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Vinylogous Addition of Siloxyfurans to Benzopyryliums: A Concise Approach to the Tetrahydroxanthone Natural Products

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Abstract

A concise approach to the tetrahydroxanthone natural products has been developed employing vinylogous addition of siloxyfurans to benzopyryliums and a late stage Dieckmann cyclization. Using this methodology, chiral, racemic forms of the natural products blennolides B and C have been synthesized in a maximum of four steps from a 5-hydroxychromone substrate. The regio- and diastereoselectivity of vinylogous additions was probed using computational studies which suggest involvement of Diels-Alder-like transition states.

Tetrahydroxanthones are a class of mycotoxins[1] bearing both monomeric and dimeric frameworks. The recently isolated tetrahydroxanthones blennolides A (**1**) and B (**2**) (Figure 1)[2] are monomer units of the antitumor agents secalonic acids B (**3**) and D (**4**),[3] the latter which exhibits antibacterial, cytostatic, and anti-HIV properties.[4] Blennolide C (**5**), the methyl isomer of **1**, and the antifungal agent parnafungin A (**6**)[5] also possess the characteristic dihydro-*2H*-xanthenone framework found in many tetrahydroxanthones. Related, isomeric natural products including paecilin B (**7**) (stereochemistry unassigned) containing the isomeric chromone lactone moiety have also been reported.[6] Recently, Bräse and Nicolaou have reported elegant approaches to blennolide C (**5**) and the related natural product diversonol employing biomimetic construction of the tetrahydroxanthone core.[7] Herein, we describe a concise approach to racemic blennolides and related tetrahydroxanthones employing a “retrobiomimetic” process[8] involving vinylogous addition of siloxyfurans to benzopyryliums.

Biosynthetically, the blennolides appear to be derived from a sequence involving oxidation of benzophenone ester **8**, *oxa*-Michael addition, and reduction to dihydro-*2H*-xanthenone **9** (Figure 2, (a)).[9] The chromone lactone structure **10** found in paecilin B (**7**)[6] appears to be derived from hydrolysis/lactonization of the tetrahydroxanthone framework.[6b,c] We envisioned that precursor **11** may be obtained by vinylogous addition of siloxyfurans[10] to activated benzopyrylium salts **12**.[11] Conjugate reduction of butenolide **11** should afford chromone lactone **10**. The last step in the sequence entails a “retrobiomimetic” transformation[8] in which tetrahydroxanthones **9** may be produced by Dieckmann cyclization[7k] of chromone lactones **10**.

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Supporting Information Available: Experimental procedures, mechanistic studies, calculation studies, complete ref. [5a], and characterization data for all new compounds described herein, CIF files for compounds **15**, **40**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

We initiated our study by treating the readily available 5-hydroxychromone **13**[12,13] with a number of Lewis acids in an effort to promote vinylogous addition of 2-trimethylsilyloxy furan (Scheme 1). Unfortunately, in our initial experiments we did not observe substantial adduct formation. In light of the high reactivity of 4-siloxy-1-benzopyrylium salts towards carbon nucleophiles,[11a,b] we focused our efforts on silyl triflate activation of chromone **13**. In particular, we reasoned that dialkylsilyl ditriflate reagents, generally used to protect diols as silylenes,[14] may directly afford activated siloxybenzopyrylium species. In the event, treatment of **13** with diisopropyl silyl ditriflate in the presence of 2,6-lutidine led to formation of benzopyrylium **14**.[13] Treatment of **14** with 2-trimethylsiloxy furan at −78 °C cleanly led to formation of chromone butenolide **15** (*dr* = 15: 1) after desilylation with $Et_3N{\cdot}3HF$. Crystallization of **15** facilitated X-ray crystal structure analysis of the major diastereomer.[13] Finally, conjugate reduction of butenolide **15** with nickel boride[15] provided chromone lactone **16**.

