

γ -Substituted Butanolides from Cyclopropane Hemimalonates: An Expedient Synthesis of Natural (*R*)-Dodecan-4-olide

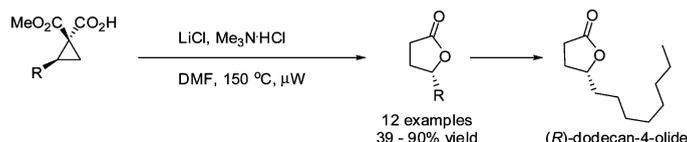
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ABSTRACT



Exploration into the reactivity of donor–acceptor cyclopropane hemimalonates has led to the facile synthesis of γ -substituted butanolides. Under microwave irradiation, cyclopropane hemimalonates undergo rapid conversion to butanolides in the presence of inorganic salts with an unprecedented retention of stereochemistry. This unique process has been applied to the total synthesis of the naturally occurring (*R*)-dodecan-4-olide.

Nitrogen- and oxygen-containing heterocycles are among the most prevalent moieties found in both pharmaceutical and naturally occurring compounds. Research and development into these compounds is of high interest and of ongoing importance in organic synthesis. One such route to the synthesis of these heterocycles has incorporated the use of cyclopropanes in dipolar cycloaddition chemistry.¹ Although significant advancements have been made in the synthesis of nitrogen-containing heterocycles from cyclopropanes, little work has been devoted toward the synthesis of butanolides (γ -lactones). Current methods in this field often suffer from harsh reaction conditions,

require structurally biased cyclopropanes, or result in low yields with major byproducts.²

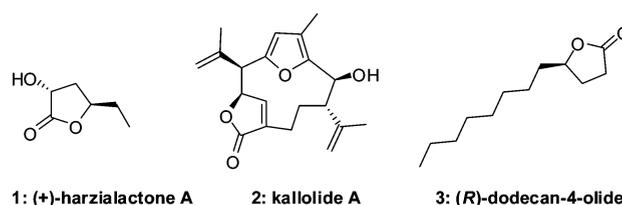


Figure 1. Butanolide-containing natural products.

Butanolides have been isolated from a variety of natural sources (Figure 1)³ and are common compounds in flavorings⁴ and insect pheromones.⁵ A unique and naturally reoccurring butanolide is (*R*)-dodecan-4-olide **3**. Isolated from an array of natural sources including the pygidial glands

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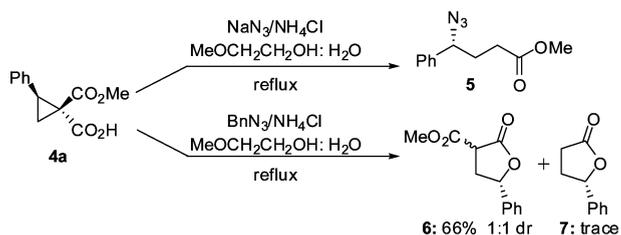
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of rove beetles,⁶ fruits,⁷ butterfat,⁸ and the territorial marking fluid of the Bengal tiger,⁹ dodecan-4-olide is a small natural product which plays a role in many different biological processes.¹⁰ Due to this compound's abundance in nature, dodecan-4-olide is one of the most common butanolides targeted for small-molecule synthesis.¹¹

Recently, in our research directed toward the utility of cyclopropane hemimalonates, we reported the synthesis of a variety of 3-azidobutyric acid esters **5** from cyclopropane hemimalonates and sodium azide (Scheme 1).¹² During the development of this chemistry, it was noted that in the presence of substituted unreactive azide sources, such as benzyl azide, the cyclopropane (**4a**) was able to undergo a unimolecular transformation to produce a mixture of butanolides **6** and **7**. The organoazide is not incorporated into the products and is thus unnecessary toward the formation of butanolides. Herein, we report the development and generalization of a γ -substituted butanolide synthesis from cyclopropane hemimalonates and its application to the synthesis of naturally occurring (*R*)-dodecan-4-olide.

