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On the Origin of Siphonariid Polypropionates: Total Synthesis of Baconipyrone A, Baconipyrone C, and Siphonarin B via their Putative Common Precursor

Garrison E. Beye and Dale E. Ward*

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada

Received March 20, 2010; E-mail: dale.ward@usask.ca

Abstract: The hypothesis that siphonariid polypropionates originate from nonenzymatic processes on acyclic biosynthetic precursors was tested by examining the properties of the putative common precursor for the *S. zelandica* decapropionates siphonarin B, caloundrin B, baconipyrone A, and baconipyrone C, i.e., (4*S*,5*S*,6*S*,8*RS*,10*S*,11*S*,12*R*,14*R*)-14-(6-ethyl-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)-5,11-dihydroxy-4,6,8,10,12-pentamethylpentadecane-3,7,9,13-tetraone. The first synthesis of such a precursor was achieved in an efficient and fully enantioselective manner using a thiopyran-based strategy for polypropionate synthesis. This putative precursor, a complex mixture of ring−chain and keto−enol tautomers, was kinetically stable and isomerized exceedingly slowly to the thermodynamically more stable siphonarin B. In the presence of imidazole, the mixture reached apparent equilibrium within several hours giving siphonarin B as the predominant component (ca. 70%), thereby constituting its enantioselective total synthesis. In the presence of alumina, both siphonarin B and the dihydroxytetraone precursor underwent retro-Claisen rearrangements (via a hemiacetal tautomer) to give baconipyrones A and C among other products. This is the first total synthesis of baconipyrone A and "biomimetic" synthesis of baconipyrone C. Control experiments suggested that baconipyrone A was produced in an unprecedented cascade process where the intermediate enol(ate) of the retro-Claisen rearrangement was directly engaged in aldol cyclization while baconipyrone C resulted from simple ketonization of the enol(ate). These experiments provide the first unambiguous demonstration that the baconipyrones are plausible isolation artifacts and suggest they are most likely derived from siphonarins rather than an "acyclic" precursor. Caloundrin B was not detected among the products from any of the isomerization experiments, suggesting the possibility that it is an unstable biosynthetic product.

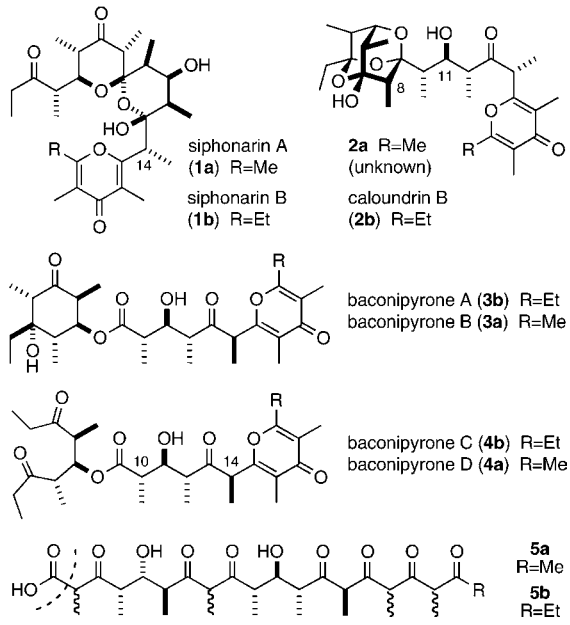
Introduction

Mollusks of the marine pulmonate genus *Siphonaria*, often referred to as false limpets, are air-breathing intertidal herbivores. Although a plethora of structurally diverse polypropionates have been isolated from extracts of siphonariids,[1] their role in the chemical ecology of these organisms is poorly understood. Indeed, the natural product status and relevance of the observed biological activities for many of the isolated compounds have been subjects of speculation for many years. In these cases, the reported structures are suggested to be isolation artifacts formed via nonenzymatic processes (e.g., cyclizations, dehydrations, retro-Claisen reactions, etc.) on unstable acyclic biosynthetic products.[1] For example, the siphonarins (**1**),[2,3] caloundrin B (**2b**),[4] and the baconipyrones (**3**, **4**)[5,6] have been isolated from extracts of *S. zelandica* (Chart 1).[7] It is noteworthy that the siphonarins and baconipyrones have identical absolute configurations at related centers, and the same configurations are presumed for caloundrin B. This relationship is consistent with the hypothesis that the structural isomers with R = Me (**1a**, **3a**, **4a**) and with R = Et (**1b**−**4b**) arise, possibly during isolation, via decarboxylaton and alternative cyclization/rearrangement cascades of the putative acyclic biosynthetic products **5a** and **5b**, respectively.[1,2b,4,5,8]

