CHAPTER 2

Diastereoselective Total Synthesis of Paeonilide

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Notes: (i) An independent figure, table, scheme, structure and reference numbers have been used for each section, (ii) detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been appropriately included at the end part of section B.
This chapter is divided into two sections. The section A presents a concise literature account on isolation, structure, activity and schematic summary of all syntheses of naturally occurring paeonilide. To date, four well-designed approaches for the synthesis of paeonilide have been reported in the literature. A concise representation on these elegant literature approaches has been exemplified in brief (Scheme 1).

Scheme 1. Fundamental Literature Approaches for the Total Synthesis of (+)/(−)-Paeonilides

The section B describes our contribution on the remarkable reactivity reversal stratagem in 3,4-disubstituted butenolides under acidic conditions and its application in diastereoselective total synthesis of paeonilide. Design of suitably substituted multifunctional butenolide followed by an acid catalyzed chemo- and diastereoselective intramolecular ring closure via the reactivity umpolung has been demonstrated to accomplish a concise total synthesis of paeonilide (Scheme 2).

Scheme 2. Concise Diastereoselective Total Synthesis of (+)-Paeonilide via Reactivity Umpolung

Overall the protocol involves one-pot reduction of an α,β-unsaturated carbon–carbon double bond and intramolecular nucleophilic insertion of oxygen function at the electron rich γ-position of butenolide. The involved mechanistic aspects have also been discussed.
## CHAPTER 2: SECTION A

**A Concise Literature Account of Paeonilide**

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2A.1 Introduction

The use of plants as medicines predates written human history. The use of herbs to treat disease is almost universal among non-industrialized societies and is often more affordable than purchasing pharmaceuticals. Ethnobotany (the study of traditional human uses of plants) is recognized as an effective way to discover future medicines (reverse pharmacology). Paeonia root bark, “mu-dan-pi” or “dan-pi” in Chinese, is one of the most important herbal drugs used in China, Japan and Korea to alleviate the syndromes of blood stasis and in an analgesic relieve for soothing muscle pain. Since Paeony roots are under chemical and pharmacological investigation for many years, several new components have been isolated, characterized and pharmacologically examined (Figure 1).

![Figure 1. Natural products isolated from paeony roots](image)

A metabolite, 7R-paeonimetaboline-I (1) isolated from bacterial digestion of paeony extracts, inhibits penetretaxole- and pentylentetrazole-induced convulsions in rats. The monoterpenoids, paonilflorigenone (2) has a blocking effect on the neuromuscular junction in phrenic nerve diaphragm preparations of mice. Paeonilactone C (5) suppresses both directly and indirectly stimulated muscle twitching of sciatic nerve-sartorius muscle from frogs. (+)-Paeonilide (6), a highly oxygenated irregular monoterpenoid-derived metabolite has been isolated by Liu and co-workers from roots of *Paeonia delavayi* in 2000. Approximately, 1.13 kg of *Paeonia delavayi* roots provided 8 mg of pure (+)-paeonilide. Its structure was established by the combination of spectroscopic and crystallographic study. Paeonilide bears a partial ring structure of the privileged class of ginkgolides from *Ginkgo biloba* which is a living fossil dating back 270 million years ago (Figure 2). Ginkgolides are known to inhibit the human platelet aggregation by inhibition of the binding of (3H)-PAF-acether to its membrane platelet receptor. The pharmacological properties are, inter alia, antagonism on PAF induced thrombosis, lung anaphylaxis, cardiac anaphylaxis and inhibition of transplant rejection.
Figure 2. Naturally occurring bioactive ginkgolides

The inspiration from structural similarity with ginkgolides and in search of new lead, (±)-paeonilide was screened for bioassays. The results confirmed a selective inhibition of the platelet aggregation induced by the platelet activating factor (PAF) with an IC₅₀ value of 8 µg/mL (25 µM), importantly, without inhibitory effect on adenoside diphosphate (ADP) or arachidonic acid (AA)-induced platelet aggregation. The platelet-activating factor receptor is a G-protein coupled receptor which shows structural characteristics of the rhodopsin gene family and binds PAF. The PAF is a phospholipid (1-O-alkyl-2-acetyl-sn-glycero-3-phosphorylcholine) which is implicated as a mediator in many pathologic processes like allergy, asthma, septic shock, arterial thrombosis and inflammation.

The probable biogenesis of paeonilide may arise from re-arrangements of the isoprene units by cleavage of the cyclic monoterpenoid p-menthan (8). A subsequent oxidation and ring formation between C-2, C-5 and C-9 carbon atoms would generate the core structure of Paeonilide (Scheme 1).

Scheme 1. Proposed Biosynthetic Pathway to Paeonilide

2A.2 Synthetic Approaches Towards Paeonilide

In a very short time paeonilide became a challenging synthetic target for many organic chemists. This is due to the combination of its interesting biological activity and the uncommonly densely oxygenated monoterpenoid attributed with an acetonyl moiety attached to the ketal function with contiguous three stereocenters on the tetrahydrofurofuran framework. In the total synthesis of paeonilide, generation of three contiguous chiral centres in an enantioselective or diastereoselective fashion is the challenging task. To date, two racemic and
two stereoselective well-organized total synthesis of paeonilide have been reported in the literature by employing new carbon–carbon/oxygen bond forming strategies. Herein a concise schematic summary on these elegant literature approaches has been presented (Schemes 2–5).

2A.2.1 Zhang’s Approach Towards Total Synthesis of (±)-Paeonilide

Zhang and co-workers\textsuperscript{13} achieved the total synthesis (±)-paeonilide in 16 steps with an overall yield of 15%. As described in Scheme 2, the synthesis started from commercially available 2-hydroxy-4-methylacetophenone (11).

Benzyl protection followed by Rubottom oxidation and TBDMS protection of resulting alcohol provided the α-hydroxy ketone compound 14. Further, one carbon Wittig olefination followed by hydroboration of the resulting olefin gave the diol 16 in 86% yield. Benzyl group was deprotected using hydrogenolysis, 1,3-diol was protected to form the corresponding acetonate and phenolic hydroxyl group was protected with TBDMS chloride to afford compound 18. The compound 18 was subjected to a Birch reduction followed by desilylation of resulting enol ether provided the desired nonconjugated enone 20 in 78% yields over two-step.

