4. High-yielding Total Synthesis of Butenolide Natural Products and their Analogues through an Organocatalytic Reductive Coupling Reaction

4.1 Introduction

To develop a simple protocol by utilizing readily available starting materials and synthesizing a library of natural products, drugs and their analogues are challenging task for synthetic chemistry community.\(^3\)\(^7\) The common drawbacks in the total synthesis of natural products and drugs are associated with multiple steps involving each step column purification, leading to increase in solvent consumption, harmful wastes and decrease in yield. Also for total synthesis of biologically important molecules to be industrially viable, use of toxic metal catalysts has to be avoided. Keeping these facts in mind, more attention has been devoted towards organocatalytic double domino, triple domino and quadruple domino sequential multi-step one-pot reactions. These sequential one-pot reactions can address the above cited problems by reducing the number of steps and thus minimizing the problems associated with it. That is why organocatalysis has been considered the green alternative route to the classical synthetic methods.\(^3\)\(^8\) Even though there exist a considerable number of organo-catalytic asymmetric methods, only a few among them made their way into the total synthesis of natural products and their analogs.\(^3\)\(^9\) Among the known organocatalytic reactions, Michael addition,\(^4\)\(^0\) aldol,\(^4\)\(^1\) Diels-Alder\(^4\)\(^2\) and Friedel-Craft\(^4\)\(^3\) reactions are the ones which have been repeatedly used in asymmetric total synthesis of natural products, drugs and drug intermediates.

Recently our laboratory discovered the organocatalytic reductive coupling (OrgRC) reaction is one of the recently developed organocatalytic selective C-alkylation protocol and it has been utilized by many other synthetic chemistry groups in total synthesis of natural products/drugs.\(^3\)\(^3\)-\(^3\)\(^5\) In our quest to develop organocatalytic methods and apply those methods in total synthesis, we choose a small library of natural products containing butenolide (3-
alkyl-5-methyl-2[5H] furanone) core as our synthetic target to synthesize through organocatalytic sequential one-pot manner.

Butenolides have attracted both isolation and synthetic chemists due to their broad range of bioactivities.\textsuperscript{44} For example, butenolide H is a component in mushroom flavor,\textsuperscript{44c} I show fungicidal activity,\textsuperscript{44d} J, K, M, N and O are\textit{ Streptomyces griseus} metabolites,\textsuperscript{44e} Ancepsenolide X has been known for its cytotoxicity and antimicrobial activity.\textsuperscript{44b} Bullatacin Q is an effective cytotoxic acetogenin. (−)-Blastmycinolactol R, (+)-blastmycinone S, (−)-NFX-2 T and (+)-antimycinone U are polyketide metabolites and show antifungal and antitumor properties, Z and Z’ are mosquito larvicides\textsuperscript{44h} (Figure 14).

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**Figure 14.** Examples of important butenolide natural products and their analogues.

### 4.2 Retrosynthetic Analysis

As outlined in Scheme 4, the alkylation at the 3-position of known chiral tetronic acid 72 can generate by using our organocatalytic reductive coupling (OrgRC) reaction, where an organic CH-acid 72 reacts with an aldehyde 1 to form olefin, which then reacts with an organic
hydrogen donor such as Hantzsch ester 11a in presence of proline 5a as a catalyst (Scheme 4). The 3-alkylated chiral tetronic acid 71 is a potent precursor for synthesis of the butenolide natural products, followed by easily deoxygenating procedures.45£g

Scheme 4. Retrosynthetic analysis.

4.3 Results and discussion

α,β-unsaturated lactones are usually found in many natural products; in this context a family of δ-butenolide natural products have a broad spectrum of biological activities. Many groups already synthesized individual butenolide natural products using different methodologies in racemic and optically active form.45 Herein, we synthesized six of natural products in butenolide family by using OrgRC reaction as the key step in the high yielding process through C-C bond formation.

Initially, we started the synthesis of monobutenolide natural products J, K and L from the chiral tetronic acid 72 and easily accessible alkyl aldehydes 1c, 1e and 1k. The OrgRC reaction of tetronic acid 72 and aldehyde 1 in presence of Hantzsch ester 11a and proline 5a-catalyst afforded alkylated compounds 71 in excellent yields. Then, the enol hydroxyl group was activated by converting to the corresponding triflate followed by palladium catalyzed reduction for the preparation of monobutenolides 70 in excellent yields compared to the previous reports.45

