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Donor–Acceptor Substituted Cyclopropane to Butanolide and Butenolide Natural Products: Enantiospecific First Total Synthesis of (+)-Hydroxyancepsenolide

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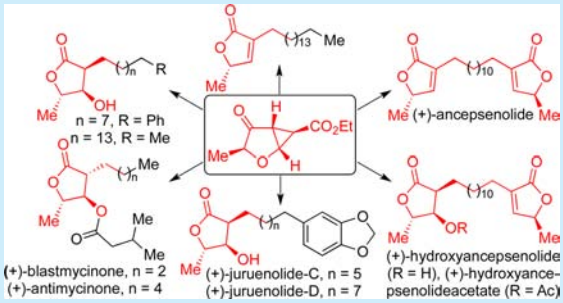
Supporting Information

ABSTRACT: An oxygen substituted donor–acceptor cyclopropane (DAC) is used as a common intermediate in the enantiospecific collective total synthesis of butanolide- and butenolide-based natural products like (+)-juruenolide C and D, (+)-blastmycinone, (+)-antimycinone, and (+)-ancepsenolide. Enantiospecific first total syntheses of (+)-hydroxyancepsenolide and its acetate are achieved confirming their absolute stereochemistry.



A substituted γ-butyrolactone or butanolide moiety bearing three contiguous stereocenters is found in many natural products (Figure 1).[1] Its unsaturated counterpart, namely, butenolide, is also ubiquitous in nature with *Annonaceous acetogenins* being the most celebrated family of natural products bearing this moiety. (+)-Blastmycinone (**1a**) and (+)-antimycinone (**1b**) isolated from *Streptomyces* sp. are the hydrolysis products of antimycin A_3 and A_1 and display antifungal and antitumor activities.[2] The γ-lactone polyketides are widely distributed in *Iryanthera* sp. and *Virola surinamensis* with lactone **2a** being isolated from the former, whereas juruenolides C and D (**2b** and **2c**) were found in the latter.[3] The marine natural product butanolide **2d**, its dehydration product butenolide **3**, (+)-ancepsenolide (**4**), and (+)-hydroxyancepsenolide (**5**) of the ancepsenolide family were isolated from the Caribbean gorgonian *Pterogorgia anceps* and are involved in the defensive mechanism of the species. While ancepsenolides (**4** and **5a**) were also isolated from *Pterogorgia citrina* as well as from *Pterogorgia guadalupensis*, (+)-hydroxyancepsenolide acetate (**5b**) was isolated only from former.[4] (+)-Ancepsenolide (**4**) represents one of the first butenolide acetogenins, plant metabolites that have shown interesting antitumoral, antimalarial, immunosuppressive, as well as pesticidal activities. Varied biological activity of butanolide and butenolide natural products coupled with structural diversity has attracted significant attention from synthetic chemists, and many of these natural products have succumbed to their total synthesis.[5−7]

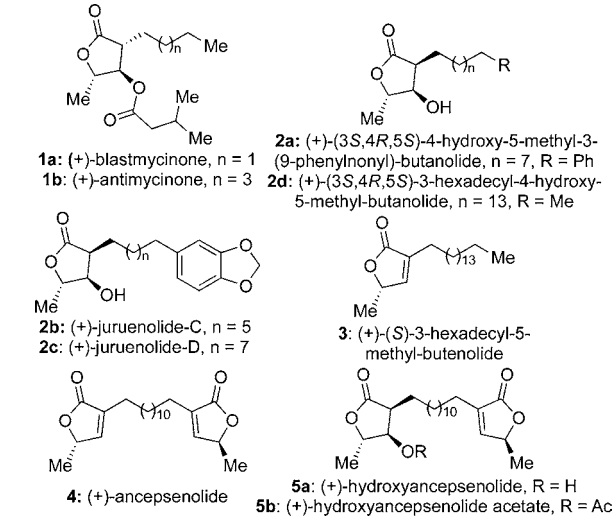


Figure 1. Butanolide- and butenolide-based natural products.