\textbf{Scheme 2.} Zhang’s Total Synthesis of (±)-Paeonilide
The cis-dihydroxylation of β,γ-olefin using osmium tetroxide selectively produced (±)-21 in 92% yield. The cause of diastereoselectivity is back side shielding by the acetonide ring. The selective IBX oxidation of secondary hydroxyl and oxidative cleavage with periodic acid generated the inisolable key intermediate 23. The constitutionally similar but topologically different hydroxyl group in intermediate 23 underwent stereoselective intramolecular cyclization to deliver the desired alcohol 24. Finally, benzoylation of free hydroxyl group provided racemic (±)-paeonilide (6). In the present synthesis use of an appropriate aromatic precursor to create all the desired functionalities in paeonilide is noteworthy.

2A.2.2 Zhang’s Approach Towards Stereoselective Synthesis of (+)-Paeonilide

Zhang and co-workers also ascertained the stereoselective synthesis of (+)-paeonilide. Starting from (R)-carvone, paeonilide was obtained in 16 steps and 6.2% overall yield (Scheme 3).14

Carvone (25) was selectively transformed into epoxide 27 via the allylic bromination, acetoxylation, Luche-reduction and hydroxyl directed chemo- and stereoselective epoxidation sequence. Regioselective epoxide opening with an in situ generated LiBr (acetyl bromide + n-BuLi) followed by ketal protection of the resulting vicinal diol 28 gave compound 29 in 92%
yields (2 steps). It was then subjected for hydroboration and the dehydrobromination was performed using \( t\)-BuOK to obtain the product 31. The intramolecular diastereoselective bromoetherification using NBS lead to furan derivative 32. Benzylation of primary alcohol followed by deketalization under acidic conditions generated diol 33 in 91% yield. The IBX oxidation to ketone 34 and subsequent oxidative cleavage using periodic acid and trapping the free acid with diazomethane afforded diastereomeric mixture of compound 35. Dehydrobromination by using DBU selectively yielded the key intermediate 36. Finally, acid promoted furan opening and diastereoselective intramolecular cyclizations provided (+)-paeonilide (6) in 40% yield. The absolute configuration assigned for the natural paeonilide was confirmed on basis of this chiral pool synthesis.

2A.2.3 Du’s Approach Towards Facile Synthesis of (±)-Paeonilide

The shortest five steps synthesis of paeonilide was published from Du’s research group\(^{15}\) with an overall yield of 59% starting from commercially available tris(hydroxymethyl)methane (39). As depicted in Scheme 4, the compound 39 was protected as the corresponding acetal 40 and subjected for a one-pot Swern oxidation and Wittig olefination to furnish the desired (\( E\))-ester 41 in 84% yield. Benzoyl peroxide promoted Michael type radical addition of aldehyde 42 to ester 41 afforded the critical ketone-ester 43 in 79% yield. Acid promoted in situ deacetalization, hemiacetal formation and lactonization followed by benzylation provided (±)-paeonilide (6) in 89% yield. Herein the selective ring closure in intermediate 44a exclusively forming the paeonilide framework is remarkable.

![Scheme 4. Du’s Total Synthesis of (±)-Paeonilide](image)

2A.2.4 Reiser’s Approach Towards Enantioselective Synthesis of (–)-Paeonilide

Very recently, Harrar and Reiser\(^{16}\) reported the enantioselective synthesis of (–)-paeonilide in 12 steps with 4.4% overall yield via an asymmetric cyclopropanation-lactonization cascade and
a stereoselective side chain insertion reactions. As portrayed in Scheme 5, The enantioselective
cyclopropanation of the furan 46 with t-butyl diazoacetate using copper(I)-bis(oxazoline)
CuOTf.A complex resulted in formation of compound 47 in 38% yield with 83% ee. Selective
hydrolysis of methyl ester in compound 47 followed by reduction of carbon–carbon double
bond provided compound 48. Acid induced cyclopropane ring-opening and lactonization
proceeded smoothly to generate the paeonilide core structure 49. It was converted to relatively
more stable bicyclo[3.3.0] frameworks 50 with larger groups on convex face, with the
epimerization of stereocenters on the ring junctions. Simultaneous lactone opening and
oxidation of the formed hemi-acetal using Jones reagent afforded dicarboxy-γ-lactone 51 in
88% yield.

Scheme 5. Reiser’s Synthesis of (−)-Paeonilide

Stereoselective installation of allyl group was achieved using addition of allylmagnesium
bromide to obtain compound 52. The combination of Jones reagent with catalytic amounts of
mercury(II)-acetate led to compound 53 in 79% yield. Finally, a reduction using BH₃·THF,
benzylation of primary alcohol and reoxidation of the secondary alcohol with Dess–Martin
periodinane (DMP) provided (−)-paeonilide (6) in three-step with 44% yield (83% ee).
Unnatural (−)-paeonilide was found inactive against the PAF receptor.
2A.3 Summary

In summary, we have presented a concise literature account on the isolation, bioactivity and syntheses of paeonilide. The key reactions that were employed to efficiently accomplish the four syntheses of paeonilide were Rubottom oxidation, Birch reduction, hydroboration, stereoselective epoxidation, bromoetherification, benzoyl peroxide mediated radical addition, topologically favored diastereoselective cyclizations, asymmetric cyclopropanation and lactonization. Overall, remarkable approaches coupled with development of novel methodologies for the synthesis of this target compound have been known in the literature. Our synthetic studies towards the synthesis of (±)-paeonilide along with development of a concept of reactivity umpolung in butenolides have been discussed in details in the section B of the present chapter.
2A.4 References

(1) http://en.wikipedia.org/wiki/Ethnobotany


(12)  http://en.wikipedia.org/wiki/Platelet-activating_factor


CHAPTER 2: SECTION B

Reactivity Umpolung in Intramolecular Ring Closure of 3,4-Disubstituted Butenolides: Diastereoselective Total Synthesis of Paeonilide

This section B of chapter 2 features the following topics:

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2B.1 Rationale of the Present Work

In standard organic reactions, the "normal" mode of reactivity is the formation of new bonds between atoms of opposite polarity. Whereas, reactivity umpolung or polarity inversion in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group. This alteration allows otherwise forbidden, secondary reactions of this functional group. The concept was introduced by D. Seebach and E. J. Corey (in German *umpolung* means reversal of polarity). For example, the use of cyanide in benzoin condensation impelled into the development of famous Corey–Seebach umpolung, Stork umpolung, Stetter reaction and, Hünig/Stork reaction. Very recently this concept has gained much consideration due to the modern development in the field of *N*-heterocyclic carbene (NHC) chemistry. The use of thiamine pyrophosphate, 3-membered rings, dithiane, oxidative couplings and organometallic reagents are the accustomed epitomes.