To reduce the number of purification steps, we tried to carry out OrgRC followed by O-triflate reaction in one pot manner. Hence we preferred anhydrous CH₂Cl₂ as the solvent for OrgRC reaction which would also serve the purpose of the next step. The reaction of (S)-4-hydroxy-5-methylfuran-2(5H)-one 72a with butyraldehyde 1c and Hantzsch ester 11a under 20 mol% of proline 5a in anhydrous CH₂Cl₂ at 25 °C for 2-4 h furnished the (S)-3-alkyl-4-hydroxy-5-methylfuran-2(5H)-one 71ac in very good conversion. After completion of OrgRC reaction, two equiv. of N,N-diisopropylethylamine (DIPEA) was added to the reaction mixture, followed by 1.5 equiv. of Tf₂O addition at -78 °C. After quenching the
reaction with saturated NH$_4$Cl solution and work-up, the crude product was used directly for the deoxygenation reaction with Pd(OAc)$_2$, 1,3-bis(diphenylphosphino)propane (DPPP) and polymethylhydrosiloxane (PMHS) in DMF at 60 °C for 24 h to furnish desired monobutenolide 70ac in 40% yield (overall three steps) (Scheme 5). The same reaction sequence was executed with two more different aldehydes 1e and 1k, the monobutenolides 70ae and 70ak were obtained in 41-52% overall yields. To our delight the reagents and by-products of OrgRC reaction did not affect the next reaction or the yield, but the final products 70ac and 70ae required careful column-chromatography to separate from Hantzsch ester pyridine.

**Scheme 5.** Synthesis of monobutenolides through sequential OrgRC/deoxygenation reactions.

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Reagents and conditions: (a) I (1 equiv.), Hantzsch ester 11a (1 equiv.) relative to the 72a, Proline 5a (20 mol%), DCM, rt, 2 to 4 h; (b) DIPEA (2 equiv.), Tf$_2$O (1.5 equiv.), DCM, −78 °C, 1 h, aq. workup; (c) Pd(OAc)$_2$ (10 mol%), DPPP (10 mol%), PMHS (2 equiv.), DMF, 60 °C, 8 to 24 h.

**Monobutenolides** 70ac, 70ae and 70ak are itself having their own biological activity and also used as intermediates in the expeditious synthesis of antifungal and antitumor polyketide metabolites. (S)-3-butyl-4-hydroxy-5-methylfuran-2(5H)-one 70ac is a potent precursor for synthesizing the (−)-blastmycinolactol R and (+)-blastmycinone S following the reported procedures.$^{45d}$ Following the same procedure (−)-NFX-2 T and (+)-antimycinone U can be obtained from butenolide 70ae as shown in literature procedure. In a similar manner, natural products V and W were synthesized by using 70ak as starting material. Overall, our method represents high-yielding formal total synthesis of these natural products R-W via OrgRC reaction as the key step.
Figure-15. $^1$H and $^{13}$C NMR spectra of the product (+)-70ac.
High-yielding Total Synthesis of Butenolide Natural Products via OrgRC reaction

Figure-16. $^1$H and $^{13}$C NMR spectra of the product (+)-70ae.
Figure-17. $^1$H and $^{13}$C NMR spectra of the product (+)-70ak.
Our next target was to synthesize (+)-ancepsenolide X (isolated from gorgonian Pterogorgia anceps), an important bis-butenoide annonaceae acetogenin. The required 1, 12-dodecanal 11 was obtained from 1, 12-dodecanol by PCC oxidation in quantitative yield. This was subjected to OrgRC reaction with chiral tetronic acid 72a, Hantzsch ester 11a and catalyst proline 5a. The reaction of 11 with 2 equivalents of tetronic acid 72a, 2 equivalents of Hantzsch ester 11a in anhydrous DCM under the proline 5a (20 mol%) catalysis furnished the bis-alkylated product 71al in >99% conversion. Interestingly compound 71al was highly polar and insoluble in the reaction solvent DCM. After completion of the reaction, the solvent was evaporated and the crude solid material was dried and used for the next step as such. Following similar deoxygenation reaction sequence as above, (+)-Ancepsenolide 70al was obtained in a satisfactory yield of 55% in overall three steps (Scheme 6).

Scheme 6. Total synthesis of (+)-Ancepsenolide.

Reagents and conditions: (a) 72a (2 equiv.), Hantzsch ester 11a (2 equiv.) relative to the 11, Proline 5a (20 mol%), DCM, rt, 6 h; (b) DIPEA (2 equiv.), Tf2O (1.5 equiv.), DCM, −78 °C, 1 h, aq. workup; (c) Pd(OAc)2 (10 mol%), DPPP (10 mol%), PMHS (2 equiv.), DMF, 60 °C, 8 to 24 h, 55% overall yield in three steps.

