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

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Supporting Information

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

Tetrahydroxanthones are a class of mycotoxins[1] bearing both monomeric and dimeric frameworks. The recently isolated tetrahydroxanthones blennolide A (**1**) and B (**2**) (Figure 1)[2] are monomer units of the antitumor agents secalonic acids B (**3**) and D (**4**), respectively,[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-2*H*-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 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-2*H*-xanthenone **9** (Figure 2a).[9] The chromone lactone structure **10** found in paecilin B (**7**)[6] appears to be derived from hydrolysis/lactonization of the tetrahydroxanthone framework.[6b,6c] 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** (Figure 2b).

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-trimethylsilyloxyfuran (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 toward carbon nucleophiles,[11a,b] we focused our efforts on silyl triflate activation of chromone **13**. In particular, we reasoned that dialkylsilyl ditriflate reagents, which are generally used to protect diols as silylenes,[14] may directly afford activated siloxybenzopyrylium species. In the event, treatment of **13** with diisopropylsilyl ditriflate in the presence of 2,6-lutidine led to the formation of benzopyrylium **14**.[13] Treatment of **14** with 2-trimethylsiloxyfuran

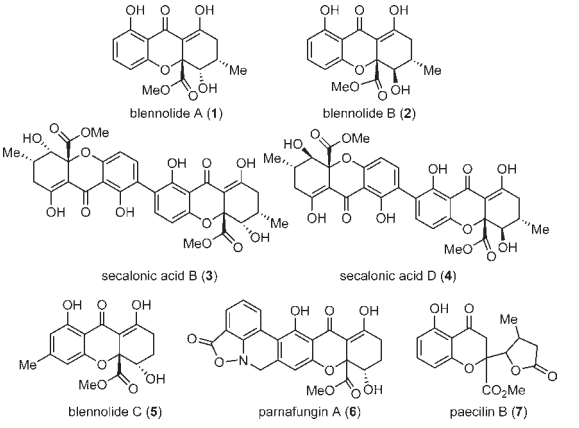

Figure 1. Tetrahydroxanthones and related natural products.

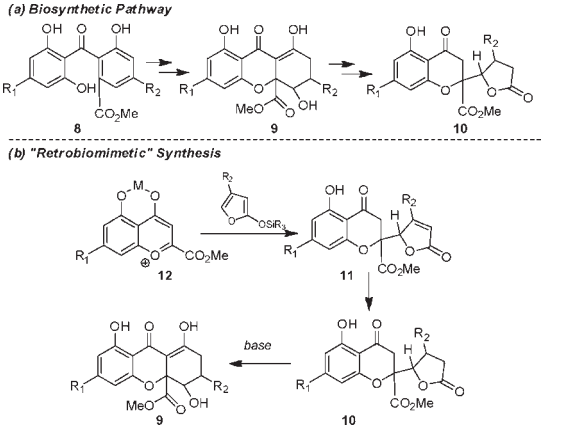

Figure 2. (a) Biosynthetic pathway vs (b) "retrobiomimetic" synthesis.

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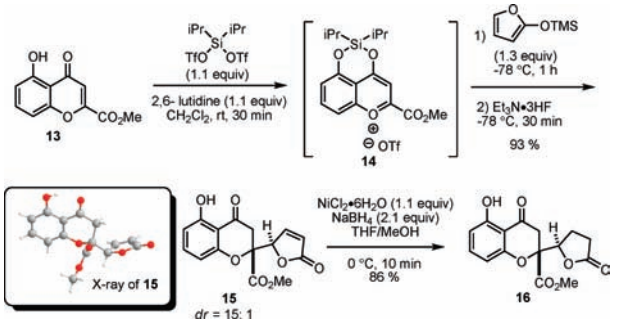
Scheme 1. Model Studies



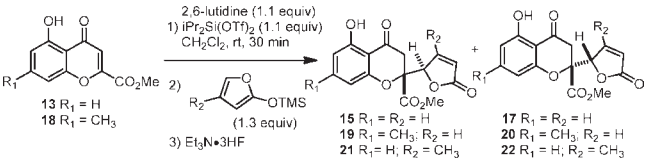
at −78 °C cleanly led to formation of chromone butenolide **15** (dr = 15:1) after desilylation with $Et_3N·3HF$. Crystallization of **15** facilitated X-ray crystal structure analysis of the major diastereomer.[13] Finally, conjugate reduction of butenolide **15** with nickel boride[15] provided chromone lactone **16**.