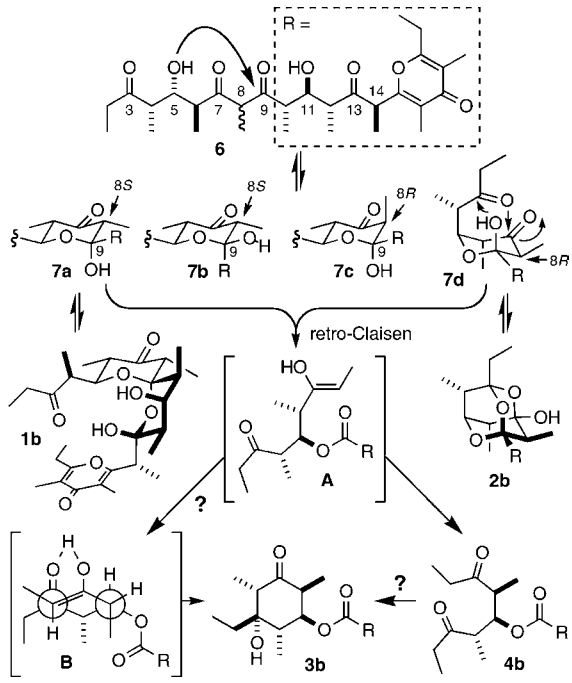
(1) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477–493.
(2) Isolation and structure: (a) Hochlowski, J.; Coll, J.; Faulkner, D. J.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748–6750. (b) Garson, M. J.; Jones, D. D.; Small, C. J.; Liang, J.; Clardy, J. *Tetrahedron Lett.* **1994**, *35*, 6921–6924. (c) For other reports of isolation, see refs 4, 5, and 10c.
(3) Total synthesis of **1b**: Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett.* **2002**, *4*, 391–394.
(4) Isolation and structure: Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. *Aust. J. Chem.* **1994**, *47*, 2255–2269.
(5) Isolation and structure: (a) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371–5374. Also see ref 10c.
(6) Total syntheses of **4b**: (a) Paterson, I.; Chen, D. Y.-K.; Acena, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513–1516. (b) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864. (c) Yadav, J. S.; Sathaiah, K.; Srinivas, R. *Tetrahedron* **2009**, *65*, 3545–3552.
(7) The baconipyrones were isolated from *S. baconi* (ref 5), a designation that is synonymous with *S. zelandica*: (a) Jenkins, B. W. *J. Malac. Soc. Aust.* **1983**, *6*, 1–35. For reports of isolation of these polypropionates from other siphonariid species, see ref 2 and: (b) Fu, X.; Zeng, L.; Su, J. *Zhongshan Daxue Xuebao, Ziran Kexueban* **1995**, *34*, 129−132; *Chem. Abstr.* **1996**, *124*, 51067.
(8) Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994**, *35*, 6929–6932.

10.1021/ja102356j

Chart 1. Polypropionates from *S. zelandica*



Scheme 1. Proposed Pathways for Formation of **1b**−**4b** from **6**



Given that spontaneous formation of 4-pyrones by dehydrative cyclization of 1,3,5-triones is unlikely to occur during isolation,[9] the above hypothesis is illustrated starting from the putative common precursor **6** (Scheme 1). The C-8 stereocenter in **6** is expected to be labile via keto−enol tautomerism of the 7,9-diketone. Of the numerous possible cyclization modes available to **6**, addition of the C-5 hydroxy group to the C-9 carbonyl produces up to four diastereomers of the hemiacetal **7**. The more stable anomer of the 8*S* diastereomers, **7a**, can cyclize directly to give siphonarin B (**1b**), while the less stable anomer of the 8*R* diastereomers, **7d**, can cyclize to give caloundrin B (**2b**). Alternatively, retro-Claisen rearrangement of any of the hemiacetal diastereomers **7** leads to baconipyrone C (**4b**) that can be converted to baconipyrone A (**3b**) via aldol cyclization. While plausible, these hypotheses have never been demonstrated experimentally and present several anomalies. If the cyclizations leading to **1b** and **2b** are thermodynamically driven nonenzymatic processes, as proposed,[1,8] then one would expect to find **1b** and **2b** together and in a ratio that reflects their relative stability. Thus, it is surprising that **1b** has been isolated several times from several sources,[2,7] but **2b** has been found only once.[4] Several "noncontiguous" polypropionate esters (e.g., **3** and **4**) have been isolated from marine sources, and these are generally suspected to be artifacts arising from retro-Claisen rearrangement of 2-hydroxydihydro-2*H*-pyran-4(3*H*)-ones (e.g., **7**).[1] Although similar transformations have been observed experimentally,[2a,3,10] the direct synthesis of a "natural product" via this process has been demonstrated only in a rather simple case.[10a] Moreover, **3b** was isolated as a single diastereomer whose formation from **4b** would require a diastereotopic group and face selective aldol reaction. It seems improbable that such a reaction would occur during isolation. Faulkner et al.[5] noted that the proposed retro-Claisen rearrangement of **7** might provide the required differentiation of the carbonyl groups via intermediate **A**, at least in a biosynthetic context. However, to the best of our knowledge, laboratory examples of such retro-Claisen/aldol cascades have not been reported. To address the above issues, we sought to prepare the putative common precursor **6** and examine its properties. Herein, we describe the first total synthesis of **6**, demonstrate its isomerization to **1b**, **3b**, and **4b**, and discuss the implication of our results on the possible origins of these sipnonariid polypropionates.

