activity and it is accepted that the natural compound occurs as a racemate, consistent with a biosynthetic pathway involving spontaneous closure of the achiral quinol **A** formed by the enzymatic hydrolysis of the glucoside cornoside.[3d,6] Moreover, since rengyolone had only been synthesised in racemic form,[6,7] the actual specific rotation of the pure enantiomers was unknown.

Menisdaurilide, **2**, is also a natural product with a benzofuran skeleton, which was first reported in 1978 as a product of the acid hydrolysis of menisdaurin, a nitrile glucoside isolated from *Menispermum dauricum*.[8] Since 1984 lactone **2** has also been isolated from several other plants.[9] The absolute configuration of natural (−)-menisdaurilide has been established as (6*S*,7a*R*) by circular dichroism of its benzoate[9c] and X-ray diffraction analysis of its *p*-bromobenzoate.[9d] 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.[10] To the best of our knowledge, there is only one reported synthesis of **2** as the racemate.[11] Herein we describe the successful synthesis of (+)-rengyolone and (+)- and (−)-menisdaurilide starting from the cyclohexane chiron **3**, which we previously prepared from an enantiopure *p*-benzoquinone monoketal.[12]

The first step in the transformation of **3** into (+)-**1** (Scheme 2) was the reduction of the ester group with lithium borohydride to deliver the diol **4** as a solid ($[\alpha]_D^{20} = +14.2$ (*c* 2.5, $CHCl_3$)) in 94% yield. Treatment of **4** with mercuric trifluoroacetate followed by reduction with sodium borohydride[13] afforded a ca. 2:1 mixture of two diastereoisomeric cyclic ethers **5** and **6** in 78% yield. Repeated column chromatography allowed the isolation of the less polar and major isomer **5** as a solid ($[\alpha]_D^{20} = +2.4$ (*c* 1.7, $CHCl_3$)) in 52% yield. Its ^{1}H NMR spectrum shows the two olefinic protons at δ 6.05 ($J = 10.0$ Hz) and δ 5.91 ($J = 10.0$ Hz, $J' = 1.5$ Hz), while that of the minor isomer displays two isocrone olefinic protons at δ 6.00. Both **5** and **6** were expected to present a *cis* fused bicyclic skeleton, according to the reported precedents in related ring closing reactions leading to the formation of benzofurans.[6,7] The NOESY spectrum of **5** was not conclusive in determining its stereochemistry, but an X-ray crystallographic analysis (Fig. 1)[14] confirmed the *cis* stereochemistry of the ring fusion and also revealed that the absolute configuration of the generated stereocenters (3a and 7a) is *S*.

Removal of the chiral auxiliary from **5** using montmorillonite K-10[15] yielded 45% of (+)-**1** as a colorless oil, whose NMR data match those reported for (±)-**1**.[1,2,3c,7a] The e.e. of the synthesised (+)-rengyolone was 85%, determined by CGC and NMR analysis assisted by the perdeuterated Pirkle alcohol[16] as chiral shift reagent, and its specific rotation was $[\alpha]_D^{20} = +48.6$ (*c* 0.3 MeOH). Since the value of the specific rotation determined for our sample of (+)-**1** with 85% e.e. is much higher than that reported for cleroindicin F[5] ($[\alpha]_D^{20} = -2.7$) it is clear that this compound should be identified as racemic rengyolone.



Scheme 2. (a) $LiBH_4$, THF, 0°C, 4 days, 94%; (b) $Hg(OCOCF_3)_2$, DME, rt, 2 h/$NaBH_4$, 1.2 M NaOH, rt, 5 min, 78%; (c) montmorillonite K-10, CH_2Cl_2, rt, 1 day, 45%.

