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

Prashant S. Deore and Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune 411 008, India

np.argade@ncl.res.in

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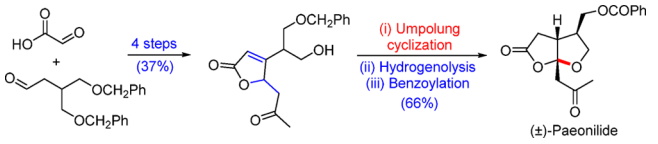
ABSTRACT



Remarkable reactivity reversal stratagem in 3,4-disubstituted butenolides under acidic conditions is described. Design of a 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. Overall, the present 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.

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.[1] 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).[2,3] 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.[4] During the course of our studies on intramolecular oxa-Michael addition reaction of suitably 3,4-disubstituted butenolide, we serendipitously witnessed an unusual redox neutral process involving 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,[5] thus our present observation is orthogonal to previous reports. In this context, we herein report an

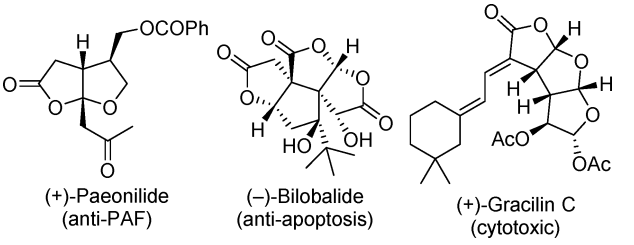


Figure 1. Furofuran-based bioactive natural products.

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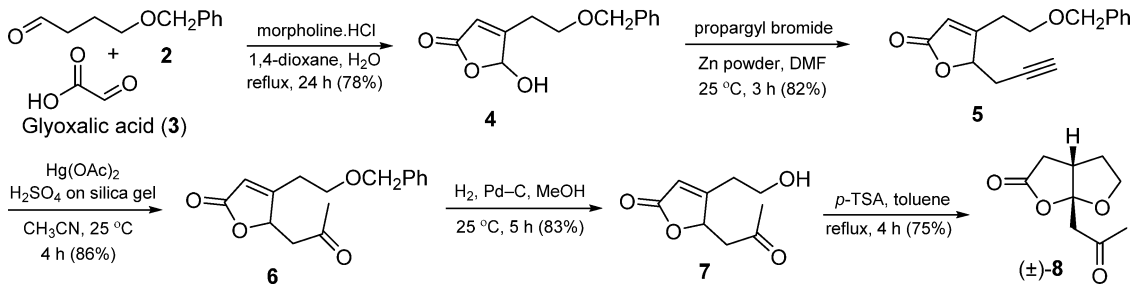
Scheme 1. Diastereoselective Synthesis of Furofuran Framework of Paeonilide via Reactivity Reversal



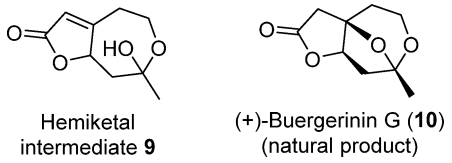
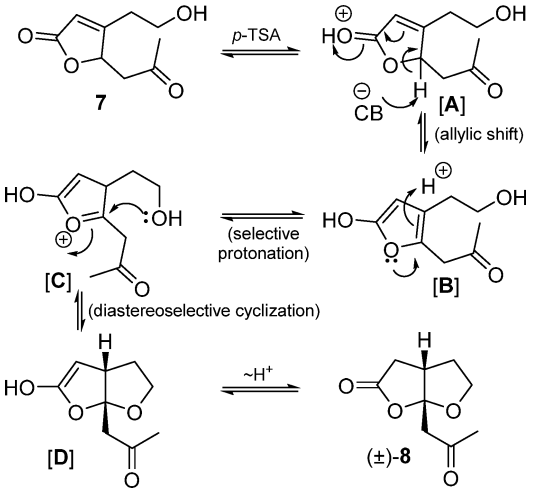


Figure 2. Plausible product via two consecutive intramolecular cyclizations of butenolide **7**.

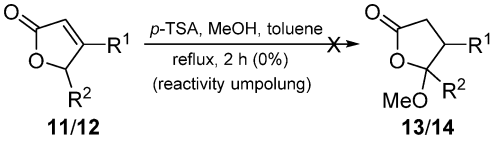
interesting instance of reactivity umpolung and its application for the total synthesis of (±)-paeonilide (**1**) (Schemes 1−5).