Further, we also accomplished the synthesis of the (+)-homoancepsenolide Y following the OrgRC/O-triflate and deoxygenation reactions in sequential manner, but unfortunately desired bis-butenoide 70am was isolated in poor yield. Hence we followed Pashkovskii’s45f approach to deoxygenated product, by converting 71am into the corresponding enamine derivative followed by the cleavage of amine moiety to get required (+)-Homoancepsenolide 70am in 39% with satisfactory overall yield (Scheme 7).
Figure-18. $^1$H and $^{13}$C NMR spectra of the product (+)-70al [(+)-Ancepsenolide].
Figure-19. $^1$H and $^{13}$C NMR spectra of the product (+)-70am [(+)-Homoancepsenolide].
Scheme 7. Total synthesis of (+)-Homoancepsenolide.

Reagents and conditions: (a) 72a (2 equiv.), Hantzsch ester 11a (2 equiv.) relative to the 1m, Proline 5a (20 mol%), DCM, rt, 6 h, 76% yield; (b) Pyrrolidine (1.5 equiv.), p-TSA (20 mol%), Toluene, reflux, 15 h, 67% yield; (c) i. NaBH₃CN (5 equiv.), MeOH, 2N HCl, rt, 15 h, aq. Work-up, ii. SiO₂ (2 equiv.), Toluene, reflux, 7 h, 76% yield in 2 steps.

The above results encouraged us to apply OrgRC reaction for the synthesis of Butenolide Z, an important natural product showing significant mosquito larvicidal property ($LC_{50} = 0.41$ ppm), along with its partially reduced counterpart $Z'$ ($LC_{50} 0.47$ ppm). The required aldehyde 1n was prepared from 1, 10-decanediol in five simple steps. Tetronic acid 72a and aldehyde 1n were subjected to an OrgRC reaction condition under the proline catalysis in DCM, and furnished the expected alkylated product 71an in 90% yield. In our efforts to get the required deoxygenated product 70an, we followed the Pashkovskii’s approach, the desired OrgRC product 71an was converted into the corresponding enamine derivative 73an followed by reducing the conjugated double bond and the elimination of amine moiety to get required butenolide 70an in 29% overall yield (Scheme 8). Another important mosquito larvicide natural product 74an is the partially reduced counterpart of 70an and can be obtained by simple functional group transformation.

Scheme 8. Total Synthesis of Mosquito Larvicidal Butenolides.
Reagents and conditions: (a) 72a (1 equiv.), Hantzsch ester 11a (2 equiv.) relative to the In, Proline 5a (20 mol%), DCM, 12 h, rt, 90% yield; (b) Pyrrolidine (1.5 equiv.), p-TSA (20 mol%), Toluene, reflux, 16 h, 85% yield; (c) i. NaBH$_3$CN (5 eq), MeOH, 2N HCl, 15 h, rt, aq. Work-up, ii. SiO$_2$ (2 equiv.), Toluene, reflux, 7 h, 38% yield in 2 steps.

4.4 Conclusions
In conclusion, we have developed a common methodology for the high-yielding total synthesis of important butenolide natural products, from readily available simple substrates through the organocatalytic reductive coupling reaction as the key step. This high yielding protocol is an ideal method to synthesize the entire family of butenolide natural products.
Figure-20. $^1$H and $^{13}$C NMR spectra of the product (+)-70an Mosquito Larvicidal Butenolide.
ANNEXURE-I: Isolation and Yield Comparative Tables of Butenolide Natural Products.

Isolation of C-4 Butenolide:

Butenolide, (S)-3-butyl-5-methyl-2[5H]furanone is metabolite from *streptomyces griseus*.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Starting material</th>
<th>Number of steps</th>
<th>Overall yield</th>
<th>$\alpha^D_{25}$</th>
</tr>
</thead>
</table>
\begin{array}{c}
\text{BOMO} \\
\text{CO}_2f-Bu \\
\text{OH}
\end{array}
\] | 2 steps | Isolated yield unknown | +11.7 (c 0.16, CHCl$_3$) |
| Nishide et al. Tetrahedron 1994 | \[
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{NH}_2
\end{array}
\] | 4 steps | 53% | +79.2 (c 1.18, CHCl$_3$) |
| Tsunoda et al. Tetrahedron Lett. 2000 | [Diagram of Tsunoda et al. reaction] | 7 steps | 11% | Racemic |
| Yan-Tao He et al. Tetrahedron 2002 | \[
\begin{array}{c}
\text{O} \\
\text{Et}
\end{array}
\] | 3 steps | 69% | +44.3 (c 1.24, CHCl$_3$) with 82% ee |
| Amonkar et al. Synthesis 2005 | \[
\begin{array}{c}
\text{Ph}_3\text{P} \\
\text{CO}_2\text{Et}
\end{array}
\] | 3 steps | 40% | Racemic |
| Ferrarini et al. Tetrahedron Lett. 2010 | \[
\begin{array}{c}
\text{C}_9\text{H}_{13} \\
\text{OH}
\end{array}
\] | 3 steps | 51% 94% ee | – |
| Present OrgRC method | \[
\begin{array}{c}
\text{OH} \\
\text{Me}
\end{array}
\] | 3 steps | 40% | +36.1 (c 0.28, CHCl$_3$) |