We next evaluated the effect of time and temperature for vinylogous additions (Table 1). Interestingly, increased reaction temperature led to reduced diastereoselectivities in additions to **14** leading to a preference for diastereomer **17** at higher temperature (*cf*. entries 1 and 2). Conducting the reaction at 0 °C for 0.5 h (entry 3) led to an inseparable 3: 1 mixture of **15: 17** which supports epimerization at higher temperatures and longer reaction times (*vide infra*).[16] Similar results were obtained for vinylogous additions to chromone **18** leading to adducts **19** and **20** (entries 5 and 6). Addition of 4-methyl-2-trimethylsiloxyfuran to **14** (entry 7) led to reduced diastereoselectivities (2: 1) in comparison to 2-trimethylsiloxyfuran (*dr* = 15: 1, *cf.* Scheme 1). Based on our experimental data, we propose the generalized mechanism shown in Scheme 2. Initial vinylogous addition of 2-trimethylsiloxyfuran to **14** at −78 °C leads to the kinetic adduct **23** which may lose TMSOTf to afford silylene **24**, a precursor to chromone **15**. At higher temperature, thermodynamic equilibration of **23** to **25** may occur by butenolide enolization[16b] through silylated intermediate **26**. The equilibration process was confirmed by ^{1}H NMR studies.[13] Computational studies indicate that adduct **27** is approximately 1 kcal/mol more stable than diastereomer **24**.[13]

In order to understand the observed regio- and diastereoselectivity, we employed DFT methods to model the reaction of benzopyrylium **14** with 2-trimethylsiloxy furan.[13] FMO analyses showed that C2 of **14** and C5 of the siloxyfuran should be the most reactive sites (Figure 3). Thirteen candidate transition state structures were generated by conformational variation about the nascent C2-C5 bond and were optimized at the B3LYP/6-31G(d) level of theory.[13] Similar transition states have been proposed for vinylogous Mukaiyama aldol reactions.[17] The lowest energy *Re*-*Si* (or *Si*-*Re*) structure (**TS-A** in Figure 4) which leads to the observed major product bears striking resemblance to an asynchronous *endo* [4+2] transition state; other TS candidates of like stereochemistry were greater than 4.3 kcal/mol higher in energy. The most favorable *Re*-*Re* (or *Si*-*Si*) TS structure (**TS-B**) is 2.68 kcal/mol above **TS-A**, consistent with the stereochemistry observed for the minor, kinetic product. With 4-methyl-2-trimethylsiloxy furan (*cf.* Table 1, entry 7), TS structures similar to **TS-A** would be disfavored by steric factors, thus explaining the loss of diastereoselectivity.

Having achieved the synthesis of chromone lactone structures, we next turned our attention to Dieckmann-type cyclizations (Scheme 3).[7k,18] Treatment of **16** with NaOMe in MeOH led exclusively to the ring-opened hydroxy ester **28**. Gratifyingly, we found that treatment of **16** with NaOMe in THF[19] led to observable precipitation to a presumed dianion intermediate and formation of dihydro-*2H*-xanthenones **29** and **30** after workup. After evaluating several bases, NaH was found to be superior to NaOMe to afford **29**/**30** in 67 % yield (*dr* = 20: 1 by ^{1}H NMR). In order to evaluate the cyclization on the diastereomer of **16**, we subjected a mixture of butenolides **17** and **15** (2: 1) to conjugate reduction (NiB_2) which

afforded an inseparable mixture of **31** and **16** in a 2: 1 ratio. Subsequent Dieckmann cyclization (NaH/THF) afforded **30** and **29** in a 1: 2 ratio. These studies support a mechanism for equilibration to favor the *syn* hydroxy configuration in **29** as shown in Scheme 5.[5,6b,c,20] Enolate **32** derived from **31** may condense with the lactone to form tetrahedral intermediate **33**. After ring-opening, the resulting dianion **34** (a precursor to **30**) may equilibrate by retro-Michael addition to **35** which may be followed by *oxa*-Michael addition[7a,b] to provide diastereomer **36** and thence **29** after workup.