A large number of the ginkgolide class of natural and unnatural hydrofurofuran systems have been known in the literature and have attributed a wide range of biological activities. More specifically, the fused tetrahydrofurofurans and hexahydrofurofurans bearing common acetal/ketal carbon atom have been imperative targets for stability reasons and well-ordered synthetic routes have been known in the literature (Figure 1).

![Figure 1. Furofuran based bioactive natural products](image)

We have been using cyclic anhydrides and their derivatives as the potential precursors for total synthesis of structurally interesting and biologically important natural products for almost the past two decades.

![Scheme 1. γ-Butenolides as the Nucleophiles in Vinylogous Addition Reactions (Reported Work)](image)
During the course of our studies on intramolecular oxa-Michael addition reaction of suitably 3,4-disubstituted butenolide, we serendipitously witnessed an unusual isomerization of carbon–carbon double bond followed by nucleophilic insertion of oxygen function at the γ-position. The normal reactivity at γ-position of butenolides is nucleophilic and they undergo facile reactions with an array of electrophiles (Scheme 1).

In this context, we herein report an interesting instance of reactivity umpolung and its application for the total synthesis of (±)-paeonilide (1) (Schemes 2–7).

2B.2 Results and Discussion

Initially, we selected the bioactive natural product buergerinin from Scrophularia buergeriana as a target compound and started the synthesis of requisite advanced butenolide intermediate (Scheme 2). Aldol condensation of O-benzyl protected aldehyde 2 with relatively more reactive glyoxalic acid (3) in the presence of morpholine-hydrochloride directly furnished the corresponding maleic anhydride derivative 4 in 78% yield via a stereoselective dehydrative cyclization pathway. Barbier reaction of propargyl bromide with lactol 4 (masked aldehyde) provided the corresponding acetylenic derivative 5 in 82% yield following a ring-opening and ring-closing pathway. Compound 5 upon treatment with sulfuric acid adsorbed on silica gel underwent smooth hydrolytic acetylene to ketone transformation and formed the required product 6 in 86% yield. Chemoselective debenzylation of compound 6 with H₂/Pd–C yielded the essential precursor 3,4-disubstituted butenolide 7 in 83% yield. The protection-free multifunctional compound 7 bearing free ketone and alcohol units at appropriate positions can theoretically form two different intramolecular cyclization products under acidic conditions (Figure 2). Namely, (i) intramolecular cyclization to the corresponding hemiketal followed by a dehydration to form furooxepine 10 and (ii) generation of hemiketal intermediate followed by a concomitant diastereoselective intramolecular oxa-Michael addition to the α,β-unsaturated carbon–carbon double bond leading to (±)-buergerinin G (11). Surprisingly, the reaction of compound 7 with p-TSA in refluxing benzene/toluene followed an alternative novel intramolecular cyclization pathway in a highly chemo- and diastereoselective fashion and exclusively delivered the exotic furofuran system (±)-8 in 75% yield.
The observed addition of oxygen function at the electron rich γ-position of butenolide is exceptional. Mechanistically, the present fact can be attributed to an acid-catalyzed structural rearrangement encompassing reactivity umpolung depicted in Scheme 3. The butenolide 7 on protonation of lactone carbonyl followed by a conjugate base induced allylic prototropic shift results in an unusual olefin isomerization to form the labile hydroxyfuran intermediate B. The possible driving forces for the present allylic shift are, (i) generation of tetrasubstituted carbon–carbon double bond between the β- and γ-positions of butenolide and (ii) formation of an aromatic furan intermediate B. Intermediate B under acidic conditions selectively transforms into oxocarbenium ion C using relatively more reactive double bond in furan ring. The synchronized intramolecular nucleophilic addition of primary alcohol forms a unique product 8. In transformation of intermediates A to D, an oxygen function adds to the electron rich γ-carbon and a proton to the electron deficient β-carbon of starting butenolide. Hence, the overall reaction process becomes viable due to reactivity umpolung at the γ-position of 3,4-disubstituted butenolide 7.
Scheme 3. Plausible Mechanism for the Reactivity Umpolung

As shown in Scheme 4, the intermolecular reactions of 3,4-disubstituted butenolide 12/13 with methanol/ethanol/isopropanol in the presence of $p$-TSA in refluxing toluene were unsuccessful to provide the corresponding desired product 14/15. In all cases, the starting butenolide was isolated back in quantitative amount. The above fact clearly reveals that the transformation of butenolide 7 into the bicyclic product 8 follows a stepwise pathway and it is a both enthalpically (formation of new carbon–oxygen bond) and entropically (formation of five-membered ring) favoured process.

Scheme 4. Attempted Intermolecular Nucleophilic Oxygen Insertions

In the next part of our study, we planned to authenticate the feasibility of reactivity umpolung conception to design a diastereoselective total synthesis of (±)-paeonilide (1). The isolation, biological activity and synthetic approaches from various research groups have been already described in section A of present chapter.5a,15

As described in Scheme 5, our synthesis of paeonilide began with morpholine-hydrochloride promoted condensation of appropriately double $O$-benzyl protected aldehyde 16 with glyoxalic acid (3). The above stated stereoselective condensation directly furnished the expected maleic anhydride derivative 17 in 64% yield following a dehydrative cyclization pathway. Barbier reaction of propargyl bromide with a masked aldehyde 17 in presence of
activated zinc powder provided the corresponding acetylenic derivative 18 in 82% yield, which on acidic hydrolysis transformed into the desired ketone 19 in 87% yield. We systematically studied the selective mono-benzyl and di-benzyl deprotections in compound 19 under various reaction conditions. The reactions of compound 19 with H₂/Pd–C in MeOH, HCOOH/Pd–C in MeOH, LiCl in DMF, BCl₃ in DCM and BBr₃ in DCM resulted in isolation of staring material and/or decomposition of reaction mixture. Fortunately, both benzyl groups in compound 19 were smoothly deprotected in the presence of excess of aluminum chloride¹⁷ in DCM plus m-xylene mixture at room temperature and delivered the essential 3,4-disubstituted butenolide 20 in 84% yield. However, the reaction of compound 20 with p-TSA in refluxing benzene/toluene furnished a complex mixture of products. We reasoned that the cause for such decomposition could be a presence of multiple oxygen-functions in the starting material 20 (C:O = 2:1 ratio).