Despite significant progress in this area, a general approach for their collective total synthesis is still uncommon. Further, there is no report on the total synthesis of lactones **2a**, **2d**, (+)-juruenolide D (**2c**), or (+)-hydroxyancepsenolide (**5a**). While semisynthesis of (+)-hydroxyancepsenolide acetate (**5b**) has been described, its total synthesis is still not documented.[4] In continuation of our interest in donor–acceptor substituted cyclopropanes (DAC),[8] herein we disclose an approach for the collective total synthesis of butanolide and butenolide natural products **1**–**5** starting from a common precursor **6**.[9]

Over the years, DACs have come to the fore as versatile synthons in organic chemistry.[10] We envision that the butanolide and butenolide natural products could all be assembled starting

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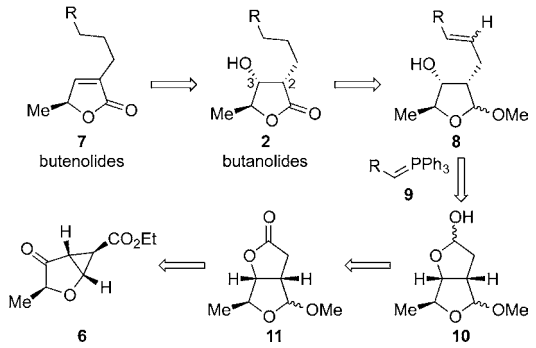
from DAC **6**. Our retrosynthetic plan is delineated in Scheme 1. Butenolide **7** could be readily prepared from the corresponding

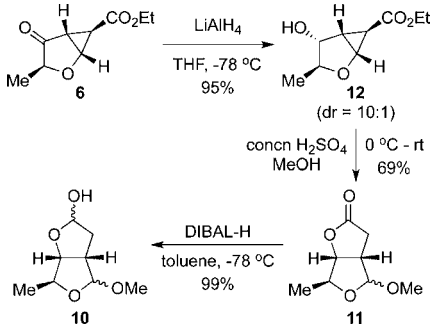
Scheme 1. Retrosynthetic Analysis for Butanolide and Butenolide Natural Products



butanolide **2** by dehydration. Butanolide **2** bearing three contiguous stereocenters could be obtained by hydrogenation followed by oxidation of the acetal **8**, which in turn could be readily assembled by the Wittig reaction of an appropriate ylide **9** with lactol **10**. The lactol **10** can be derived from the DAC **6** through the intermediate **11** bearing differentially oxidized lactone moieties. We have already described stereoselective synthesis of DAC **6** starting from (*S*)-ethyl lactate.[8a] It was also noted that butanolide natural products like (+)-blastmycinone (**1a**) and (+)-antimycinone (**1b**) can be prepared from the appropriate butanolide **2** by epimerization of the C-2 stereocenter.

The synthesis began with the conversion of the DAC **6** into the lactol **10**, which is a common intermediate for the synthesis of all butanolide and butenolide natural products **1**−**5**. Thus, chemo- and stereoselective reduction of the ketone moiety in DAC **6** with $LiAlH_4$ furnished the alcohol **12** (Scheme 2).[8a] Treatment

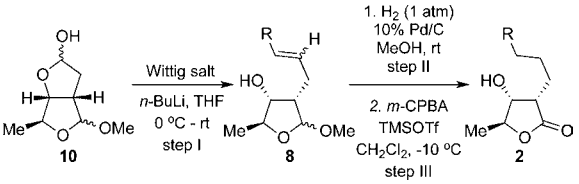
Scheme 2. Synthesis of the Common Intermediate Lactol 10

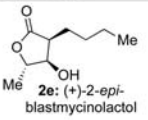
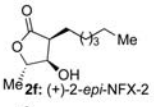
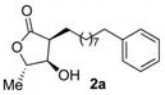
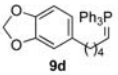
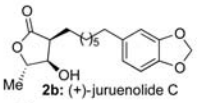
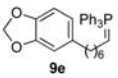
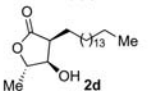


of the alcohol **12** with a catalytic amount of concd H_2SO_4 in MeOH led to the lactone **11** via a tandem regioselective cyclopropane ring opening−trapping of the oxonium ion with a MeOH−intramolecular lactonization sequence. Reduction of the lactone **11** with DIBAL-H gave the requisite advanced intermediate lactol **10**.