Scheme 1. Previous Work with Cyclopropane Hemimalonates



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Initial attempts to optimize this cyclopropane reorganization proved quite fruitful, allowing access to butanolide **6** in an 82% yield upon heating in 2-methoxyethanol in the presence of a slight excess of ammonium chloride (Table 1, entry 1). In the absence of the salt, the reaction failed to proceed. Although the use of ammonium chloride gave a high yield of **6**, it also led to a trace amount of inseparable butanolide **7**, a product of a dealkoxycarbonylation. While a variety of salts promoted the reaction, ammonium chloride salts seemed to be superior. It was never possible to obtain **6** as the sole product in our hands.

Table 1. Reaction Optimization

entry	additive (1.4 equiv)	solvent/temp (°C)	time ^a	product (%)
1	NH ₄ Cl	2-MeO(CH ₂) ₂ OH/reflux	2 h	82% 6 , trace 7
2	NH ₄ Cl	DMSO/135 °C	1 h	87% 6 , trace 7
3	NH ₄ Cl	5:1 DMSO:H ₂ O/135 °C	1 h	mixture ^b
4	NaCl	DMSO/135 °C	1 h	mixture ^b
5	KCl	DMSO/135 °C	1 h	mixture ^b
6	LiCl	DMSO/135 °C	24 h	mixture ^b
7	NaCN	DMSO/135 °C	24 h	no rxn
8	Me ₃ N·HCl	DMSO/135 °C	24 h	mixture ^b
9	NH ₄ Cl/NaCN	DMSO/135 °C	1/6 h	65% 7
10	LiCl/Me ₃ N·HCl	DMSO/135 °C	24 h	mixture ^b
11	LiCl/Me ₃ N·HCl	DMSO/reflux	24 h	mixture ^b
12 ^c	LiCl/Me ₃ N·HCl	DMSO/150 °C	40 min	71% 7
13 ^c	LiCl/Me ₃ N·HCl	DMF/150 °C	40 min	82% 7
14 ^{c,d}	LiCl/Me ₃ N·HCl	DMF/150 °C	40 min	45% 7

^a Time to complete consumption of starting material by TLC analysis. ^b A 1:1 mixture of compounds **6** and **7**. ^c Performed in microwave reactor. ^d The corresponding methyl diester was used.

Frustrated with the inability to form **6** cleanly, it was decided to focus on pushing the reaction toward the formation of **7** as the sole product. Reaction conditions were modified by using DMSO, a solvent commonly used in Krapcho dealkoxycarbonylation reactions. The use of ammonium chloride in DMSO (entries 2 and 3) with and without water improved the overall reaction time and yield; however, both **6** and **7** were still obtained as an inseparable mixture. A variety of additives were explored in hopes to promote the smooth conversion to **7**, but to no avail (entries 4–8). It is noteworthy that, with the exception of sodium cyanide, all additives induced the initial lactone formation, but the dealkoxycarbonylation step was sluggish and incomplete. It was at this point that a one-pot, two-step process was engaged, using ammonium chloride to promote initial butanolide formation followed by the addition of sodium cyanide to facilitate the dealkoxycarbonylation (entry 9). We were pleased to find that the two-step process worked, giving **7** in a 65% yield as the sole product.

Spurred by this success, we next examined the use of standard dealkoxycarbonylation salt systems, which could