The controlled reaction of compound 19 with a use of precise amount of AlCl₃ (1.50 equiv) in DCM plus m-xylene mixture at room temperature was selective and formed the expected mono-deprotected pair of diastereomers 21 in 81% yield with nearly 1:1 ratio (by ¹H NMR). An attempted flash silica gel column chromatographic separation of the diastereomeric 21 resulted in their ~9:1 and ~1:4 mixtures (by ¹H NMR), which were used as such for the cyclizations. Gratifyingly, the reactions of 1:1 mixture of diasteromers of compound 21 and their partially purified forms with p-TSA in refluxing toluene were highly chemo- and diastereoselective resulting in the same desired product (±)-22 in 73% yield via structural rearrangement following an intramolecular cyclization pathway with reactivity umpolung.

![Scheme 5. A Concise Diastereoselective Total Synthesis of (±)-Paeonilide via Reactivity Umpolung](image-url)

The plausible mechanism for involved diastereoselectivity and reactivity umpolung in the formation of preferred product (±)-22 is represented in Scheme 6. As described therein, the cause for diastereoselectivity is formation of the labile hydroxyfuran intermediate (±)-E, tentatively nullifying the chirality at γ-position of both diastereomers of butenolide 21 to
generate a pair of enantiomers. The cause for reactivity umpolung is generation of oxocarbenium ion intermediate (±)-F with a highly diastereoselective in situ protonation. The intermediate F undergoes further instantaneous diastereoselective intramolecular ring closure to yield the desired product 22 as a racemic mixture.

Finally, O-benzyl group in compound (±)-22 was deprotected under H₂/Pd–C conditions to form the known ultimate stage intermediate alcohol (±)-23 in 91% yield. Primary alcohol 23 on treatment with benzoyl chloride/pyridine in DCM furnished the desired natural product (±)-paenilide (1) in 99% yield. The analytical and spectral data obtained for paenilide (1) was in complete agreement with the reported data⁵,¹⁵ and starting from glyoxalic acid it was obtained in seven steps with 24% overall yield.

![Scheme 6. Plausible Mechanism for the Diastereoselective Ring Closure](image)

Herein we also describe the synthesis of starting material 13 from Scheme 4. Compound 13 is a natural product chenopanone which was isolated in the year 2000 from an Egyptian collection of aerial parts of C. ambrosioides L. (Chenopodiaceae) extract.¹⁸ The genus Chenopodium consists of 120 plus species which are imperative due to their wide range of medicinal properties.¹⁹ The crude extract of C. ambrosioides is known to possess antifungal acitity.²⁰ The structure of chenopanone was established as 4-isopropyl-5-(2-oxopropyl)furan-2(5H)-one (13) on the basis of MS and NMR spectroscopic data.
We reasoned that isopropylmaleic anhydride or its equivalent would be a potential precursor for the synthesis of chenopanone and completed the first synthesis of this simple target molecule (Scheme 7).

Scheme 7. Synthesis of Chenopanone

For a simplicity reasons, we decided to start our synthesis from readily available glyoxalic acid to design the requisite hydroxylactone.\textsuperscript{11} The morpholinum hydrochloride induced reaction of glyoxalic acid with 3-methylbutanal (isovaleraldehyde) exclusively furnished the desired lactol 25 in 78\% yield via a selective dehydrative intermolecular condensation and intramolecular cyclization pathway. The selective zinc promoted Barbier reaction of propargyl bromide with a masked aldehyde 25 gave the required acetylenic $\gamma$-lactone 26 in 87\% yield with overall substitution of hydroxy group in the lactol by a propargyl group. The structure of product 26 was confirmed on the basis of analytical and spectral data. Finally, the hydration of an acetylenic unit in product 26 to the corresponding ketone unit provided the desired chenopanone (13) in 97\% yield. The analytical and spectral data obtained for synthetic 13 were in complete agreement with the reported data.\textsuperscript{18} The natural product 13 was obtained in three steps with 66\% overall yield.
2B.3 Summary

In summary, we have demonstrated a novel reactivity umpolung in 3,4-disubstituted butenolides and accomplished the diastereoselective total synthesis of paeonilide. The observed chemo- and diastereoselectivity in the intramolecular cyclization leading to a paeonilide is noteworthy from a basic chemistry point of view. The overall reactivity umpolung process involves insertion of oxygen function at the electron rich γ-carbon. The enzymatic meso-desymmetrization of the corresponding diacetate derivative will also provide access to the corresponding enantiomerically pure forms of paeonilide. The present convergent access to fused furofuran systems has a broad scope and it will be useful to design several focused minilibraries of their natural and unnatural analogues and congeners for SAR studies. We believe that our present redox protocol will also work equally well to plan the corresponding furopyran based structural architectures. Finally, the present reactivity umpolung opens a new avenue in the significant field of butenolide chemistry.
2B.4 Experimental Section

General Description. Melting points are uncorrected. The $^1$H NMR spectra were recorded on 200 MHz NMR spectrometer, 400 MHz NMR spectrometer and 500 MHz NMR spectrometer using TMS as an internal standard. The $^{13}$C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz) and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 and 200–400 mesh). Commercially available glyoxalic acid monohydrate, propargyl bromide (80% solution in toluene), Zn powder, Hg(OAc)$_2$, Pd on charcoal (10 wt%), p-TSA, anhydrous AlCl$_3$ and benzoyl chloride were used. The starting aldehydes 2 and 16 were prepared by using known procedures.$^{10,16}$

4-(2-(Benzyloxy)ethyl)-5-hydroxyfuran-2(5H)-one (4).