After completion of the model studies, we synthesized both (±)-*epi*-blennolide C (Scheme 6) and (±)-blennolide C (Scheme 7) from butenolides **19** and **20**. Conjugate reduction of **19** and **20** (20: 1) using NiB_2 led to chromone lactones **37** (*dr* = 20: 1). Dieckmann cyclization of **37** using NaH/THF led to production of *epi*-blennolide C **39** (72 % isolated yield). Similar transformations were used to obtain blennolide C (**5**) from a 2: 1 mixture of **20: 19** *via* lactone **38**. The spectroscopic properties of synthetic **5** and *epi*-blennolide C **39** were in complete agreement with previously published data.[2,7b,c]

The natural product blennolide B (**2**)[2] has *syn*, *anti* stereochemistry of ester, hydroxyl, and methyl groups on the dihydro-*2H*-xanthenone core. Based on our model studies and the hypothesis that butenolide reduction should occur *anti* to the 5-substituent,[15a] we initiated our synthesis from a 2: 1 mixture of butenolides **21** and **22** (Table 1, Entry **7**). In this case, nickel boride chemoselectively reduced the butenolide to afford a mixture of four chromone lactone diastereomers. Interestingly, when Rh/Al_2O_3 was used for conjugate reduction,[21] we obtained **40** as a single diastereomer as well as the separable, overreduced hydroxyl chromone lactones **41** and **42**. Alcohols **41** and **42** could be reoxidized to lactones **40** and **44**, respectively, using the Bobbitt reagent **43** (50 wt% on SiO_2).[22] The stereochemistry of chromone lactones **40** and **44** were confirmed by X-ray crystal structure analyses (Figure 5). NMR data for chromone lactones **40** and **44** were not in agreement with data reported for paecilin B[6] (Figure 1) indicating that **7** is a diastereomer of both **40** and **44**. Treatment of **40** with NaH in THF afforded (±)-blennolide B (**2**) whose spectroscopic properties were identical to reported data.[2,13] Interestingly, cyclization of chromone lactone **44** (NaH) led to the isolation of (±)-blennolide B (73 %) with negligible amounts of diastereomer **45** observed in the crude ^1H NMR spectrum. This result further supports the isomerization process shown in Scheme 5 which in this case likely occurs due to unfavorable repulsion between the ester and methyl groups in diastereomer **45**.[13]

In conclusion, we have developed a concise and “retrobiomimetic” approach to tetrahydroxanthones employing vinylogous addition of siloxyfurans to benzopyryliums as a key step. The regio- and diastereoselectivity of vinylogous additions was probed using computational studies which suggest involvement of Diels-Alder-like transition state. Using this methodology, the natural products (±)-blennolides B and C were synthesized in a maximum of 4 steps from readily available 5-hydroxychromones. Further studies, including development of an asymmetric variant of the vinylogous addition, are currently under investigation and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. See Supporting Information for complete experimental and computational details.
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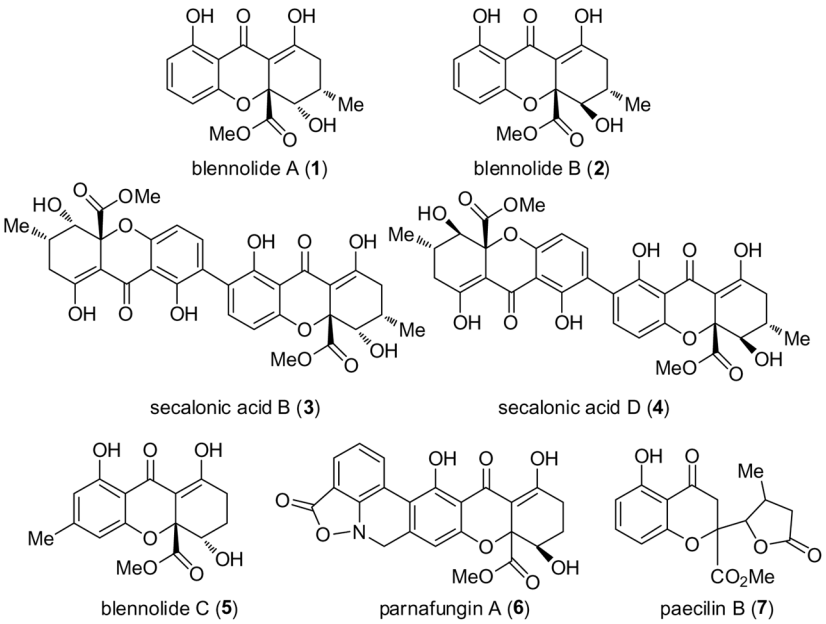


Figure 1.
Tetrahydroxanthones and related natural products.