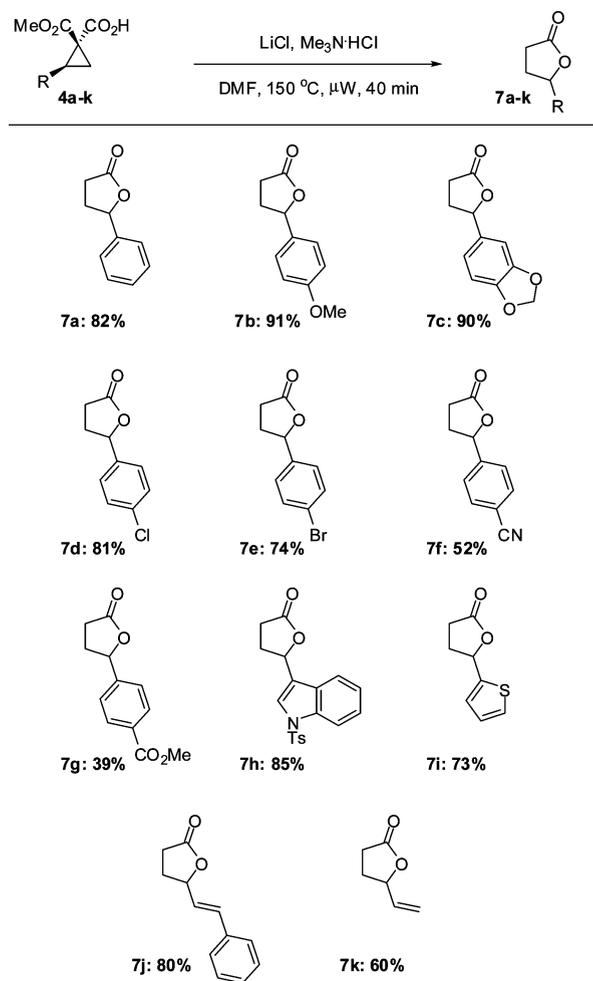
also promote the butanolide formation. The use of lithium chloride and trimethyl ammonium chloride together at 135 °C and reflux unfortunately led to a 1:1 mixture of **6** and **7** even after extended reaction times (entries 10 and 11). To circumvent the problem with incomplete conversion, microwave irradiation was employed. Gratifyingly, the reaction proceeded well at 150 °C in both DMSO and DMF, giving rise to adduct **7** in excellent yields of 71 and 82%, respectively (entries 12 and 13). Finally, the cyclopropane *diester* was subjected to the optimized reaction conditions of lithium chloride and trimethyl ammonium chloride in DMF at 150 °C. However, only a small amount of the desired product could be isolated, along with a significant amount of starting material decomposition (entry 14).

With successful reaction conditions and a variety of readily available cyclopropane hemimalonates¹³ in hand, we next set forth to determine the scope of this transformation (Scheme 2). Both electron-donating and halogen-substituted phenyl cyclopropanes effectively underwent the butanolide conversion in moderate to excellent yields (adducts **7b**, **7c**, **7d**, and **7e**). In contrast, electron-withdrawing phenyl cyclopropanes decreased the reactivity of butanolide production, resulting in lower isolated yields (adducts **7f** and **7g**), a trend common to donor–acceptor cyclopropane reactivity. The heteroaromatic-substituted cyclopropanes (3-*N*-tosylindolyl and 2-thienyl) underwent the transformation with great success, leading to isolated yields of 85 and 74% butanolides **7h** and **7i**, respectively. Alkenyl-substituted cyclopropanes were able to withstand the reaction conditions, allowing access to the β -styrenyl-substituted adduct **7j** in 80% yield as well as the vinyl adduct **7k** in 60% yield. The lower yield of **7k** can be attributed to the highly reactive nature of this cyclopropane toward polymerization. Finally, alkyl-substituted cyclopropanes were subjected to the reaction conditions (not in scheme); however, no product formation was achieved.

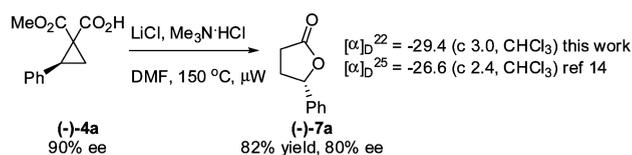
To shed light onto the mechanism, optically enriched phenyl cyclopropane (–)-**4a** was subjected to the reaction conditions (Scheme 3). Smooth transformation **7a** led to an isolated 82% yield of enriched butanolide **7a**, with only slight erosion of enantiomeric excess (determined by a Mosher's ester sequence). Optical rotation analyses of the product support the (*S*) isomer butanolide being isolated.¹⁴ This outcome suggests that the reaction occurs with *retention* of stereochemistry, a result unusual in donor–acceptor cyclopropane chemistry. A proposed mechanism for this transformation can be seen in Scheme 4.