Results and Discussion

The total synthesis of **6** was expected to be challenging because, in addition to the stereochemical complexity, the embedded 5-hydroxy 3,7,9-trione moiety is known to be highly sensitive to acid and base, and the isomerization products **1b**−**4b** are also reported to be unstable. Thus, extrapolating from our earlier model study,[11] we planned to obtain **6** under mild conditions by unraveling the thermodynamically unstable 8*S*-epimer of **2b** (i.e., **8**) available via desulfurization of **9** (Scheme 2). The latter would result from acid-catalyzed deprotection and cyclization of **10** that, in turn, could be assembled from suitably protected derivatives of the known ketone **13**[12] and aldehyde **15**. A plausible path to **15** would involve annulation of the pyrone onto the known ketone **17**[12b] using the method[13] we recently developed for this purpose. In this thiopyran-based approach to polypropionate synthesis, it is noteworthy that 28 of the 29 carbons in **6** would originate from simple 3-carbon carboxylic acid derivatives (i.e., **21** and **22**) and that six of the seven stereocenters arise from highly enantioselective organo-

(9) (a) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619–5620. (b) Pratt, N. E.; Zhao, Y.; Hitchcock, S.; Albizati, K. F. *Synlett* **1991**, 361–363. (c) Arimoto, H.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 4581–4584.

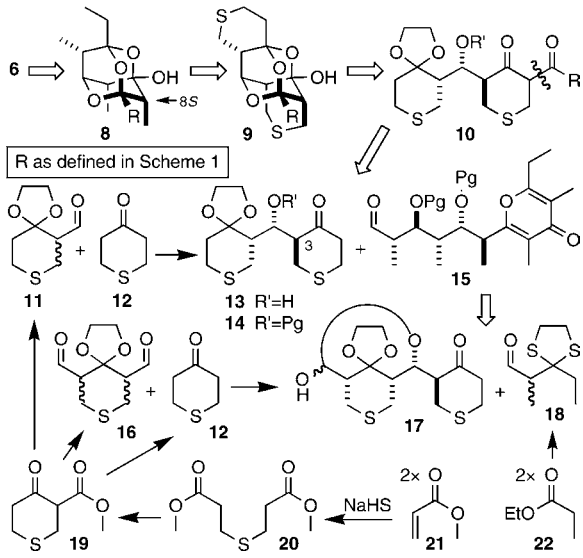
(10) (a) Hochlowski, J. E.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3838–3840. (b) Sundram, U. N.; Albizati, K. F. *Tetrahedron Lett.* **1992**, *33*, 437–440. (c) Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497–2502. (d) Lister, T.; Perkins, M. V. *Aust. J. Chem.* **2004**, *57*, 787–797. (e) Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827–1830.

(11) Beye, G. E.; Goodman, J. M.; Ward, D. E. *Org. Lett.* **2009**, *11*, 1373–1376.

(12) (a) Ward, D. E.; Jheengut, V.; Beye, G. E. *J. Org. Chem.* **2006**, *71*, 8989–8992. (b) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181–1184.

(13) The details of the development, scope, and limitations of this protocol will be reported separately.

Scheme 2. Retrosynthetic Analysis of **6**



catalyzed direct aldol reactions[12] of **12**[14] with racemic **11**[15] and meso/dl **16**,[12b] respectively.