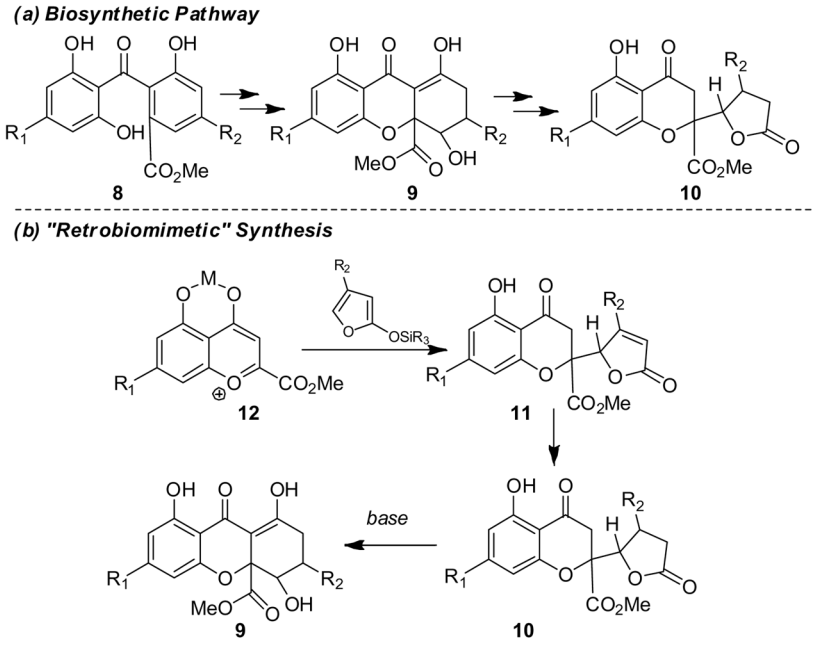


Figure 2.
Biosynthetic pathway *vs.* "retrobiomimetic" synthesis.

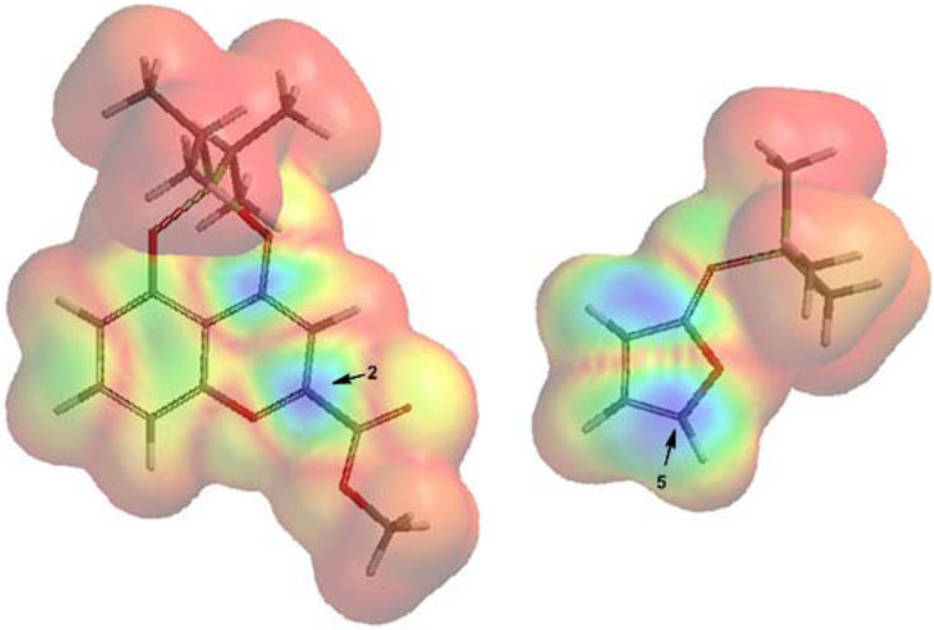


Figure 3.
Composite surfaces of the B3LYP/6-31G(d) LUMO of **14** and HOMO of 2-trimethylsiloxyfuran, mapped onto an electron density isosurface using Spartan ‘08. Reactive sites are shown in blue.