We next evaluated the effect of time and temperature for vinylogous additions (Table 1). Interestingly, increasing the reaction temperature led to reduced diastereoselectivities in additions to **14**, leading to a preference for diastereomer **17** at higher temperature (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** and **17** which supports epimerization at higher temperatures and longer reaction times (see below).[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 diastereoselectivity (2:1) in comparison with 2-trimethylsiloxyfuran (dr = 15:1; cf. Scheme 1). On the basis of 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 indicated that adduct **27** is ∼1 kcal/mol more stable than diastereomer **24**.[13]

To understand the observed regio- and diastereoselectivity of vinylogous additions, we employed density functional theory methods to model the reaction of benzopyrylium **14** with 2-trimethylsiloxyfuran.[13] Frontier molecular orbital analyses showed that C2 of **14** and C5 of the siloxyfuran should be the most reactive sites (Figure 3). Thirteen candidate transition state (TS) structures were generated by conformational variation about the nascent C2−C5 bond and optimized at the B3LYP/6-31G(d) level of theory.[13] Similar TSs have been proposed for vinylogous Mukaiyama aldol reactions.[17] The lowest-energy *Re*−*Si* (or *Si*−*Re*) structure (**TS-A** in Figure 4) that leads to the observed major product bears a striking resemblance to an asynchronous endo [4 + 2] TS; other TS candidates of like stereochemistry were > 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-trimethylsiloxyfuran (cf. Table 1, entry 7), TS structures similar to **TS-A** would be disfavored by steric factors, 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

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] Determined by crude ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Determined by crude ^{1}H NMR analysis.

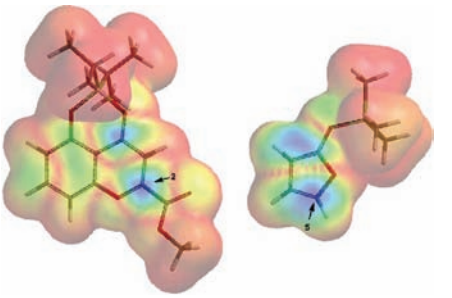
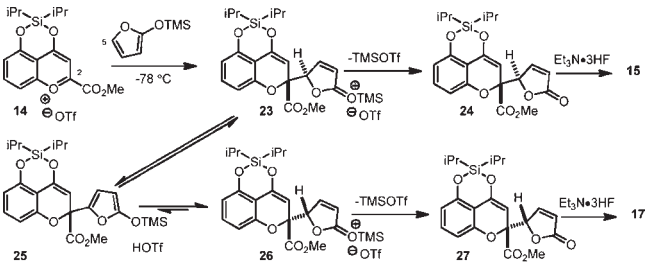


Figure 3. Composite surfaces of the B3LYP/6-31G(d) LUMO of **14** and HOMO of 2-trimethylsiloxyfuran mapped onto an electron density isosurface using Spartan '08. Reactive sites are shown in blue.

Scheme 2. Proposed Mechanism for Vinylogous Addition



found that treatment of **16** with NaOMe in THF[19] led to observable precipitation to a presumed dianion intermediate and formation of dihydro-2*H*-xanthenones **29** and **30** after workup. After evaluation of several bases, NaH was found to be superior to NaOMe, affording **29** in 67% yield (dr = 20:1 by ^{1}H NMR analysis). To evaluate the cyclization of the diastereomer of **16**, we subjected a 2:1 mixture of butenolides **17** and **15** 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 (Scheme 4). These studies support a mechanism for equilibration to favor the syn configuration of the hydroxyl group 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

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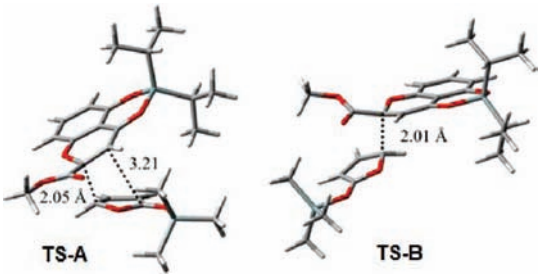
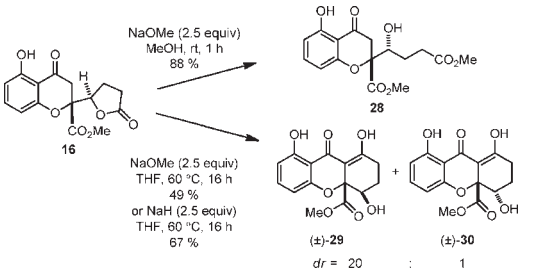
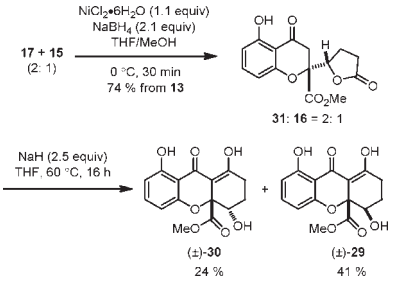


Figure 4. Lowest-energy transition state structures for *Re*−*Si* (**TS-A**) and *Re*−*Re* (**TS-B**) addition in the reaction of **14** and 2-trimethylsiloxyfuran.