To a stirred homogeneous suspension of glyoxalic acid monohydrate (194 mg, 2.10 mmol) and powdered morpholinium hydrochloride (260 mg, 2.10 mmol) in 1,4-dioxane (4 mL) plus water (60 µL) mixture was added aldehyde 2 (356 mg, 2.00 mmol). The reaction mixture was stirred at 25 °C for 1 h and refluxed for 24 h. Solvent was evaporated under vacuo and water (10 mL) was added to the reaction mixture. It was extracted with ethyl acetate (15 mL × 3), dried over Na$_2$SO$_4$ and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (3:2) as an eluent to yield the pure product 4 as thick oil (364 mg 78% yield). $^1$H NMR (CDCl$_3$, 200 MHz) δ 2.55–2.83 (m, 2H), 3.71 (t, $^J$= 6 Hz, 2H), 4.52 (s, 2H), 5.47 (br s, 1H), 5.91 (q, $^J$= 2 Hz, 1H), 5.97 (d, $^J$= 2 Hz, 1H), 7.23–7.42 (m, 5H); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 27.8, 66.9, 73.1, 99.4, 118.4, 127.8, 127.9, 128.4, 137.2, 166.9, 171.8; ESIMS (m/z) 257 [M+Na]$^+$; HRMS (ESI) calcd for C$_{13}$H$_{14}$O$_4$Na 257.0784, found 257.0784; IR (CHCl$_3$) $\nu_{\text{max}}$ 3350, 1758, 1649 cm$^{-1}$.

4-(2-(Benzyloxy)ethyl)-5-(prop-2-yn-1-yl)furan-2(5H)-one (5).

To a stirred solution of compound 4 (360 mg, 0.154 mmol) in dimethylformamide (4 mL) at 0 °C was added propargyl bromide (174 µL, 80 wt% in toluene, 1.84 mmol) and zinc power (300 mg, 4.60 mmol). The reaction mixture was stirred at 25 °C for 3 h and quenched with saturated aqueous NH$_4$Cl
solution (2 mL). After 0.5 h the reaction mixture was diluted with ethyl acetate (20 mL) and filtered to remove the zinc residues. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (4:1) as an eluent to yield the pure product 5 as thick oil (322 mg, 82% yield). \(^1\)H NMR (CDCl₃, 200 MHz) \(\delta\) 2.00 (t, \(J = 4\) Hz, 1H), 2.50–2.90 (m, 4H), 3.55–3.80 (m, 2H), 4.53 (s, 2H), 5.02 (dt, \(J = 6\) and 2 Hz, 1H), 5.95 (s, 1H), 7.20–7.43 (m, 5H). \(^1^C\) NMR (CDCl₃, 50 MHz) \(\delta\) 22.1, 28.5, 66.9, 71.9, 73.0, 76.6, 80.8, 117.6, 127.5, 128.3, 137.4, 168.5, 172.3; ESIMS (\(m/z\)) 279 [M+Na]+; HRMS (ESI) calcd for C₁₆H₁₆O₃Na 279.0992, found 279.0992; IR (CHCl₃) \(v_{\text{max}}\) 2100, 1756, 1641 cm\(^{-1}\).

**4-(2-(Benzyloxy)ethyl)-5-(2-oxopropyl)furan-2(5H)-one (6).**

\[
\text{OCH}_2\text{Ph}
\]

To a stirred solution of compound 5 (320 mg, 1.26 mmol) in acetonitrile (4 mL) plus water (0.20 mL) mixture at 25 °C was added con H₂SO₄ impregnated on a silica gel (40 mg, 10 wt%) and mercury(II) acetate (40 mg, 0.12 mmol). The reaction mixture was stirred for 4 h and diluted with ethyl acetate (15 mL). The filtered organic layer was dried over Na₂SO₄ and concentrated in vacuo. The silica gel column chromatographic purification of the resulting residue using petroleum ether and ethyl acetate mixture (7:3) as an eluent afforded the pure product 6 as a thick oil (306 mg, 86% yield). \(^1\)H NMR (CDCl₃, 200 MHz) \(\delta\) 2.17 (s, 3H), 2.45–2.68 (m, 2H), 2.67 (dd, \(J = 18\) and 8 Hz, 1H), 2.89 (dd, \(J = 16\) and 4 Hz, 1H), 3.56–3.77 (m, 2H), 4.51 (s, 2H), 5.39 (ddd, \(J = 8, 4\) and 2 Hz, 1H), 5.90 (d, \(J = 2\) Hz, 1H), 7.23–7.43 (m, 5H). \(^1^C\) NMR (CDCl₃, 50 MHz) \(\delta\) 28.5, 30.3, 45.1, 67.0, 73.1, 79.8, 116.8, 127.6, 127.7, 128.3, 137.3, 169.9, 172.3, 203.9; ESIMS (\(m/z\)) 297 [M+Na]+; HRMS (ESI) calcd for C₁₆H₁₈O₄Na 297.1097, found 297.1100; IR (CHCl₃) \(v_{\text{max}}\) 1756, 1722, 1638 cm\(^{-1}\).

**4-(2-Hydroxyethyl)-5-(2-oxopropyl)furan-2(5H)-one (7).**

\[
\text{OH}
\]

To a stirred solution of compound 6 (280 mg, 1.02 mmol) in methanol (4 mL) under the balloon pressure hydrogen atmosphere was added activated Pd–C (40 mg, 10 wt%). The reaction mixture was stirred at 25 °C for 5 h, filtered to remove Pd–C and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (1:4) as an eluent provided the pure product 7 as a thick oil (156 mg, 83% yield). \(^1\)H NMR (CDCl₃, 200 MHz) \(\delta\) 1.60–1.95
(br s, 1H), 2.25 (s, 3H), 2.43–2.87 (m, 2H), 2.76 (dd, J = 18 and 8 Hz, 1H), 2.96 (dd, J = 18 and 6 Hz, 1H), 3.78–4.02 (m, 2H), 5.44 (ddd, J = 7, 5 and 2 Hz, 1H), 5.96 (d, J = 2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 30.8, 31.0, 45.1, 59.8, 80.1, 117.1, 170.3, 172.8, 204.6; ESIMS (m/z) 207 [M+Na]$^+$; HRMS (ESI) calcd for C$_9$H$_{12}$O$_4$Na 207.0628, found 207.0621; IR (CHCl$_3$) $\nu_{\text{max}}$ 3433, 1769, 1716 cm$^{-1}$.