Attention was next turned toward using this lactol **10** in the divergent synthesis of butanolide natural products **1** and **2**. A three-step protocol of Wittig olefination, hydrogenation, and chemoselective oxidation was used to achieve this (Table 1). When a simple Wittig reaction of the ylide **9a** derived from ethyltriphenylphosphonium bromide in the presence of *n*-BuLi with the lactol **10** was performed, the corresponding olefin **8a**

Table 1. Synthesis of Butanolide Natural Products and Epimers



entry	ylide[a]	yield %	butanolide
1.	 9a	step I: 76 step II: 95 step III: 75	 **2e:** (+)-2-*epi*-blastmycinolactol
2.	 9b	step I: 72 step II: 97 step III: 83	 **2f:** (+)-2-*epi*-NFX-2
3.	 9c	step I: 62 step II: 93 step III: 74	 **2a**
4.	 9d	step I: 65 step II: 95 step III: 78	 **2b:** (+)-juruenolide C
5.	 9e	step I: 76 step II: 95 step III: 75	 **2c:** (+)-juruenolide D
6.	 9f	step I: 86 step II: 96 step III: 76	 **2d**

[a]For the synthesis of ylide **9f**, KHMDS was used as base and reaction was carried out in pet. ether:THF (1:1).

was obtained in 76% yield as a mixture of diastereomers. No effort was made to separate the diastereomers at this stage as in the subsequent steps; the acetal would be oxidized to lactone. Thus, catalytic hydrogenation of the olefin **8a** using 10% Pd/C in MeOH furnished the acetal **13a**. Finally, the acetal functional group in **13a** was chemoselectively oxidized employing *m*-CPBA and TMSOTf to obtain (+)-2-*epi*-blastmycinolactol (**2e**) in good yield. Repetition of the same reaction sequence starting with ylide **9b** furnished (+)-2-*epi*-NFX-2 (**2f**) in good overall yield (Table 1, entry 2). It is worth noting that this is the first enantiospecific synthesis of epimers of natural products blastmycinolactol (**2e′**) and NFX-2 (**2f′**). This strategy proved to be quite general and starting with appropriate ylides (**9c,d**), butanolide natural products lactone (+)-**2a** [$[\alpha]_D^{25}$ = +2.7 (*c* 0.16, MeOH), lit.[3c] $[\alpha]_D^{25}$ = +2.0 (*c* 0.16, MeOH)], (+)-juruenolide C (**2b**) [$[\alpha]_D^{25}$ = +24.8 (*c* 0.2, MeOH), lit.[6] $[\alpha]_D^{25}$ = +26.0 (*c* 0.3, MeOH)], and (+)-juruenolide D (**2c**) [$[\alpha]_D^{24}$ = +11.6 (*c* 0.16, MeOH), lit.[3d] $[\alpha]_D^{25}$ = +12.0 (*c* 0.1, MeOH)] could be assembled in excellent overall yields (Table 1, entries 3−5). It is pertinent to mention here that in the total synthesis of natural product lactone (+)-**2d** [$[\alpha]_D^{26}$ = +9.0 (*c* 0.9, $CHCl_3$), lit.[4f] $[\alpha]_D^{20}$ = +7.0 (*c* 1.1, $CHCl_3$)], in the Wittig olefination reaction step, ylide **9f** had to be prepared using KHMDS as the base and petroleum ether−THF (1:1) as a solvent for efficient reaction. Spectral data for all these butanolide natural products **2a**−**d** were in good agreement with those reported. It should be noted that these are enantiospecific first total syntheses of butanolide (+)-**2a**,

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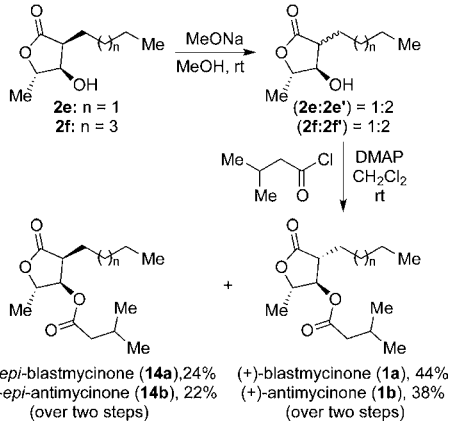
(+)-juruenolide D (**2c**), and butanolide (+)-**2d**, thus establishing their absolute stereochemistry.