Scheme 3. Dieckmann Cyclization



Scheme 4. Equilibration of Dieckmann Products

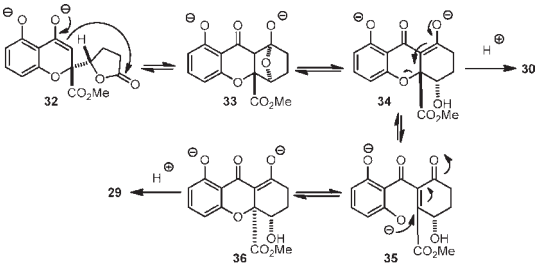


resulting dianion **34** (a precursor to **30**) may equilibrate by retro-Michael addition to **35**, which may be followed by oxa-Michael addition[7a,b] to provide diastereomer **36** and thence **29** after workup.

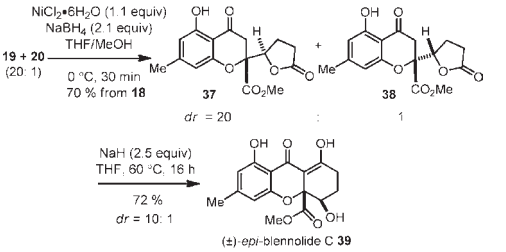
After completion of the model studies, we synthesized both (±)-*epi*-blennolide C (Scheme 6) and (±)-blennolide C (Scheme 7) from butenolides **19** and **20**. Conjugate reduction of a 20:1 mixture of **19** and **20** using NiB_2 led to chromone lactones **37** (dr = 20:1). Dieckmann cyclization of **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** and **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 the ester, hydroxyl, and methyl groups on the dihydro-2*H*-xanthenone core. Based on our model studies and the hypothesis that butenolide reduction should occur anti to the 5-substituent,[15] we initiated our synthesis from a 2:1 mixture of butenolides **21** and **22** (Table 1, entry 7). Nickel boride chemoselectively reduced the butenolide to afford a mixture of four chromone lactone diastereomers. Interestingly, when Rh/Al_2O_3 was used for the conjugate reduction,[21] we obtained **40** as a single diastereomer and the separable, overreduced hydroxyl chromone lactones **41** and **42** (Scheme 8).

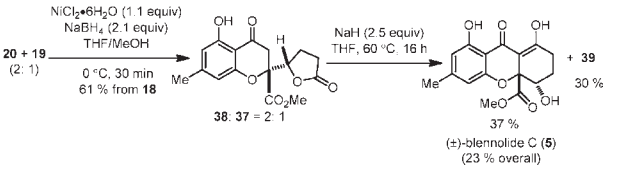
Scheme 5. Proposed Mechanism for Cyclization/Isomerization



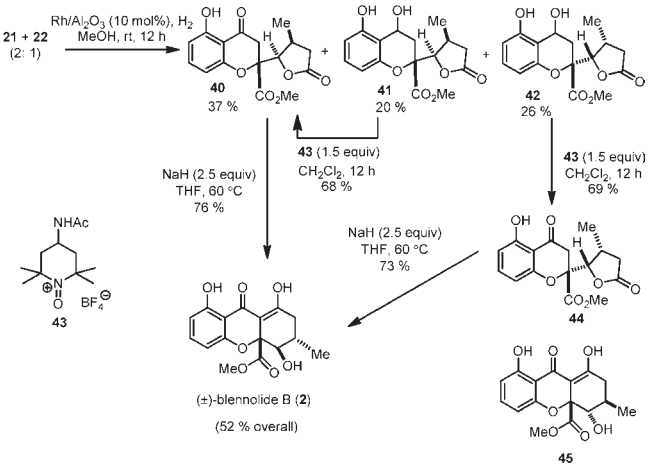
Scheme 6. Synthesis of (±)-*epi*-Blennolide C



Scheme 7. Synthesis of (±)-Blennolide C



Scheme 8. Synthesis of (±)-Blennolide B



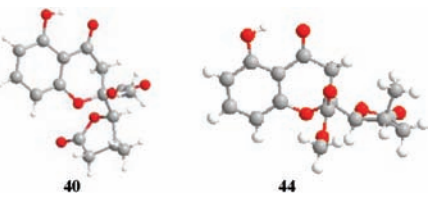


Figure 5. X-ray crystal structures of compounds **40** and **44**.

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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 stereochemistries of chromone lactones **40** and **44** were confirmed by X-ray crystal structure analyses (Figure 5). The 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 only negligible amounts of diastereomer **45** being observed in the crude ^{1}H NMR spectrum. This result further supports the isomerization process shown in Scheme 5 which 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 the vinylogous additions was probed using computational studies, which suggested the involvement of Diels−Alder-like transition states. With this methodology, the natural products (±)-blennolides B and C were synthesized in a maximum of four steps from readily available 5-hydroxychromones. Further studies, including the development of an asymmetric variant of the vinylogous addition, are currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental and computational details, complete ref 5a, and CIF files for **15**, **40**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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