Our synthesis commenced with the pivaloylation of **17** (92% ee)[12b] followed by Raney nickel desulfurization (Scheme 3). The latter occurred with partial reduction (<10%) of the ketone necessitating oxidation of the crude with 2-iodoxybenzoic acid (IBX) to obtain **23** as a 1:1 mixture of epimers in good yield. In a three-step sequence, the LDA-generated enolate of **23** reacted with (±)-**18**[16] and the resulting complicated mixture of aldols was oxidized with IBX in DMSO to give a mixture of diketones that was subjected to IBX and trifluoromethansulfonic acid (TfOH) in acetonitrile to the give the pyrone−dihydropyrone **24** in 62% yield from **23**. Although formation of the pyrone was expected from this sequence,[13] the facile elimination of the pivaloate and hydrolysis of the ketal were not anticipated. To take advantage of the transformation of **23** into **24** requires regeneration of the stereocenter at C-5″ that was lost as a consequence of the pivaloate elimination; however, stereoselective hydration of C-5 substituted 2*H*-pyran-4(3*H*)-ones (e.g., **24**) or analogous 3,4-dihydro-2*H*-pyran-4-ols (e.g., **25**) appears to be unprecedented.[17] Toward that end, stereoselective reduction (dr >20:1) of **24** followed by benzylation of the resulting alcohol gave **25b**. After considerable experimentation, **25b** was converted the desired **26a** (62%) along with the corresponding C-6′ epimer (16%) by adaptation of Piancatelli's oxymercuration protocol.[18] The C-3′ hydroxy group in **26a** was surprisingly[3] resistant to Et_3SiOTf in the presence of 2,6-lutidine, facilitating a simple "one pot" procedure for its selective protection as a methoxymethyl (MOM) ether. Oxidation of the resulting alcohol **26c** with IBX gave aldehyde **15a** in quantitative yield.

The C-6′ configuration in **26a** was assigned on the basis of the close correspondence of the ^{13}C NMR spectra of **26a** and the known[6] **26b** (Scheme 3). To verify that conclusion, **25c** was subjected to $Hg(OAc)_2/NaBH_4$ to obtain **26b** (51%) along with its C-6′ epimer (16%). The endgames for the three previous syntheses of baconipyrone C (**4b**) are identical and involve a two-step oxidation of **26b** to the corresponding ketoacid followed by esterification with **27** and deprotection of the PMB group.[6] To complete a formal synthesis of **4b** according to that route, we prepared **27** from **13**[12a] in a single step by Raney nickel desulfurization with an acidic workup. Our syntheses of **26b** and **27** (24 total steps; longest linear sequence: 14 steps, 7.8%) compare favorably with the others[6] in terms of the total number of steps, longest linear sequence, and overall efficiency.[16]

Aldol reaction of the Cl_3Ti enolate of **14a** (>98% ee)[12] with **15a** gave adduct **28** essentially as a single diastereomer presumably with the indicated configurations at C-3″ and C-7′ (Scheme 4). The stereoselectivities of similar aldol reactions under these conditions are largely governed by the diastereoface selectivities of the reactants with little preference for the relative topicity (i.e., no mismatched reaction).[19a] Additions to the enolate of **14a** are known[19] to occur selectively from the face *trans* to the C-3 substituent, and additions to aldehyde **15a** are expected[20] to be highly Felkin-selective due to the *anti* relative configuration of the α-methyl and *β*-*O*-benzyl substituents. Accordingly, aldol coupling of **14a** with **15a** is expected to give the 3″,5″-*trans*-7′,6′-*syn* adduct **28** selectively and requires *syn* relative topicity. IBX oxidation of **28** produced the corresponding dione (enol and *β*-diketone tautomers); however, despite considerable experimentation we were unable to induce its transformation to the desired trioxadithiapentacycle analogous to **9**.[11] Alternatively, desulfurization of **28** followed by $FeCl_3$-mediated[11,21] hydrolysis of the acetals provided **29a** in excellent yield. Selective protection of the C-5 alcohol in **29a** was required to advance to **6**, and this was achieved by treatment with Et_3SiOTf in the presence of 2,6-lutidine to give a 5:1 mixture of triethylsilyl (TES) ethers, **29c**, and presumably its 9-*O*-TES regioisomer, respectively (50%), along with the bis-TES derivative **29b** (10%) and recovered **29a** (35%). Because separation of the two mono-TES ethers was inefficient, the reaction was run to high conversion to deplete the minor isomer[22] and obtain **29c** conveniently and in serviceable yield (46%; 85% based on recovered **29a** obtained by deprotection of **29b**) along with **29b** (44%). Treatment of **29c** with IBX produced the tetraone **30a** that was a mixture of enol (ca. 25%) and *β*-diketone tautomers (ca. 75%; ca. a 6:1 mixture of diastereomers) by NMR in $CDCl_3$ solution. Sequential removal of the benzyl and silyl ethers in **30a** efficiently provided the desired **6** as a complex mixture of ring−chain and keto−enol tautomers. Careful analysis of the ^1H and ^{13}C NMR spectra of **6** in $CDCl_3$ suggested the presence of a 2:1:4 mixture of three major hemiacetal forms (OH signals at δ_H 6.46, 6.39, 6.19, respectively, and acetal carbons at δ_C 104.4, 104.6, 104.7, respectively; ca. 80% of the mixture) along with minor amounts