Initially, we selected the bioactive natural product buergerinin from *Scrophularia buergeriana*[6] as a target compound and started the synthesis of requisite advanced butenolide intermediate (Scheme 1). Aldol condensation of *O*-benzyl-protected aldehyde **2**[7] 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.[8] Barbier reaction[9] 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 H_2/Pd−C yielded the essential precursor 3,4-disubstituted butenolide **7** in

Scheme 2. Plausible Mechanism for the Reactivity Umpolung



Scheme 3. Attempted Intermolecular Nucleophilic Oxygen Insertions



11/13: $R^1 = R^2 = Me$; **12/14**: $R^1 = i\text{-Pr}$, $R^2 = CH_2COCH_3$

83% yield. The protection-free multifunctional compound **7** bearing free ketone and alcohol units at appropriate positions can theoretically form an intramolecular cyclization product (±)-buergerinin G (**10**) under acidic conditions via the generation of hemiketal intermediate **9** followed by a concomitant diastereoselective oxa-Michael addition route (Figure 2). 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.

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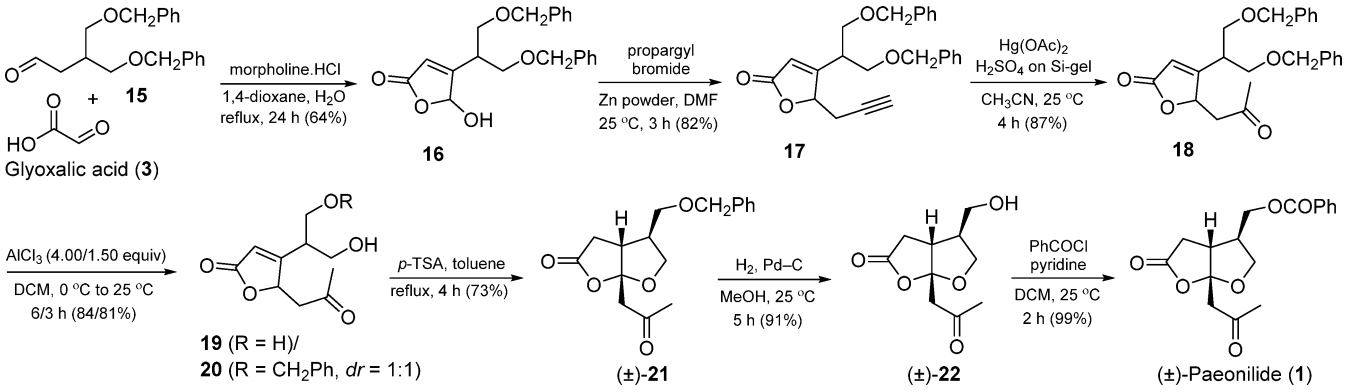
Scheme 4. Concise Diastereoselective Total Synthesis of (±)-Paeonilide via Reactivity Umpolung



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 2. The butenolide **7** on protonation of lactone carbonyl followed by a conjugate base induced allylic prototropic shift results in an unusual olefin isomerization[10] 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[11] at the γ-position of 3,4-disubstituted butenolide **7**. As shown in Scheme 3, the intermolecular reactions of 3,4-disubstituted butenolide **11**/**12** with methanol in the presence of *p*-TSA in refluxing toluene were unsuccessful to provide the corresponding desired product **13**/**14**. In both 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** proceeds smoothly in a forward direction due to overall negative Gibbs free energy.

In the next part of our study, we planned to authenticate the feasibility of reactivity umpolung conception to design a diastereoselctive total synthesis of (±)-paeonilide (**1**). The (+)-paeonilide with a novel monoterpenoid skeleton has been isolated by Liu and co-workers from the roots of *Paeonia delavayi*.[2a] It selectively inhibited platelet aggregation induced by the platelet activating factor (PAF) with an IC_{50} value of 8 μg/mL, importantly, without inhibitory effect on adenoside diphosphate (ADP) or arachidonic acid (AA)-induced platelet aggregation.[2a] In the total synthesis of paeonilide, generation of three contiguous chiral centers in a enantioselective or diastreoselective fashion is the challenging task. To date, two racemic[12a,b] and two stereoselective[12c,d] well-organized total synthesis of paeonilide have been reported in the literature by employing new carbon−carbon/oxygen bond forming strategies.[12] Specifically, Du's group reported an efficiant strategy for the synthesis of racemic paeonilide in five steps with 59% overall yield.[12b]

