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Enantioselective synthesis of (−)-paeonilide†

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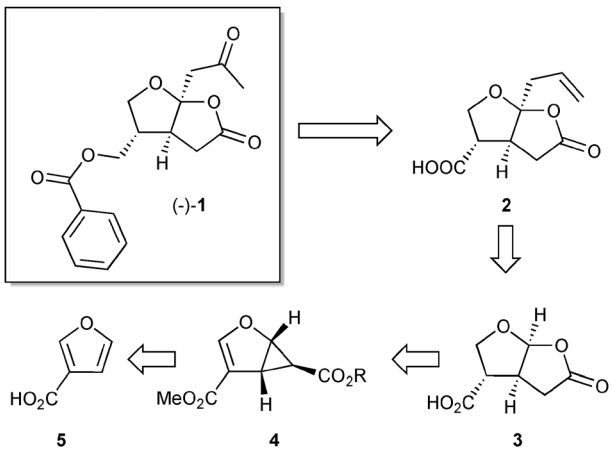
The first enantioselective synthesis of (−)-paeonilide is reported. Starting from inexpensive furan-3-carboxylic acid the targeted monoterpene was obtained in 12 steps *via* an asymmetric cyclopropanation-lactonization cascade and a stereoselective side chain insertion at an acetal-like position.

Natural products of herbal origin had an indisputable impact on modern medicinal chemistry and still break ground for new drugs. Paeonia root bark containing prescriptions like the multiherbal formula GuiZhiFuLing-Wan are employed in China, Japan and Korea to alleviate the syndromes of blood stasis and stiffness of abdominal muscles.[1–3] (+)-Paeonilide (+)-(**1**), a monoterpenoid isolated from *Paeonia delavayi*,[4] is a substructure of the privileged class of ginkgolides. In bioassays it showed selective inhibition of the platelet aggregation induced by PAF (platelet activating factor) with an IC_{50} value of 8 μg mL^{-1}, but importantly, no effect on the platelet aggregation induced by adenoside diphosphate (ADP) or arachidonic acid (AA).[4]

Two racemic[5,6] and one *ex-chiral pool*[7] synthesis of paeonilide have been reported to date, the latter achieved the synthesis of (+)-paeonilide (+)-(**1**) starting from chiral (−)-carvone. We report here a strategy that allows facile access to either enantiomer of paeonilide. Since only the (+)-enantiomer was tested in bioassays until now, we opted to demonstrate our strategy with the synthesis of its antipode to gain further insight into the biological activity of **1**.

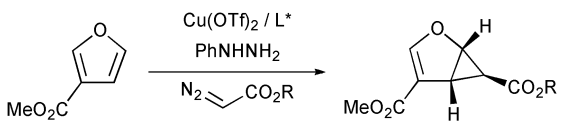
The three key steps of our strategy are the synthesis of **4** by an enantioselective cyclopropanation of **6** derived from commercially available furan-3-carboxylic acid (**5**) (Scheme 1 and Table 1), its transformation to the core structure **3** by donor–acceptor substituted cyclopropane ring-opening/intramolecular lactonization cascade of **4**, and synthesis of **2** by introducing an allyl side chain at the acetal-like position in **3**.

We had previously developed the cyclopropanation of furan-2-carboxylic acid esters with ethyl diazoacetate[8] as a facile entry into various γ-butyrolactone containing natural products,[9] which proceeds in the presence of copper(I)-bis(oxazoline) CuOTf·**8a** in 94% *ee*. The asymmetric cyclopropanation of the corresponding 3-methylester **6** turned out to be more challenging,



Scheme 1 Retrosynthetic analysis of (−)-paeonilide (−)-(**1**).

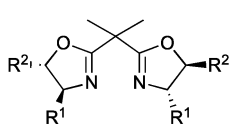
Table 1 Asymmetric cyclopropanation of **6**



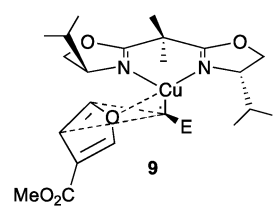
6 **4a**: R = Et **4b**: R = tBu

Entry	Diazoester R	Ligand	Yield [%]	% ee
1	Et	**7**[a]	27	74
2	tBu	**7**	38	65
3	Et	**8a**[a]	22	74
4	Et	**8b**	31	83
5	tBu	**8b**	38[b]	83
6	tBu	**8c**	34	19

[a] Ref. 8*b*. [b] 53% based on recovered starting material.