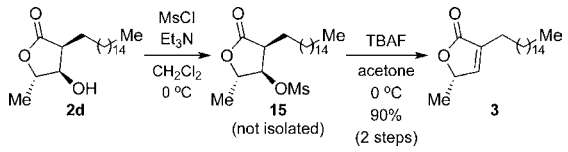
At this juncture, having epimers (+)-2-*epi*-blastmycinolactol (**2e**) and (+)-2-*epi*-NFX-2 (**2f**) in hand, attention was turned toward total synthesis of (+)-blastmycinone (**1a**) and (+)-antimycinone (**1b**). Toward this end, lactone **2e** was subjected to treatment with sodium methoxide, which resulted in partial epimerization of the C-2 stereocenter. Since the separation of epimers **2e** and **2e′** was found to be difficult, they were subjected to acylation with isovaleryl chloride to furnish (+)-blastmycinone (**1a**) [$[\alpha]_D^{25}$ = +8.7 (*c* 0.5, $CHCl_3$), lit.[5b] $[\alpha]_D^{20}$ = +11.2 (*c* 0.7, $CHCl_3$)] and (+)-2-*epi*-blastmycinone (**14a**) [$[\alpha]_D^{25}$ = +25.0 (*c* 0.6, $CHCl_3$)], which were separated by silica gel column chromatography (Scheme 3). In a similar manner, the (+)-2-*epi*-NFX-2 (**2f**) was used to synthesize (+)-antimycinone (**1b**) [$[\alpha]_D^{25}$ = +8.0 (*c* 0.5, $CHCl_3$), lit.[5b] $[\alpha]_D^{20}$ = +10.6 (*c* 1.0, $CHCl_3$)] and (+)-2-*epi*-antimycinone (**14b**) [$[\alpha]_D^{25}$ = +103.0 (*c* 0.5, $CHCl_3$)].

Scheme 3. Total Synthesis of (+)-Blastmycinone (1a) and (+)-Antimycinone (1b)



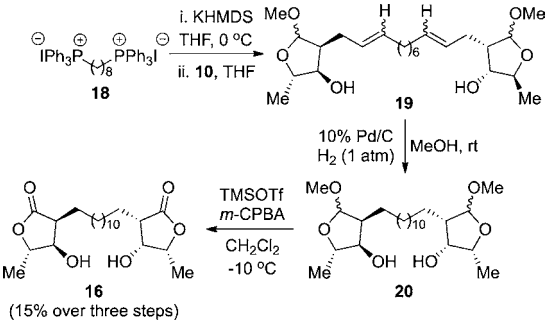
Attention was next turned toward synthesis of butenolide natural product **3**. To this end, the butanolide **2d** was treated with MsCl in the presence of Et_3N to obtained the mesylate **15**, which was found to be unstable. The crude reaction mixture was therefore subjected to treatment with TBAF to give the butenolide **3** in 90% yield (over two steps) [$[\alpha]_D^{23}$ = +22 (*c* 1.0, $CHCl_3$), lit.[4f] $[\alpha]_D^{20}$ = +22 (*c* 1.1, $CHCl_3$)] (Scheme 4).

Scheme 4. Total Synthesis of (+)-Butenolide 3



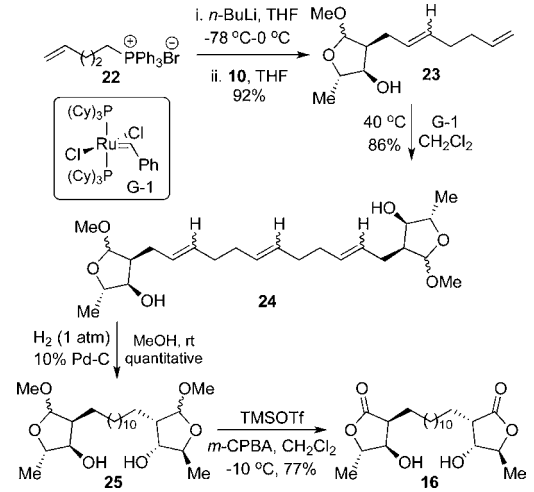
For the synthesis of bis-lactone natural products (+)-ancepsenolide (**4**), (+)-hydroxyancepsenolide (**5a**), and (+)-hydroxyancepsenolide acetate (**5b**) of the ancepsenolide family, bis-butanolide **16** was identified as a common precursor. For the synthesis of this bis-butanolide **16**, to begin with, a double-Wittig reaction based strategy was conceived. The synthesis commenced by the double-Wittig reaction of the lactol **10** with the ylide **17** (generated using bis-phosphonium salt **18** and KHMDS), which led to the bis-acetal olefin **19** as a mixture of diastereomers. The diastereomeric mixture of olefin **19** was then hydrogenated using 10% Pd/C as the catalyst to furnish the acetal **20**, which upon Lewis acid mediated oxidation gave the bis-lactone **16**, albeit in only 15% overall yield (Scheme 5). The major stumbling block in this approach was double-Wittig reaction. All our efforts to optimize this reaction by changing reaction conditions or reagents failed, and hence, an alternate approach was explored for the synthesis of bis-lactone natural products **4** and **5**.