Isolation of C-6 Butenolide:

Butenolide, (S)-3-hexyl-5-methylfuran-2(5H)-one is metabolite from *streptomyces griseus*.
Isolation of C-16 Butenolide: 44i

C-16 butenolide was first isolated from gorgonian *pterogorgia* spp. in 2006 by Lorenzo *et al.* and its enantiomer was isolated from gorgonian *pterogorgia aniceps* in 1999 by Guo *et al.* Prior to its isolation C-16 butenolide was reported by Ortuno *et al.* who isolated it as an intermediate while attempting to synthesize 3,4,5-trisubstituted furanones.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Starting material</th>
<th>Number of steps</th>
<th>Overall yield</th>
<th>$\alpha_{25}^D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amonkar <em>et al.</em> Synthesis 2005</td>
<td><img src="image1.png" alt="Butenolide Structure" /></td>
<td>3 steps</td>
<td>49.6%</td>
<td>Racemic</td>
</tr>
<tr>
<td>Ferrarini <em>et al.</em> Tetrahedron Lett. 2010</td>
<td><img src="image2.png" alt="Butenolide Structure" /></td>
<td>3 steps</td>
<td>51.8% 96% ee</td>
<td>–</td>
</tr>
<tr>
<td>Present OrgRC method</td>
<td><img src="image3.png" alt="Butenolide Structure" /></td>
<td>3 steps</td>
<td>39.7%</td>
<td>+ 24.9 (c 0.28, CHCl₃)</td>
</tr>
</tbody>
</table>

Isolation of Ancepsenolide: 44b

(+)-Ancepsenolide was isolated from gorgonian *pterogorgia aniceps*, a marine organism in 1966. Later in 1971, Schimtz *et al.* isolated it from another gorgonion *pterogorgia*...
guadalupensis and in 1994 Rodriguez et al. reported its isolation from pterogorgia citrina.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Starting material</th>
<th>Number of steps</th>
<th>Overall yield</th>
<th>$\alpha_{D}^{25}$</th>
</tr>
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<tbody>
<tr>
<td>Podraza, et al. J. Nat. Pro., 1985</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>4 steps</td>
<td>19%</td>
<td>Racemic</td>
</tr>
<tr>
<td>Larson, et al. J. Org. Chem., 1985</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>3 steps</td>
<td>77%</td>
<td>Racemic</td>
</tr>
<tr>
<td>Trost and Muller J. Am. Chem. Soc., 1994 J. Am. Chem. Soc., 1995</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>7 steps</td>
<td>31%</td>
<td>+39.6 (c 0.4, CHCl$_3$)</td>
</tr>
<tr>
<td>Takai and Iriye Bio. Bio. Bio., 2001</td>
<td><img src="image4" alt="Chemical structure" /></td>
<td>3 steps</td>
<td>10%</td>
<td>+20.0 (c 0.1, CHCl$_3$)</td>
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<tr>
<td>Ghobril et al. Eur. J. Org. Chem., 2011</td>
<td><img src="image5" alt="Chemical structure" /></td>
<td>4 steps</td>
<td>12%</td>
<td>+45.53 (c 0.43, CHCl$_3$)</td>
</tr>
<tr>
<td>Present OrgRC method</td>
<td></td>
<td>3 steps</td>
<td>55%</td>
<td>+30.5 (c 0.12, CHCl$_3$)</td>
</tr>
</tbody>
</table>

**Isolation of Larvicidal Butenolides:**

Butenolides $Z$ was isolated by Ratnayake et al. in 2001 from three species of Hortonia genus and known to exhibit mosquito larvicidal activity.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Starting material</th>
<th>Number of steps</th>
<th>Overall yield</th>
<th>$\alpha_{D}^{25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al. Chinese J. Chem, 2002</td>
<td><img src="image6" alt="Chemical structure" /></td>
<td>10 steps</td>
<td>7.6%</td>
<td>+ 30.6 (c 0.5, CHCl$_3$)</td>
</tr>
<tr>
<td>Yan-Tao He et al. Tetrahedron 2002</td>
<td><img src="image7" alt="Chemical structure" /></td>
<td>3 steps</td>
<td>46.4%</td>
<td>+ 30.3 (c 0.4, CHCl$_3$)</td>
</tr>
<tr>
<td>Present OrgRC method</td>
<td></td>
<td>4 steps</td>
<td>29%</td>
<td>+30.6 (c = 0.1, CHCl$_3$)</td>
</tr>
</tbody>
</table>