(14) Ward, D. E.; Rasheed, M. A.; Gillis, H. M.; Beye, G. E.; Jheengut, V.; Achonduh, G. T. *Synthesis* **2007**, 1584–1586.
(15) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618–1629.
(16) See the Supporting Information for details.
(17) For a multistep solution to this problem, see: Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862–867.
(18) (a) Bettelli, E.; Cherubini, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G. *Tetrahedron* **1998**, *54*, 6011–6018. (b) Passacantilli, P.; Centore, C.; Ciliberti, E.; Leonelli, F.; Piancatelli, G. *Eur. J. Org. Chem.* **2006**, 3097–3104.
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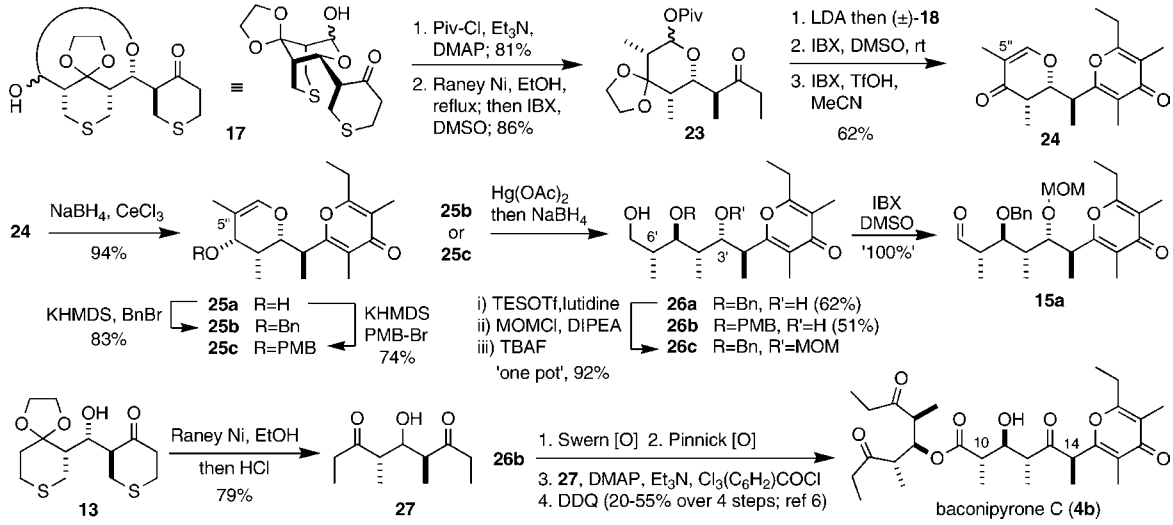
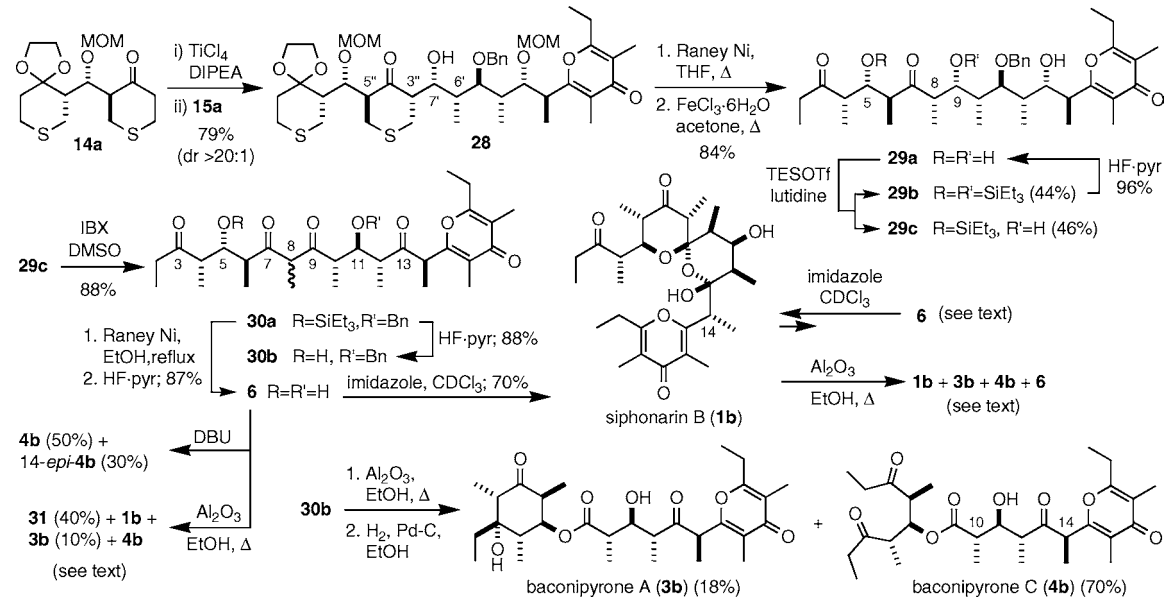
(20) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.
(21) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684–6686.
(22) The regioisomeric purity of products from a chemoselective reaction increases with conversion if the groups can react sequentially. For a discussion and analysis of this phenomenon, see: Ward, D. E.; Liu, Y.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429–1446.