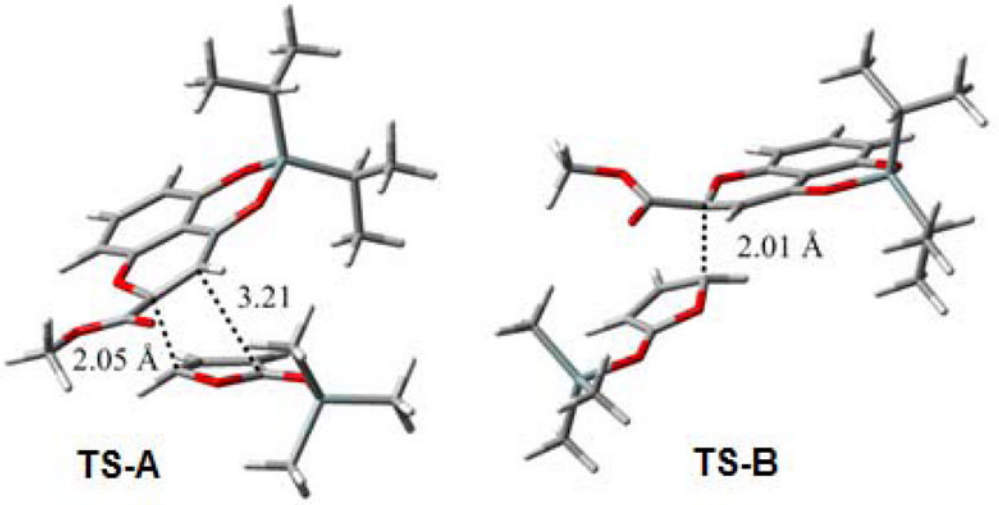


Figure 4.
Lowest energy transition state structures for *Re-Si* (**TS-A**) and *Re-Re* (**TS-B**) addition in the reaction of **14** and 2-trimethylsiloxyfuran.