(±)-6a-(2-Oxopropyl)tetrahydrofuro[2,3-b]furan-2(3H)-one (8).

To a stirred solution of compound 7 (120 mg, 0.66 mmol) in dry toluene (4 mL) under argon atmosphere was added anhydrous p-TsOH (22 mg, 0.14 mmol). The reaction mixture was refluxed for 4 h and concentrated in vacuo. The direct silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (7:3) as an eluent gave the pure product 8 as a thick oil (90 mg, 75% yield). $^1$H NMR (CDCl$_3$, 200 MHz) δ 1.77 (ddd, J = 12, 6 and 2 Hz, 1H), 2.05–2.35 (m, 1H), 2.19 (s, 3H), 2.43 (dd, J = 16 and 2 Hz, 1H), 2.97 (d, J = 18 Hz, 1H), 3.03–3.28 (m, 2H), 3.29 (d, J = 16 Hz, 1H), 3.85 (ddd, J = 12, 10 and 6 Hz, 1H), 4.05 (dt, J = 8 and 2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 31.0, 33.5, 36.7, 41.0, 49.2, 66.5, 115.3, 175.1, 204.5; ESIMS (m/z) 207 [M+Na]$^+$; HRMS (ESI) calcd for C$_9$H$_{12}$O$_4$Na 207.0628, found 207.0627; IR (CHCl$_3$) $\nu_{\text{max}}$ 1775, 1721 cm$^{-1}$.

4-(1,3-Bis(benzyloxy)propan-2-yl)-5-hydroxyfuran-2(5H)-one (17).

It was obtained from glyoxalic acid monohydrate (97 mg, 1.05 mmol), morpholinium hydrochloride (130 mg, 1.05 mmol) and aldehyde 16 (314 mg, 1.00 mmol) using the same procedure as described for compound 4, as a thick oil (226 mg, 64%). $^1$H NMR (CDCl$_3$, 200 MHz) δ 3.14 (quintet, J = 6 Hz, 1H), 3.60–3.80 (m, 4H), 4.49 (s, 2H), 4.51 (s, 2H), 4.96 (d, J = 8 Hz, 1H), 5.99 (s, 1H), 6.00 (d, J = 8 Hz, 1H), 7.20–7.45 (m, 10H); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 39.2, 69.0, 73.3, 99.1, 119.4, 127.6, 127.8, 128.4, 137.2, 167.6, 171.1; ESIMS (m/z) 377 [M+Na]$^+$; HRMS (ESI) calcd for C$_{21}$H$_{22}$O$_5$Na 377.1359, found 377.1358; IR (CHCl$_3$) $\nu_{\text{max}}$ 3394, 1760, 1648 cm$^{-1}$.

4-(1,3-Bis(benzyloxy)propan-2-yl)-5-(prop-2-yn-1-yl)furan-2(5H)-one (18).

It was obtained from compound 17 (190 mg, 0.54 mmol), propargyl bromide (83 µL, 80 wt% in toluene, 0.64 mmol) and zinc power (105 mg,
1.61 mmol) using the same procedure as described for compound 5, as a thick oil (165 mg, 82%). $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.96 (t, $J$ = 2 Hz, 1H), 2.75 (ddq, $J$ = 18, 4 and 2 Hz, 2H), 2.94 (quintet, $J$ = 6 Hz, 1H), 3.56 (t, $J$ = 8 Hz, 1H), 3.60–3.80 (m, 3H), 4.48 (s, 2H), 4.51 (s, 2H), 5.11 (dt, $J$ = 4 and 2 Hz, 1H), 5.97 (s, 1H), 7.18–7.50 (m, 10H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 22.4, 39.7, 68.6, 70.1, 72.1, 73.4, 76.9, 81.1, 117.9, 127.7, 128.0, 128.5, 137.5, 170.0, 172.4; ESIMS (m/z) 399 [M+Na]$^+$; HRMS (ESI) calcd for C$_{24}$H$_{24}$O$_4$Na 399.1567, found 399.1568; IR (CHCl$_3$) $\nu_{\text{max}}$ 2100, 1760, 1722, 1635 cm$^{-1}$.

4-(1,3-Bis(benzyloxy)propan-2-yl)-5-(2-oxopropyl)furan-2(5H)-one (19).

It was obtained from compound 18 (160 mg, 0.43 mmol), con H$_2$SO$_4$–Si (20 mg, 10 wt%) and mercury(II) acetate (14 mg, 0.04 mmol) using the same procedure as described for compound 6, as a thick oil (146 mg, 87%). $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 2.09 (s, 3H), 2.58 (dd, $J$ = 18 and 8 Hz, 1H), 2.85 (quintet, $J$ = 6 Hz, 1H), 2.91 (dd, $J$ = 18 and 4 Hz, 1H), 3.53 (dd, $J$ = 9 and 7 Hz, 1H), 3.60–3.77 (m, 3H), 4.47 (s, 2H), 4.49 (s, 2H), 5.45 (ddd, $J$ = 8, 4 and 2 Hz, 1H), 5.90 (s, 1H), 7.20–7.45 (m, 10H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 30.4, 39.8, 45.3, 69.3, 69.8, 73.4, 80.0, 116.9, 127.8, 127.9, 128.5, 137.3, 171.6, 172.4, 204.0; ESIMS (m/z) 395 [M+H]$^+$; HRMS (ESI) calcd for C$_{24}$H$_{26}$O$_5$Na 417.1672, found 417.1672; IR (CHCl$_3$) $\nu_{\text{max}}$ 3450, 1784, 1715 cm$^{-1}$.

4-(1,3-Dihydroxypropan-2-yl)-5-(2-oxopropyl)furan-2(5H)-one (20).