Scheme 3. Synthesis of Aldehyde **15a** and Formal Synthesis of Baconipyrone C (**4b**)



Scheme 4. Synthesis of **6**, Siphonarin B (**1b**), Baconipyrone A (**3b**), and Baconipyrone C (**4b**)



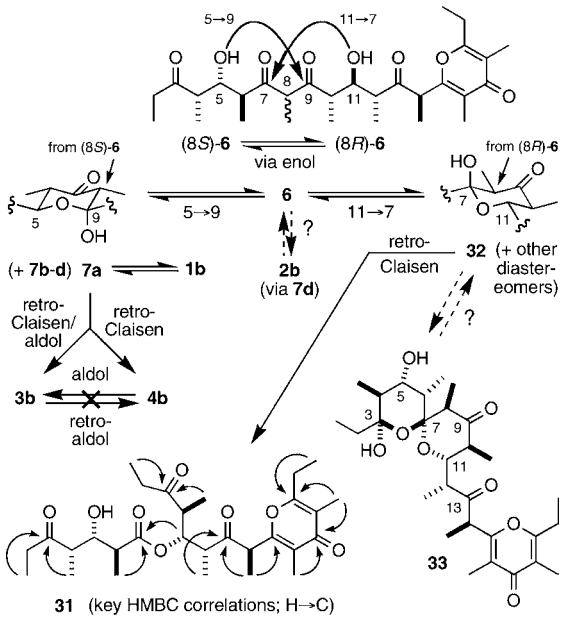
of other hemiacetals, enol (OH signal at δ_H 17.05), β-diketone tautomers (2 diastereomers; C-8 signals at δ_C 61.9, 61.1), and a trace of siphonarin B (**1b**) (OH signal at δ_H 5.12; ca. 2% of the mixture). We believe the major hemiacetals present include **7a** and **32** (vide infra). The ratio of tautomers remained essentially unchanged on standing in $CDCl_3$ solution at rt; after 28 days, the ratio of major hemiacetals was 2:1:3 and ca. 9% of **1b** was present.

The isomerization of **6** was examined under the conditions that proved efficacious in our model study (Scheme 4).[11] Treatment of **6** with HF·pyridine and pyridine in THF slowly produced siphonarin B (**1b**). After 16 h, a 2.5:1 ratio of **6** (mainly an ca. 2:1:3 mixture of 3 hemiacetals; 60% isolated) and **1b** (20% isolated), respectively, along with several unidentified byproducts were observed by ^{1}H NMR; however, the reaction was not clean, and prolonged reaction did not improve the isolated yield of **1b**. In the presence of imidazole, a solution of **6** in $CDCl_3$ (initially a 2:1:4 mixture of hemiacetal forms along with ca. 2% of **1b**) isomerized to siphonarin B (**1b**, ca. 70%), an unidentified product (OH signal at δ_H 5.01; ca. 10%), and **6** (as a 0.1:1.5:1 mixture of hemiacetals; ca. 20%) after 24 h (by ^{1}H NMR after work up), and siphonarin B (**1b**) was isolated in 70% yield from the mixture. This ratio of products appeared to represent equilibrium as a similar ratio was also observed after exposure of either **6** or **1b** to imidazole in $CDCl_3$ solution for 48 h. Interestingly, the ^{1}H NMR spectrum of a natural sample of **1b** suggests the presence of the same minor products as evidenced by observable signals at ca. 6.46, 6.39, 6.19, and 5.01 ppm.[23] Unfortunately, we were unable to isolate the product responsible for the ^{1}H NMR signal at δ_H 5.01 but suggest that it may be the alternative spiroacetal **33** (Scheme 5) or perhaps a diastereomer of **1b** (e.g., 14-*epi*-**1b**). We did not detect the presence of **2b** in any of the above experiments or similar ones conducted at 40 °C.[11]

Addition of DBU to a solution of **6** in C_6D_6 resulted in retro-Claisen rearrangement and produced a 2:1 mixture (by ^{1}H NMR) of baconipyrone C (**4b**; 50% isolated) and 14-*epi*-**4b** (30% isolated), respectively, within 1 h (Scheme 4). Other products

(23) This spectrum is included in the Supporting Information of ref 3.