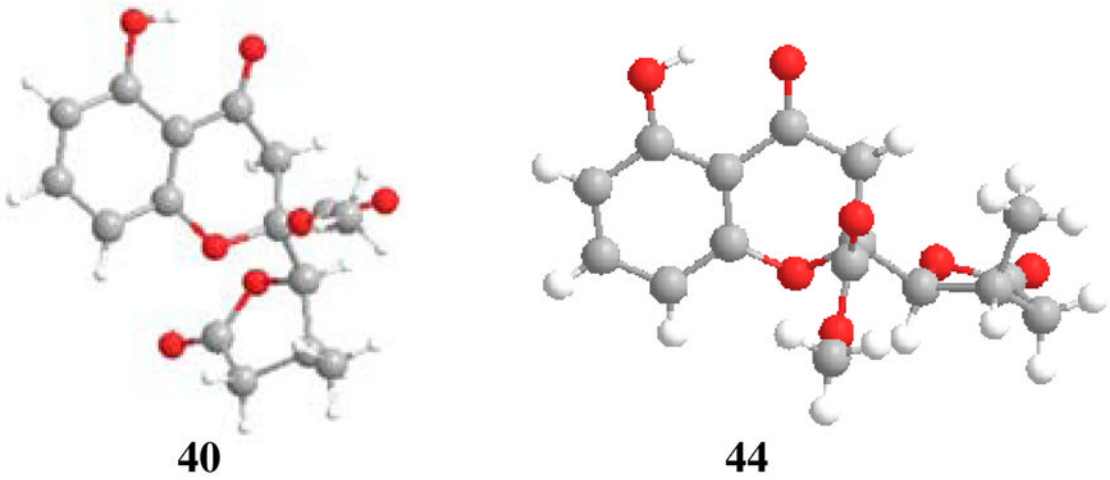
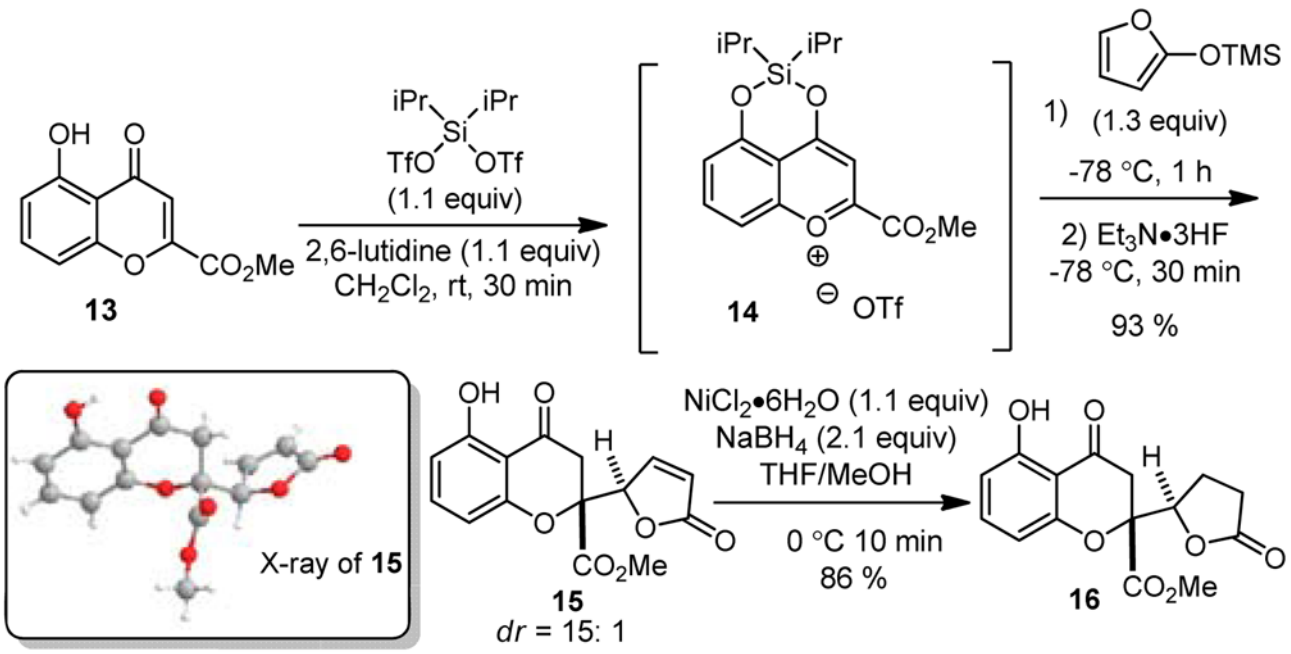
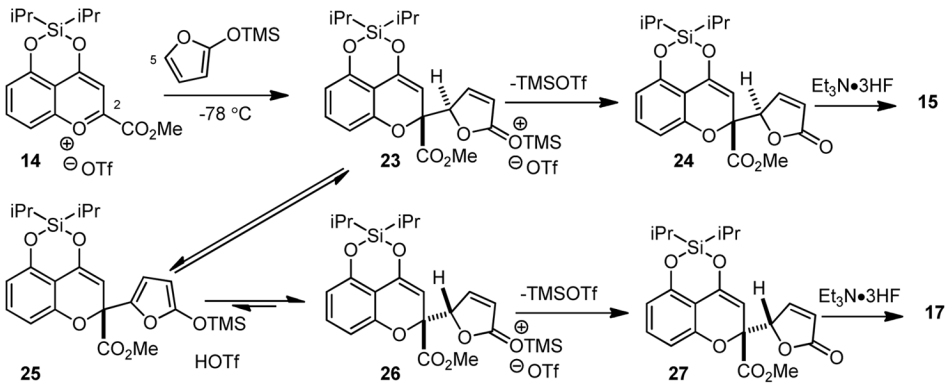