To a stirred solution of compound 19 (60 mg, 0.16 mmol) in dry dichloromethane (4 mL) at 0°C under argon atmosphere was added anhydrous aluminium chloride (80 mg, 0.62 mmol). The reaction mixture was allowed to warm gradually to 25°C and stirred for 6 h. Reaction was quenched with water (1 mL) and it was extracted with dichloromethane (10 mL × 3). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using ethyl acetate as an eluent furnished the pure product 20 as a thick oil (28 mg, 84% yield). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.00–2.25 (br s, 2H), 2.25 (s, 3H), 2.72 (quintet, $J$ = 5 Hz, 1H), 2.80 (dd, $J$ = 15 and 5 Hz, 1H), 3.05 (dd, $J$ = 15 and 5 Hz, 1H), 3.88 (dd, $J$ = 5 and 5 Hz, 2H), 3.96 (dd, $J$ = 5 and 5 Hz, 2H), 5.47 (ddd, $J$ = 8, 4 and 2 Hz, 1H), 6.02 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 31.2, 42.9, 44.9, 62.8, 63.5, 79.9, 117.7, 170.4, 172.1, 204.8; ESIMS (m/z) 237 [M+Na]$^+$; HRMS (ESI) calcd for C$_{10}$H$_{14}$O$_5$Na 237.0733, found 237.0733; IR (CHCl$_3$) $\nu_{\text{max}}$ 3300, 1738, 1722, 1667 cm$^{-1}$.
4-(1-(Benzyloxy)-3-hydroxypropan-2-yl)-5-(2-oxopropyl)furan-2(5H)-one (21).

To a stirred solution of compound 19 (100 mg, 0.25 mmol) in dry dichloromethane (5 mL) at 0 °C under argon atmosphere was added anhydrous aluminium chloride (51 mg, 0.38 mmol). The reaction mixture was allowed to warm gradually to 25 °C and stirred for 3 h. It was quenched with water (1 mL) and extracted with dichloromethane (15 mL × 3). The organic layer was dried over Na₂SO₄ and concentrated in vacuo to obtain mixture of diastereomers of (±)-21 as a thick oil in 1:1 ratio (63 mg, 81% yield). The silica gel flash column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (2:3) as an eluent yielded the mixture of two diastereomers of 21 in 9:1 and 1:4 ratios as thick oils.

Data for major isomer from 9:1 mixture: ¹H NMR (CDCl₃, 500 MHz) δ 2.19 (s, 3H), 2.72 (dd, J = 18 and 8 Hz, 1H), 2.79 (quintet, J = 5 Hz, 1H), 2.95 (dd, J = 15 and 5 Hz, 1H), 3.74 (dd, J = 5 and 2 Hz, 2H), 3.83 (quintet, J = 5 Hz, 2H), 4.54 (s, 2H), 5.48 (ddd, J = 10, 5 and 2 Hz, 1H), 5.94 (s, 1H), 7.25–7.40 (m, 5H); ¹³C NMR (CDCl₃, 125 MHz) δ 30.8, 41.5, 45.2, 63.2, 69.9, 73.7, 79.8, 117.4, 127.9, 128.1, 128.6, 137.2, 171.0, 172.4, 204.6; ESIMS (m/z) 327 [M+Na]⁺; HRMS (ESI) calcd for C₁₇H₂₀O₃Na 327.1203, found 327.1202; IR (CHCl₃) νmax 3600, 1733, 1632 cm⁻¹.

Data for major isomer from 1:4 mixture: ¹H NMR (CDCl₃, 500 MHz) δ 2.21 (s, 3H), 2.71 (dd, J = 18 and 8 Hz, 1H), 2.78 (quintet, J = 5 Hz, 1H), 3.00 (dd, J = 15 and 5 Hz, 1H), 3.61 (dd, J = 10 and 5 Hz, 1H), 3.69 (dd, J = 10 and 5 Hz, 1H), 3.91 (t, J = 10 Hz, 2H), 4.50 (s, 2H), 5.41 (ddd, J = 10, 5 and 2 Hz, 1H), 5.98 (s, 1H), 7.25–7.40 (m, 5H); ¹³C NMR (CDCl₃, 125 MHz) δ 30.9, 41.4, 44.9, 62.5, 70.3, 73.6, 80.1, 117.2, 127.8, 128.1, 128.6, 137.1, 171.0, 172.4, 204.5; ESIMS (m/z) 327 [M+Na]⁺; HRMS (ESI) calcd for C₁₇H₂₀O₃Na [M+Na]⁺ 327.1203, found 327.1202; IR (CHCl₃) νmax 3600, 1732, 1633 cm⁻¹.

(±)-4-((Benzyloxy)methyl)-6a-(2-oxopropyl)tetrahydrofuro[2,3-b]furan-2(3H)-one (22).

It was obtained from compound 21 (50 mg, 0.17 mmol) and anhydrous p-TsOH (6 mg, 0.03 mmol) using the same procedure as described for compound 8, as a thick oil (36 mg, 73%). ¹H NMR (CDCl₃, 200 MHz) δ 2.15 (s, 3H), 2.23–2.38 (m, 1H), 2.47 (dd, J = 18 and 2 Hz, 1H), 2.76 (d, J = 18 Hz, 1H), 2.89 (td, J = 10 and 2 Hz, 1H), 3.22 (d, J = 6 Hz, 1H), 3.24–3.42 (m, 3H), 3.89 (dd, J = 10 and 2 Hz, 1H), 3.97 (dd, J = 10 and 4 Hz, 1H), 4.46 (d, J = 12 Hz, 1H), 4.54 (d, J =
12 Hz, 1H), 7.25–7.40 (m, 5H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 30.9, 36.7, 44.2, 47.5, 49.5, 68.5, 70.7, 73.2, 115.2, 127.8, 127.9, 128.5, 137.7, 174.9, 204.4; ESIMS (m/z) 327 [M+Na]$^+$; HRMS (ESI) calcd for C$_{17}$H$_{20}$O$_5$Na 327.1203, found 327.1201; IR (CHCl$_3$) $\nu_{\text{max}}$ 1754, 1719, 1629 cm$^{-1}$.

(±)-4-(Hydroxymethyl)-6a-(2-oxopropyl)tetrahydrofuro[2,3-b]furan-2(3H)-one (23).