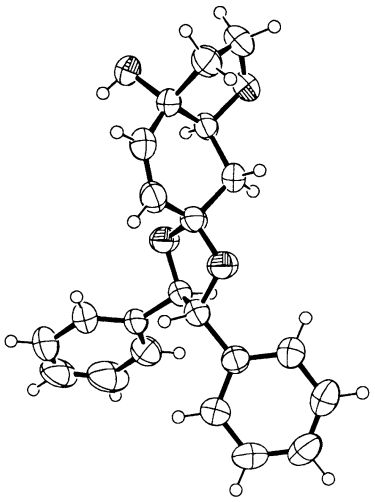
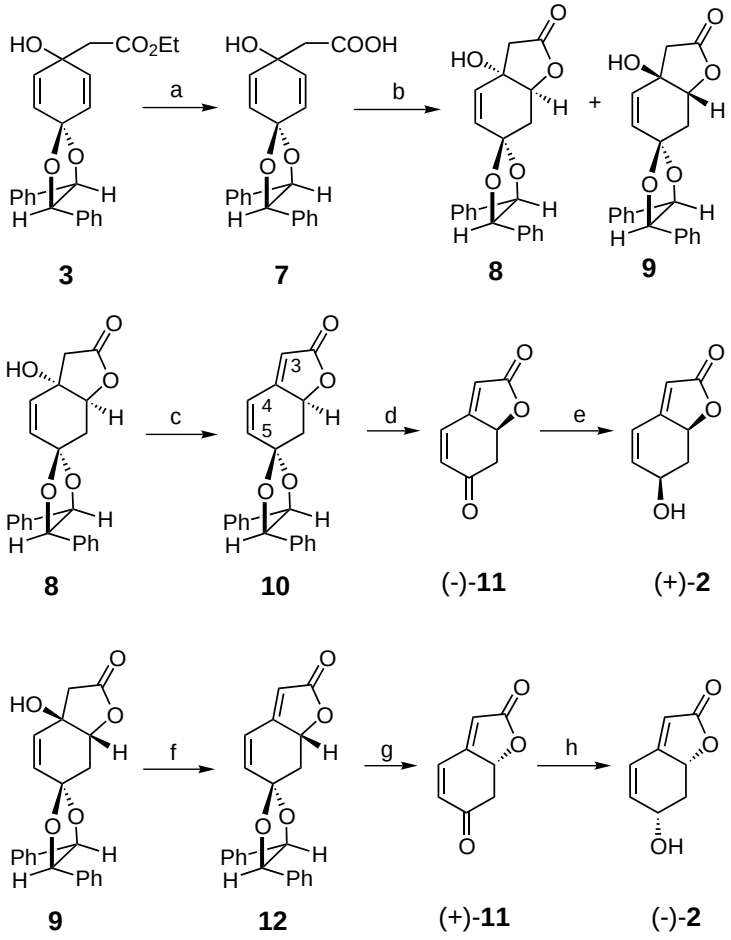


Figure 1. Molecular structure of **5** (ellipsoids at the 50% level).

The first step for the synthesis of **2** was the potassium hydroxide-mediated saponification of **3** (Scheme 3), providing acid **7** as a white solid (IR 1709 cm^{-1}, $[\alpha]_D^{20}=+14.8$ (*c* 1.2, $CHCl_3$)) in 84% yield. The formation of the γ-lactone was achieved by intramolecular addition of the carboxylic acid to the olefin promoted either by trifluoroacetic acid or mercury trifluoroacetate.[17] In both cases, crystalline lactones **8** (IR 1774 cm^{-1}) and **9** (IR 1785 cm^{-1}) were exclusively produced (60 and 28 or 30 and 45% yields, respectively), both of them with a *cis* ring fusion (vide infra). Lactone **8** could be isolated in pure form ($[\alpha]_D^{20}=+15.6$ (*c* 1.0, $CHCl_3$)), while **9** ($[\alpha]_D^{20}=+18.0$ (*c* 1.0, $CHCl_3$)) was contaminated with ca. 7% of **8**, according to NMR analysis. The synthesis of menisdaurilide was continued from each diastereoisomer independently. Dehydration of the tertiary alcohol of **8** with thionyl chloride afforded **10** in 84% yield ($[\alpha]_D^{20}=-96.6$ (*c* 4.7, $CHCl_3$)). In the ^1H NMR spectrum of **10**, the olefin protons H-3, H-4 and H-5 absorb at δ 5.92, 6.31 and 6.74 as two double doublets and a doublet, respectively, and the IR spectrum shows the characteristic absorptions of a butenolide at 1785 and 1758 cm^{-1}. Removal of the acetal was again performed by treatment of **10** with montmorillonite K-10. This reaction furnished 49% yield of the benzofuranone **11** ($[\alpha]_D^{20}=-207.4$ (*c* 1.2, acetone)), which spectroscopic data are identical to those reported for racemic **11**.[11b] Finally, (+)-menisdaurilide ($[\alpha]_D^{20}=+27.6$ (*c* 0.6, MeOH)) was