Scheme 5. Revised Scheme for Isomerizations of **6** and **1b**



were not detected in the reaction mixture. Previous syntheses of **4b** have reported the formation of a minor diastereomer, suspected to be 14-*epi*-**4b**, originating during esterification[6a] of **27** or spontaneously[6b] from **4b**. Spectral data for our 14-*epi*-**4b** were distinct from those reported[24] previously. Two lines of evidence support our assignment. First, the most acidic proton in **4b** is expected to be HC-14 (vinylogous β-ketoester), and treatment of **4b** with DBU in C_6D_6 rapidly produces a mixture of **4b** and 14-*epi*-**4b**. Second, the ^{13}C NMR spectra of **4b** and 14-*epi*-**4b** are very similar, giving $\Delta\delta$'s of $\leq$0.2 ppm for 21 carbons; 0.5 ppm for 3 carbons; 0.8−1.2 ppm for C-10, C-11, C-12, and C-15; 2.5 ppm for C-14.[16] In contrast, comparison of the ^{13}C NMR spectra of **4b** and the diastereomer previously suspected as 14-*epi*-**4b** (assignments not available)[24] reveals at least seven carbons with $\Delta\delta$ >1.5 and significant differences in the chemical shifts for the methyl carbons. We suspect the latter diastereomer is 10-*epi*-**4b** considering that it originates during esterification (i.e., formed by enolization of the active ester or via the ketene); however, the available data are insufficient for an unambiguous assignment. Contrary to a previous report,[6b] we found **4b** to be stable (in solution or neat) for at least 2 months at room temperature.

In an effort to induce retro-Claisen rearrangement without concomitant epimerization, we treated **6** with neutral alumina[10b] in refluxing ethanol for 1 h to give a 10:3:7:5 mixture of **31** (40% isolated), **3b** (10% isolated), **4b**, and **1b**, respectively, by ^1H NMR (Scheme 4). The structure of **31** was determined by extensive 1D and 2D NMR experiments; all ^1H spin systems were identified and their connectivities established by the indicated HMBC correlations (Scheme 5). The relative and absolute configurations in **31** are assumed on the basis of the structure of **6**. The hypothesis outlined in Scheme 1 readily explains the formation of **1b**, **3b**, and **4b** from **6** (via **7a** or diastereomer). The concurrent formation of **31** must result from retro-Claisen rearrangement of the alternative hemiacetal **32** (or diastereomer). Subjecting siphonarin B (**1b**) to the identical conditions gave a 2.3:3:1:1 mixture of **1b**, **4b**, **3b**, and **6** (as a mixture of hemiacetals), respectively (by ^1H NMR), with little or no **31** present. Importantly, both baconipyrone A (**3b**) and baconipyrone C (**4b**) were stable to these conditions. These experiments suggest that both **3b** and **4b** are formed by an irreversible retro-Claisen rearrangement of **7**. Ketonization of the intermediate enol(ate) product (e.g., **A** in Scheme 1) produces **4b**, whereas as **3b** is formed in a retro-Claisen/aldol cascade where the enol(ate) product of the retro-Claisen rearrangement (e.g., **A** in Scheme 1) is directly engaged in the aldol cyclization. To the best of our knowledge, this is the first example of such a process. Reaction via intermediate enol **A** and transition-state model **B** accounts for the diastereotopic group and face selectivity of the aldol cyclization leading to **3b** (Scheme 1). The transition-state model **B** is analogous to the model proposed by Vogel et al.[25] for a closely related aldol cyclization via a Bu_3Sn enolate. The required (*Z*)-enol(ate) in **A** and **B** would result from retro-Claisen rearrangement of **7a**. These experiments provide the first unambiguous demonstrations of the hypotheses that the baconipyrone A (**3b**) and baconipyrone C (**4b**) can be isolation artifacts originating from retro-Claisen rearrangement of hemiacetal **7a** formed either by cyclization of the "acyclic" precursor **6** or by ring-opening of siphonarin B (**1b**). Interestingly, we could not find evidence for the presence of **2b** among the products from any of the above experiments.