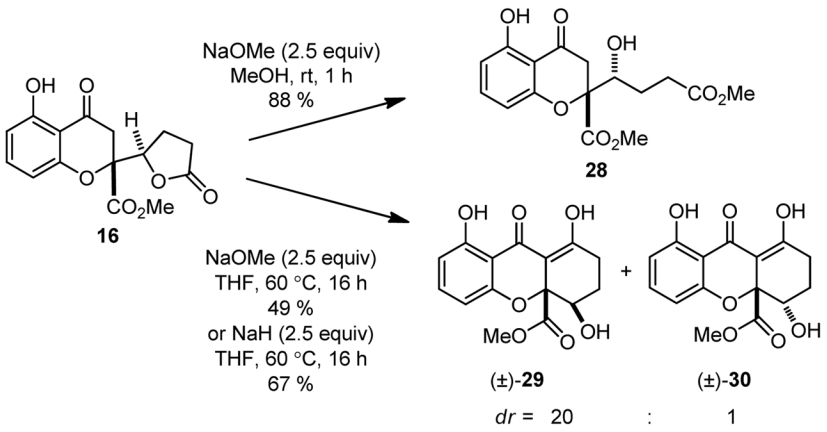
Figure 5.
X-ray crystal structures of compounds **40** and **44**.



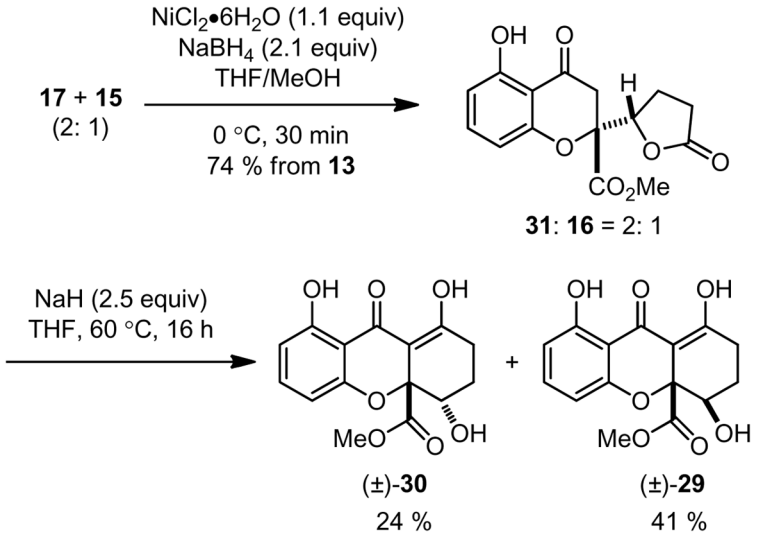
Scheme 1.
Model Studies



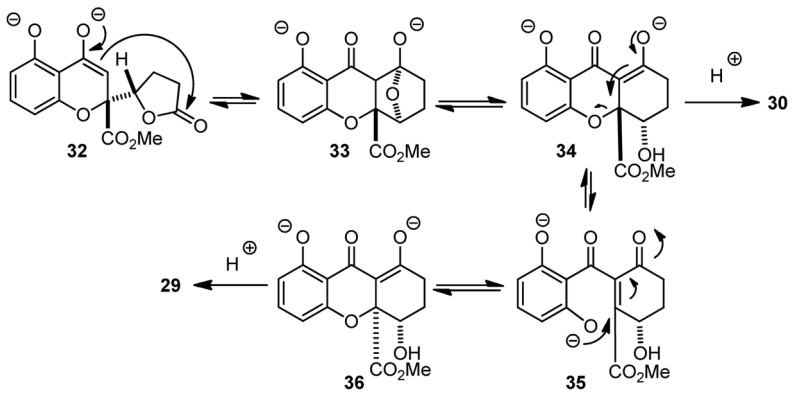
Scheme 2.
Proposed Mechanism for Vinylogous Addition