7: R^1 = CH_2OH, R^2 = Ph
8a: R^1 = tBu, R^2 = H
8b: R^1 = iPr, R^2 = H
8c: R^1 = Ph, R^2 = H



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most likely due to the fact that the ester group in the 3-position is too far away to effectively interact with the catalyst, as depicted in the transition state **9** that rationalizes the asymmetric pathway

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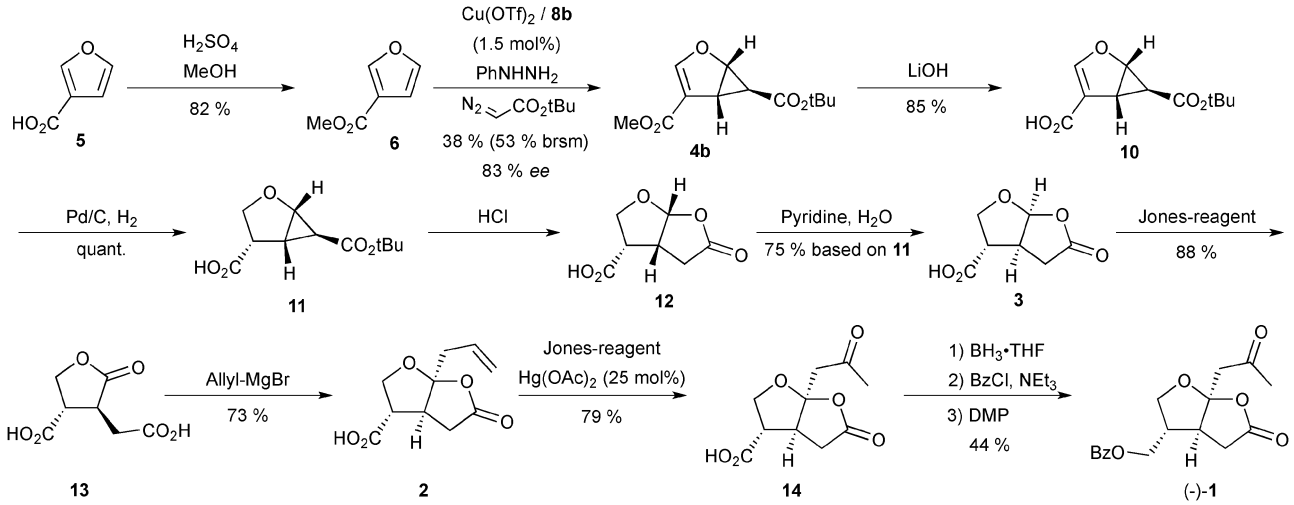


Scheme 2 Synthesis of (−)-paeonilide (−)-(**1**).

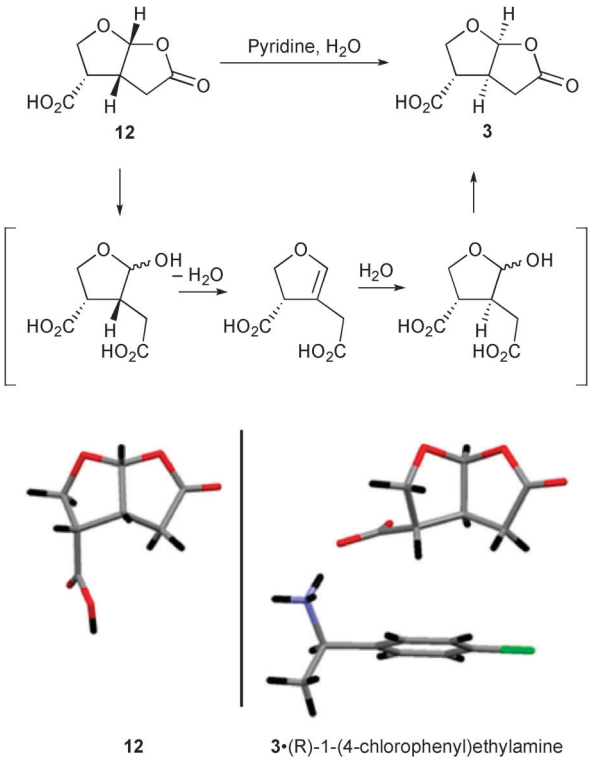
of the process. Nevertheless, **4** could be obtained in 83% *ee* using CuOTf·**8b** (Table 1, entries 4 and 5), being surprisingly more selective than the sterically more bulky catalysts CuOTf·**8a** (entry 3) or CuOTf·**8c** (entry 6). In order to avoid the competing twofold cyclopropanation, it turned out to be advantageous to run the reaction only to about 50% conversion, nevertheless, **4b** could be readily produced on a 20 g scale. Unfortunately, all efforts to enhance the enantiomeric excess *via* recrystallization at this stage failed due to the excellent solubility of **4b** in most solvents.

In order to transform the hydroxycyclopropane ester unit into the desired lactone, it was necessary to first reduce the double bond in **4b** to avoid rearomatization to a furan during the ring opening of the donor–acceptor-substituted cyclopropane. However, direct hydrogenation of **4b** under a variety of conditions only proceeded in low yields.