Scheme 3. (a) KOH, H_2O:EtOH, rt, 5 h, 84%; (b) CF_3COOH, $CHCl_3$, rt, 2 days, 60% of **8** and 28% of **9** or $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, 1 day, 30% of **8** and 45% of **9**; (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%.

prepared in 74% yield by reduction of the ketone function of (−)-**11** using Luche's reagent, as previously described for the synthesis of (±)-**2**.[11] In a similar way, the levorotatory natural isomer of **2** was synthesised from lactone **9**. Dehydration of **9** afforded **12** as a solid ($[\alpha]_D^{20}=+222.8$ (*c* 4.3, $CHCl_3$)) in 89% yield. Removal of the chiral auxiliary provided a 65% yield of the solid benzofuranone (+)-**11** ($[\alpha]_D^{20}=+165.6$ (*c* 1.3, acetone)), which was reduced by the same procedure described for its enantiomer, affording 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** were −28.9 (*c* 0.13, MeOH)[9b] and −27.3 (*c* 0.31, MeOH).[9d]

The spectral data of both (+)-**2** and (−)-**2** matched exactly those of (±)-**2**.[9b–d,11b] The enantiomeric purity of our samples was determined by NMR analysis in the presence of perdeuterated Pirkle alcohol[16] as chiral shift reagent. The measured e.e. of (+)-**2** was >98% and that of (−)-**2** 80%.

In conclusion, we have accomplished the first synthesis of (+)-rengyolone, (+)- and (−)-menisdaurilide from the common cyclohexane building block (+)-**3** in 22, 15 and 14% overall yields, respectively. The specific rotation of synthetic (+)-**1** demonstrates that the isolated compound named cleroindicin F is rengyolone. Enantioselective syntheses of other natural products with the benzofuran-2-one structure from chiral building blocks derived from *p*-benzoquinone monoketals are now being pursued.

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14. X-Ray single-crystal structure determination of **5** (crystallized from ethyl acetate/hexane). Crystal dimensions: 0.65×0.65×0.50 mm, colorless prisms. Empirical formula $C_{22}H_{22}O_4$. Molecular weight 350.40. Crystal system: orthorhombic. Space group $P2_12_12_1$ (No. 19). Lattice parameters: $a=9.4207(13)$, $b=10.4392(16)$, $c=19.1629(18)$ Å, $V=1884.6(4)$ Å^3, $Z=4$. Calculated density 1.235 g cm^{-3}. $F(000)=744$. μ(Mo Kα) = 0.084 mm^{-1}. Data were collected at 293(2) K on an Enraf Nonius CAD4 diffractometer using Mo Kα radiation ($\lambda=0.71069$ Å) yielding 1653 independent reflections. The structure was solved by direct methods (SHELXS-86[a]) and refined by least-squares on F^2 for all reflections (SHELXL-97[b]). Non-hydrogen atoms were refined anisotropically. The hydrogen atom bonded to oxygen was located on a difference Fourier map and refined isotropically. Hydrogen atoms bonded to carbon were placed in calculated positions with isotropic displacement parameters 1.2 times the U_{eq} values of corresponding carbons. Refined parameters 239. Goodness-of-fit on F^2: 1.081. $R(F)=0.035$ for 1458 reflections with $I>2\sigma(I)$, $R_w(F^2)=0.096$ for all data. (a) Sheldrick, G. M. SHELXS-86. *Crystallographic Computing 3*; Sheldrick, G. M.; Krüger, C.; Goddard, R., Eds.; Oxford University Press: Oxford, 1985; (b) Sheldrick, G. M. SHELXL-97, Program for the Refinement of Crystal Structures, Göttingen, 1997. The crystallographic data for **5** have been deposited with the CCDC as supplementary publication number CCDC 180290. Copies of the data can be obtained, free of charge, on application to CCDC, 12

Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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