To a stirred solution of compound 22 (30 mg, 0.10 mmol) in methanol (2 mL) was added activated Pd–C (5 mg, 10 wt%) under the balloon pressure hydrogen atmosphere. The reaction mixture was stirred at 25 °C for 5 h, filtered to remove Pd–C and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (3:1) as an eluent gave the pure product (±)-23 as a thick oil (19 mg, 91% yield). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.76 (br s, 1H), 2.20 (s, 3H), 2.20–2.28 (m, 1H), 2.52 (dd, J = 16 and 4 Hz, 1H), 2.93–2.98 (m, 1H), 2.97 (d, J = 16 Hz, 1H), 3.29 (dd, J = 20 and 12 Hz, 1H), 3.32 (d, J = 16 Hz, 1H), 3.58 (d, J = 8 Hz, 2H), 3.95 (dd, J = 8 and 2 Hz, 1H), 4.01 (dd, J = 10 and 6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 31.0, 36.7, 44.0, 49.3, 49.5, 63.8, 68.4, 115.4, 174.8, 204.6; ESIMS (m/z) 237 [M+Na]$^+$; HRMS (ESI) calcd for C$_{10}$H$_{14}$O$_5$Na 237.0733, found 237.0734; IR (CHCl$_3$) $\nu_{\text{max}}$ 3435, 1762, 1715 cm$^{-1}$.

(±)-(5-Oxo-6a-(2-oxopropyl)hexahydrofuro[2,3-b]furan-3-yl)methyl Benzoate (Paeonilide, 1).

To a stirred solution of compound 23 (15 mg, 0.07 mmol) in dry dichloromethane (1 mL) at 0 °C under argon atmosphere was added pyridine (0.10 mL) and benzoyl chloride (10 µL, 0.08 mmol). The reaction mixture was stirred at 25 °C for 2 h and diluted with dichloromethane (10 mL). The organic layer was washed with saturated aqueous NaHCO$_3$, brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. The silica gel column chromatographic purification of the obtained residue using petroleum ether and ethyl acetate mixture (7:3) as an eluent furnished the pure product (±)-1 as white needles (22 mg, 99% yield). MP 165–166 °C (lit. 144–145 °C); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.20 (s, 3H), 2.52–2.56 (m, 1H), 2.55 (dd, J = 20 and 2 Hz, 1H), 2.93–3.00 (m, 1H), 2.96 (d, J = 20 Hz, 1H), 3.35 (dd, J = 20 and 10 Hz, 1H), 3.42 (d, J = 15 Hz, 1H), 4.00–4.07 (m, 2H), 4.19 (dd, J = 10 and 10 Hz, 1H), 4.30 (dd, J = 10 and 5 Hz, 1H), 7.47 (t, J = 10 Hz, 2H), 7.60 (t, J = 10 Hz, 1H), 8.02
(d, $J = 10$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 30.9, 36.6, 44.4, 46.7, 49.5, 64.9, 67.9, 115.0, 128.6, 129.5, 129.6, 133.4, 166.4, 174.5, 204.4; ESIMS (m/z) 341 [M+Na]$^+$; HRMS (ESI) calcd for C$_{17}$H$_{18}$O$_6$Na 341.0996, found 341.0995; IR (CHCl$_3$) $\nu_{\text{max}}$ 1775, 1711 cm$^{-1}$.

**5-Hydroxy-4-isopropylfuran-2(5H)-one (25).**

It was obtained from glyoxalic acid monohydrate (920 mg, 10 mmol), morpholinium hydrochloride (1.36 g, 11.00 mmol) and isobutyraldehyde (860 mg, 10.00 mmol) using the same procedure as described for compound 4, as a white solid (1.11 g, 78% yield).$^{11}$ Mp. 77–80 °C; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.20 (d, $J = 6$ Hz, 3H), 1.24 (d, $J = 8$ Hz, 3H), 2.77 (doublet of septet, $J = 8$ and 2 Hz, 1H), 5.37 (br s, 1H), 5.81 (s, 1H), 6.12 (s, 1H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 19.9, 20.9, 27.3, 98.8, 115.7, 172.5, 175.9; ESIMS: (m/z) 143 [M+H]$^+$; IR (CHCl$_3$) $\nu_{\text{max}}$ 3368, 1745, 1642 cm$^{-1}$.

**4-Isopropyl-5-(prop-2-ynyl)furan-2(5H)-one (26).**

It was obtained from compound 25 (710 mg, 5.00 mmol), propargyl bromide (0.84 mL, 80 wt% in toluene, 7.50 mmol) and zinc power (975 mg, 15.00 mmol) using the same procedure as described for compound 5, as a thick oil (710 mg, 87% yield).$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.18 (d, $J = 6$ Hz, 3H), 1.26 (d, $J = 8$ Hz, 3H), 2.02 (t, $J = 2$ Hz, 1H), 2.50–2.90 (m, 3H), 5.06 (t, $J = 6$ Hz, 1H), 5.84 (s, 1H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 20.3, 21.7, 22.5, 27.5, 72.0, 76.5, 79.7, 115.0, 172.5, 177.0; ESIMS: (m/z) 187 [M+Na]$^+$; HRMS (ESI) calcd for C$_{10}$H$_{13}$O$_2$ 165.0910, found 165.0910; IR (CHCl$_3$) $\nu_{\text{max}}$ 2121, 1752, 1635 cm$^{-1}$.

**4-Isopropyl-5-(2-oxopropyl)furan-2(5H)-one (Chenopanone, 13).**

It was obtained from compound 26 (500 mg, 5.00 mmol), con H$_2$SO$_4$–Si (100 mg, 10 wt%) and mercury(II) acetate (150 mg, 0.5 mmol) using the same procedure as described for compound 6, as a thick oil (538 mg, 97% yield).$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.17 (d, $J = 6$ Hz, 3H), 1.24 (d, $J = 8$ Hz, 3H), 2.25 (s, 3H), 2.49 (septet, $J = 8$ Hz, 1H), 2.68 (dd, $J = 16$ and 8 Hz, 1H), 2.84 (dd, $J = 16$ and 4 Hz, 1H), 5.43 (ddd, $J = 8$, 4 and 2 Hz, 1H), 5.80 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 20.2, 21.4, 27.3, 30.6, 45.2, 78.6, 114.1, 172.4, 178.3, 203.8; ESIMS: (m/z) 205 [M+Na]$^+$; IR (CHCl$_3$) $\nu_{\text{max}}$ 1756, 1728, 1634 cm$^{-1}$. 

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Comparison of $^1$H and $^{13}$C NMR Data between Natural and Synthetic Paeonilide in Tabular Form

![Paeonilide (1)](image)

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$^#$The corrected proton assignments has been included (see references 15a and 15c).
2B.6 References