In contrast, the carboxylic acid **10** being obtained by selective hydrolysis of **4b** allowed the quantitative transformation to **11**, in which the carboxylic acid group is placed selectively on the concave face of the bicycle. Acid induced cyclopropane ring-opening/lactonization[10] proceeded smoothly to **12**, establishing the core structure of paeonilide in which the relative stereochemistry of the acid substituent with respect to the ring junctions needs to be corrected. Treatment of **12** with pyridine gave rise to **3**, exploiting the higher stability of bicyclo[3.3.0] frameworks that orient larger groups on its convex face. Notably, the stereocenters on the ring junctions undergo epimerization as proved by X-ray-structure analysis of **12** and the ammonium salt obtained from **3** and (*R*)-1-(4-chlorophenyl)ethylamine (Scheme 3), being also in agreement with epimerization studies of similar furolactones.[11]

The final challenge towards paeonilide (**1**) consisted of the introduction of the side chain at the acetal-like position of **3**, thus requiring the creation of a quaternary stereocenter to arrive at **15** (Scheme 4).

All attempts to realize this goal by a direct C–H insertion of a carbene following leads known in the literature[12] for achieving such transformations at the 2-position of THF or at the acetal carbon of 1,3-dioxolanes with diazoesters in the presence of copper or rhodium catalysts failed. As an alternative, lactone opening followed by oxidation to **13** was envisioned, which should allow

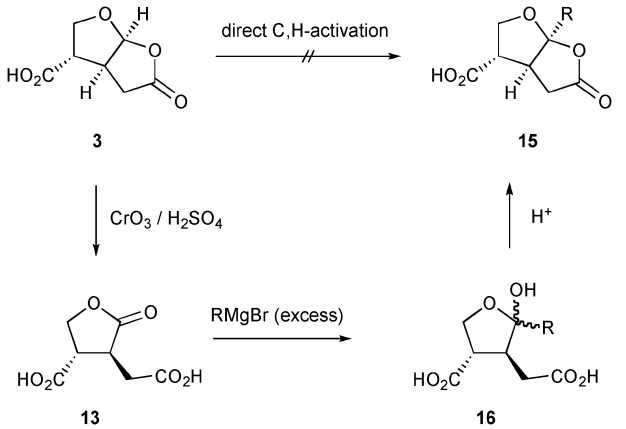


Scheme 3 Base induced isomerization of **12** to **3**.

the addition of nucleophiles to **16** followed by relactonization to give the desired **15**.

In practice (Scheme 2), lactone **3** was treated with Jones-reagent, simultaneously opening the lactone and oxidizing the hemi-acetale to the α,β-dicarboxy-γ-lactone **13** in very good yield. Addition of allylmagnesiumbromide followed by acidic workup gave rise to **2** in which an allyl group was installed stereoselectively into the bicyclic framework.

Reduction of the carboxylic acid at this stage to create the required alcohol functionality afforded only very low yields. Oxidizing the allyl substituent with Jones-reagent combined with catalytic amounts of mercury(II)-acetate led to **14**, while the oxidation under Wacker conditions afforded the desired



Scheme 4 Synthetic strategy for the introduction of side chains R at the acetal-like position of furolactones.

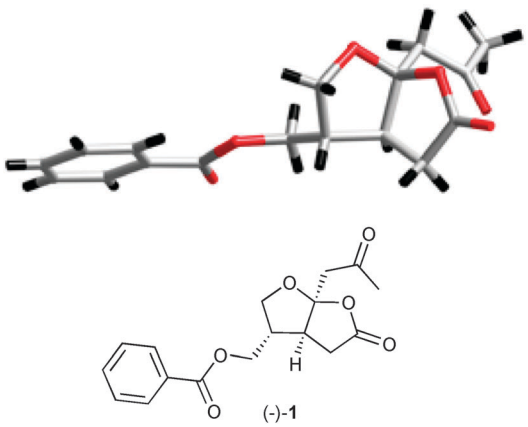


Fig. 1 X-Ray structure of (−)-paeonilide (−)-(**1**).

product as well but was accompanied by several by-products. Finally, a reduction–benzoylation–oxidation sequence of **14** *via* the corresponding diol selectively allowed functionalization of the primary alcohol. Final oxidation of the secondary alcohol with Dess–Martin periodinane (DMP) yielded (−)-paeonilide (−)-(**1**) in 83% *ee* corresponding to the enantioselectivity achieved in the cyclopropanation of **6**. All spectroscopic data were in accordance to literature data, furthermore, the structure of (−)-**1** was confirmed by X-ray crystallography (Fig. 1).

The antagonistic activity of (−)-**1** against the PAF receptor was found to be negligible compared to the naturally occurring enantiomer (+)-**1**: the thrombocyte aggregation was inhibited only by 20% at a concentration of 30 μg mL^{-1} (94 μM) of (−)-**1** (*cf.* (+)-**1** (IC_{50} = 8 μg mL^{-1}, 25 μM)). Presumably, the antagonism observed is caused by the impurity of the eutomeric (+)-**1** in the measured sample.

In conclusion we reported the first enantioselective synthesis of the natural product (−)-paeonilide (−)-(**1**), which was synthesized in 12 steps and an overall yield of 4.4% (7.7% brsm) starting from 3-furoic acid (**5**). Biological tests implicate the inactivity of (−)-**1** against the PAF receptor, giving further credit to the unique and selective activity of naturally occurring (+)-paeonilide (+)-(**1**).

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