There occurred to us to be two possible mechanistic explanations for this transformation. First, solvolytic cleavage of the cyclopropane bond in **4a** may occur to produce a benzylic carbocation and a malonate ion in an intimate ion pair **8** as proposed by Johnson.¹⁵ The cation moiety

Scheme 2. Substrate Scope



Scheme 3. Optically Enriched Example



would undergo attack by the malonate in an O-alkylation event to produce the lactone **6** as the observed mixture of diastereomers. Subsequent Krapcho dealkoxycarbonylation would yield **7a**. Alternatively, the cyclopropane **4a** may undergo nucleophilic attack by chloride with inversion of configuration to yield the benzylic chloride **9**. O-Alkylation of the putative malonic anion with a second inversion would yield lactone **6**, again as a mixture of diastereomers. Any small erosion of stereochemistry could be rationalized in the first case by bond rotation of the cationic moiety in **8** or a Finkelstein inversion of the chloride in **9**. We are unsure at this time of the most likely scenario.

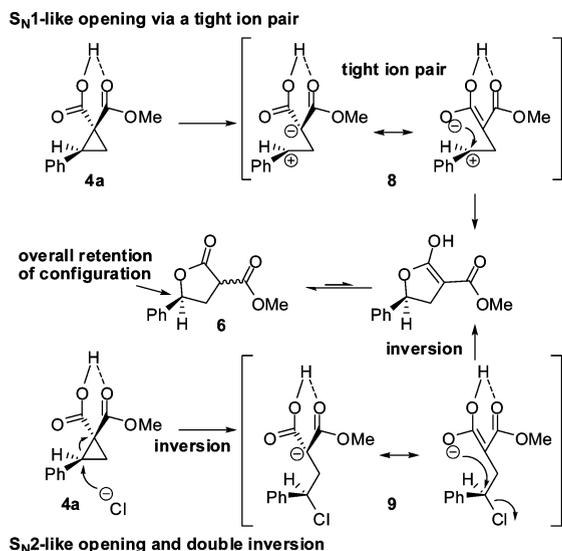
To display the utility of this reaction, the natural lactone (*R*)-dodecan-4-olide was targeted for total synthesis

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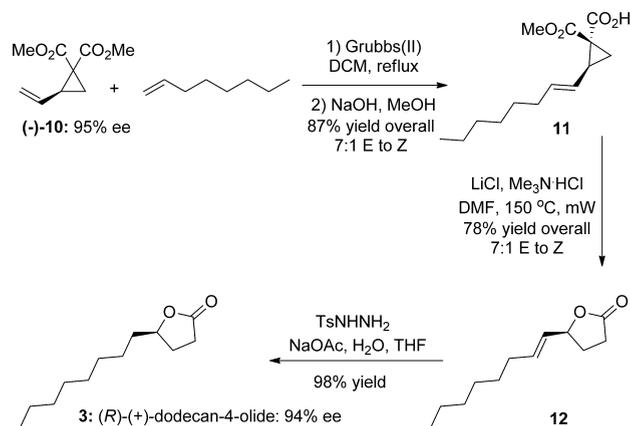
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Scheme 4. Proposed Mechanism



(Scheme 5). Readily available dimethyl ester vinyl cyclopropane **10** was subjected to cross-metathesis conditions with oct-1-ene in the presence of Grubbs second generation ruthenium catalyst to access the crude octenyl cyclopropane. Following monosaponification, cyclopropane hemimalonate **11** was isolated in an 87% yield over two steps. Hemimalonate **11** was then exposed to the standard butanolide synthesis conditions, and alkenyl butanolide **12** was isolated in 78% yield. Reduction of the π -system proved to be the most difficult step in synthesis, resulting in over reduction of the lactone ring under standard conditions including hydrogenation over Pd on carbon or PtO₂. The π -system reduction of butanolide **12** was finally achieved using tosylhydrazide as a hydrazine source, allowing access to (*R*)-dodecan-4-olide **3** in 98% yield and 94% ee (determined by a Mosher's ester sequence).

Scheme 5. Total Synthesis of Natural (*R*)-Dodecan-4-olide



In conclusion, we have developed an efficient approach to the synthesis of γ -substituted butanolides via a tandem cyclopropane hemimalonate reorganization/dealkoxy-carbonylation. The application of this method has resulted in the four-step 67% overall yield synthesis of naturally occurring (*R*)-dodecan-4-olide.

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Supporting Information Available. Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.