As described in Scheme 4, our synthesis of paeonilide began with morpholine hydrochloride promoted aldol condensation of appropriately double *O*-benzyl-protected aldehyde **15**[13] with glyoxalic acid (**3**). The above stated stereoselective condensation directly furnished the expected maleic anhydride derivative **16** in 64% yield following a dehydrative cyclization pathway. Barbier reaction of propargyl bromide with a masked aldehyde **16** in presence of activated zinc powder provided the corresponding acetylenic derivative **17** in 82% yield, which on acidic hydrolysis transformed into the desired ketone **18** in 87% yield. We systematically studied the selective monobenzyl and dibenzyl deprotections in compound **18** under various reaction conditions. The reactions of compound **18** with H_2/Pd−C in MeOH, HCOOH/Pd−C in MeOH, LiCl in DMF, BCl_3 in DCM, and BBr_3 in DCM resulted in isolation of staring material and/or decomposition of reaction mixture. Fortunately, both benzyl groups in compound **18** were smoothly deprotected in the presence

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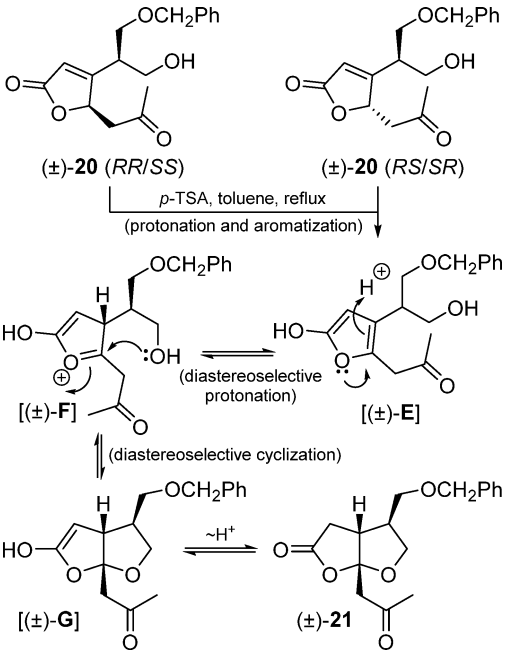
of excess of aluminum chloride[14] in DCM plus *m*-xylene mixture at room temperature and delivered the essential 3,4-disubstituted butenolide **19** in 84% yield. However, the reaction of compound **19** with *p*-TSA in refluxing benzene/toluene furnished a complex mixture of products. We reasoned that the cause for such decomposition could be a presence of several oxygen-functions in the starting material **19**, wherein the ratio of number of carbon atoms to oxygen atoms is 2:1, imparting the instability under reaction conditions. The controlled reaction of compound **18** with a use of precise amount of $AlCl_3$ (1.50 equiv) in DCM plus *m*-xylene mixture at room temperature was selective and formed the expected monodeprotected pair of diastereomers **20** in 81% yield with nearly 1:1 ratio (by ^{1}H NMR). An attempted flash silica gel column chromatographic separation of the diastereomeric **20** resulted in their ~9:1 and ~1:4 mixtures (by ^{1}H NMR), which were used as such for the cyclizations. Gratifyingly, the reactions of 1:1 mixture of diasteromers of compound **20** and their partially purified forms with *p*-TSA in refluxing toluene were highly chemo- and diastereoselective resulting in the same desired product (±)-**21** in 73% yield via structural rearrangement following an intramolecular cyclization pathway with reactivity umpolung.

The plausible mechanism for involved diastereoselectivity and reactivity umpolung in the formation of preferred product (±)-**21** is represented in Scheme 5. 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 **20** 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 **21** as a racemic mixture. Finally, *O*-benzyl group in compound (±)-**21** was deprotected under H_2/Pd−C conditions to form the known ultimate stage intermediate alcohol (±)-**22** in 91% yield. Primary alcohol **22** on treatment with benzoyl chloride/pyridine in DCM furnished the desired natural product (±)-paeonilide (**1**) in 99% yield. The analytical and spectral data obtained for paeonilide (**1**) was in complete agreement with the reported data,[2,12] and starting from glyoxalic acid it was obtained in seven steps with 24% overall yield.

In summary, we have demonstrated a novel reactivity umpolung in 3,4-disubstituted butenolides and accomplished the diastereoselctive total synthesis of paeonilide. The observed chemo- and diastereoselctivity 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 a 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.

Scheme 5. Plausible Mechanism for the Diastereoselective Ring Closure



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Supporting Information Available. Experimental procedures, tabulated analytical and spectral data, and ^{1}H NMR, ^{13}C NMR, and DEPT spectra of compounds **1**, **4**–**8**, and **16**–**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.