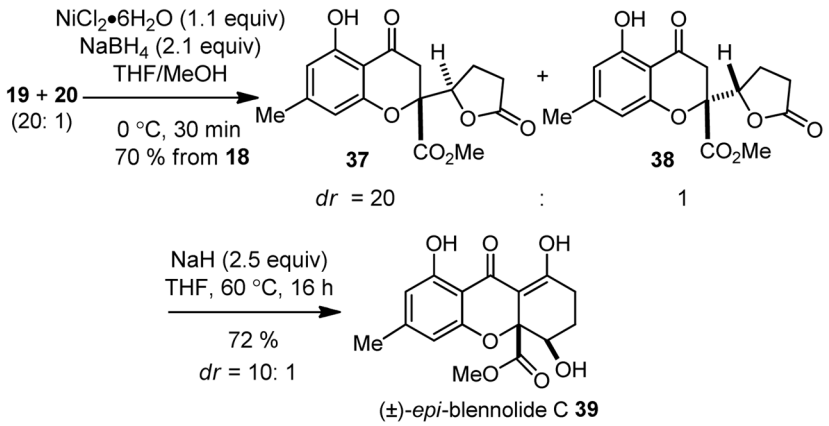
Scheme 3.
Dieckmann Cyclization



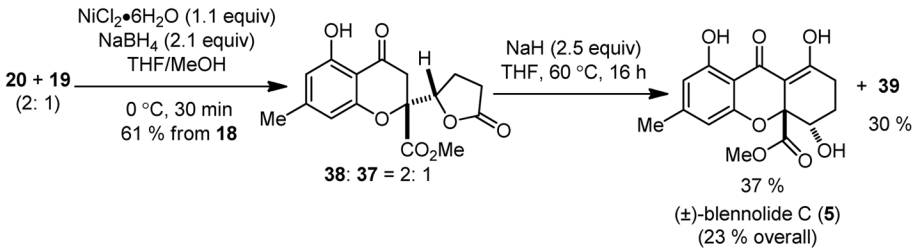
Scheme 4.
Equilibration of Dieckmann products



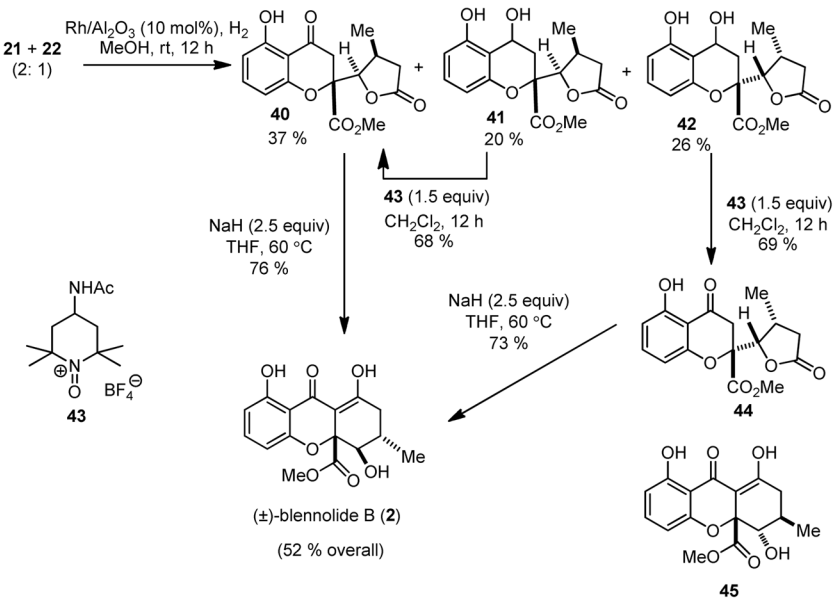
Scheme 5.
Proposed Mechanism for Cyclization/Isomerization



Scheme 6.
Synthesis of (±)-*epi*-Blennolide C



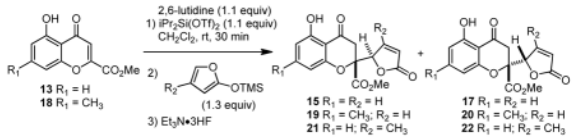
Scheme 7.
Synthesis of (±)-Blennolide C



Scheme 8.
Synthesis of (±)-Blennolide B

Table 1

Evaluation of Time and Temperature



entry	R_1	R_2	temp (°C)	time (h)	yield (%)[a]	ratio[b]
1	H	H	−30	3	95	3: 1 (**15: 17**)
2	H	H	0	3	90	1: 2 (**15: 17**)
3	H	H	0	0.5	91	3: 1 (**15: 17**)
4	H	H	40	3	64	1: 2 (**15: 17**)
5	Me	H	−78	1	96	20: 1(**19: 20**)
6	Me	H	0	3	97	1: 2 (**19: 20**)
7	H	Me	−78	1	89	2: 1 (**21: 22**)
8	H	Me	0	3	85	1: 2 (**21: 22**)

[a] Yield determined based on crude H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

[b] Ratio determined based on crude ^{1}H-NMR analysis.