Scheme 5. Double-Wittig Reaction Based Approach to the Synthesis of Bis-butanolide 16



In an alternate approach, a cross-metathesis−homodimerization reaction was planned as key reaction to assemble bis-butanolide **16**. Thus, Wittig reaction of the lactol **10** with the ylide **21** generated from the pentenylphosphonium bromide (**22**), and *n*-BuLi furnished the olefin **23** in 92% yield (Scheme 6). It was gratifying to see that the olefin **23** underwent a regioselective homodimerization by cross-metathesis reaction in the presence of Grubbs' first-generation catalyst (G-1) to furnish the corresponding *bis*-acetal olefin **24** as a mixture of diastereomers in excellent yield.[11] Subsequent hydrogenation and Lewis acid mediated oxidation proceeded smoothly, and bis-lactone **16** was obtained in good overall yield.

Scheme 6. Cross-Metathesis Homodimerization Based Approach to Bis-butanolide 16



With the bis-butanolide **16** in hand, the stage was set for the total synthesis of ancepsenolides. The bis-butanoilde **16** was treated with excess MsCl in the presence of Et_3N and DMAP in CH_2Cl_2 to obtain (+)-ancepsenolide (**4**) [$[\alpha]_D^{25}$ = +41.8 (*c* 0.4, $CHCl_3$), lit.[7d] $[\alpha]_D^{25}$ = +39.6 (*c* 0.4, $CHCl_3$)] in 76% yield. On the other hand, when the bis-lactone **16** was exposed to 1 equiv of

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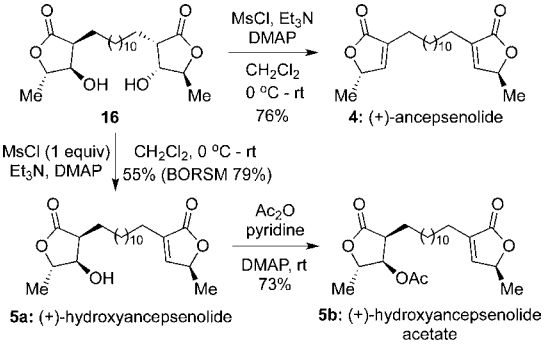
MsCl in the presence of Et_3N and DMAP in CH_2Cl_2, only one of the hydroxy group was eliminated and the (+)-hydroxyancepsnolide (**5a**) [$[\alpha]_D^{20}$ = +20.4 (*c* 0.6, $CHCl_3$), lit.[4f] $[\alpha]_D^{20}$ = +20.0 (*c* 0.59, $CHCl_3$)] was obtained in 55% yield (along with 30% of unreacted lactone **16**) constituting the enantiospecific first total synthesis and establishing its absolute configuration. Acylation of (+)-hydroxyancepsenolide (**5a**) with Ac_2O in pyridine in the presence of catalytic amount of DMAP furnished (+)-hydroxyancepsenolide acetate (**5b**) [$[\alpha]_D^{21}$ = +18.5 (*c* 0.6, $CHCl_3$), lit.[4d] $[\alpha]_D^{25}$ = +3.7 (*c* 2.2, $CHCl_3$)] (Scheme 7). Their structures were confirmed by the comparison of spectral data with those reported in the literature.

Scheme 7. Total Synthesis of (+)-Ancepsenolide (4), (+)-Hydroxyancepsnolide (5a), and (+)-Hydroxyancepsenolide Acetate (5b)



In conclusion, we have developed a general enantiospecific approach for the synthesis of butanolide and butenolide based natural products using DAC **6** as a common precursor. A common strategy was used to achieve the first total syntheses of butanolides **2a**, **2d**, (+)-juruenolide D (**2c**), butenolide **3**, (+)-hydroxyancepsenolide (**5a**), and (+)-hydroxyancepsnolide acetate (**5b**). The protocol also gave an efficient access to the total synthesis of (+)-juruenolide C (**2b**), (+)-ancepsenolide (**4**), (+)-blastmycinone (**1a**), and (+)-antimycinone (**1b**).

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor U. V. Varadaraju, IIT Madras, on the occasion of his 60th birthday.

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