It is reasonable to assume that **7a** and **32** are among the three major ring−chain tautomers of our synthetic **6** (Scheme 5). These hemiacetals should be similar in energy because they have identical relative and absolute configurations about their tetrahydropyrone rings and only relatively subtle differences in the nature of the substituents at C-5 and C-9 in **7a** vs those at C-11 and C-7 in **32**. In analogy with previous molecular modeling studies,[11] **7a** should be the most stable hemiacetal from (8*S*)-**6** and **31** the most stable hemiacetal from (8*R*)-**6** with the epimers **7c** and 8-*epi*-**32** expected to be 1−2 kcal/mol higher in energy. Although synthetic **6** initially existed in three major hemiacetal forms, only two of these are present to a significant degree after equilibration in the presence of imidazole. We believe the latter are the more stable hemiacetals **7a** and **32** with the kinetically stable but thermodynamically unstable third isomer initially present being either **7c** or 8-*epi*-**32**.[26] Under these conditions, **1b** emerges as the most stable tautomer along with minor amounts of **7a**, **32**, and a new isomer, possibly **33** resulting from cyclization of **32**. The concurrent formation of **1b**, **3b**, **4b**, and **31** on heating a solution of **6** (mainly as a mixture of hemiacetals **7a** and **32**) in the presence of alumina can be rationalized by assuming that retro-Claisen rearrangement of **32** is faster than its equilibration to **7a** and **1b**. The same assumption explains the formation of **3b** and **4b**, but not **31**, on reaction of **1b** under these conditions. Alternatively, reaction of **6** with DBU at ambient temperature produces **4b** and 14-*epi*-**4b** but not **31**, implying, in this case, that equilibration of **32** is faster than its retro-Claisen rearrangement.

We reasoned that using a derivative of **6** where the hydroxy group at C-11 was protected would facilitate selective formation of **2b** or **3b** and **4b**. Such derivatives cannot form a hemiacetal analogous to **32** and are not expected[3] to cyclize to a C-11-

(24) Chen, D. Y.-K. Ph.D. Thesis, University of Cambridge, Cambridge, U.K., 2002.

(25) Turks, M.; Murcia, M. C.; Scopelliti, R.; Vogel, P. *Org. Lett.* **2004**, *6*, 3031–3034.

(26) For a related hemiacetal that is kinetically stable (i.e., isolable) but thermodynamically unstable relative to other diastereomers, see compound **11** in: Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608–1610.

protected derivative of **1b**; with these forms removed from the equilibrium, it was hoped that the cyclization cascades could be directed toward C-11-protected derivatives of **2b** or **3b** and **4b**. The desired **30b** was readily obtained on treatment of **30a** with HF·pyridine (Scheme 4). Unfortunately, we were unable to detect the presence of the 11-OBn derivative of **2b** among the products obtained after exposure of **30b** to imidazole in $CDCl_3$. Surprisingly, **30b** was stable to neutral alumina in refluxing ethanol for 1 h; however, using basic alumina under the same conditions for 7 h cleanly produced a 4:1 mixture of retro-Claisen products that gave **3b** (18%) and **4b** (70%) after hydrogenolysis of the benzyl ether. Reaction of **4b** under the latter conditions produced 14-*epi*-**4b** (ca. 40%) but not **3b**.

Summary and Conclusions

In summary, we have achieved the first total synthesis of **6**, the putative common precursor of the siphonariid polypropionates siphonarin B (**1b**), caloundrin B (**2b**), baconipyrone A (**3b**), and baconipyrone C (**4b**). The fully enantioselective synthetic route highlights the power and versatility of our thiopyran-based strategy. The synthesis proceeds in only 20 total steps (longest linear sequence: 18 steps, 3.1%) by convergent aldol coupling of the readily available simple precursors (±)-**11**, **12** (×2), (*meso/dl*)-**16**, and (±)-**18**. Enantioselective organocatalyzed direct aldol reactions of **12** with (±)-**11** and with (*meso/dl*)-**16**, processes that proceed with dynamic kinetic resolution, generate five of the seven stereocenters in **6** (C-4, 5, 6, 12, 14; dr >20:1).[12] The remaining two stereocenters result from substrate-controlled carbonyl reduction (C-11; dr >20:1) and an unusual enol ether oxymercuration/reductive demercuration (C-10; dr 3.5:1). It is noteworthy that 28 of the 29 carbons in **6** originate from methyl acrylate or ethyl propanoate.

Synthetic **6** initially exists as complex mixture of ring−chain and keto−enol tautomers; however, the three hemiacetal forms **7a**, **32**, and either **7c** or 8-*epi*-**32** predominate. These hemiacetals show remarkable kinetic stability (i.e., unchanged on SiO_2 chromatography, on storage, and in $CDCl_3$ solution for weeks) with exceedingly slow accumulation of the thermodynamically more stable **1b**. However, in the presence of imidazole, equilibration occurs within several hours giving **1b** (70% isolated) and three significant minor tautomers (**7a**, **32**, and perhaps **33**) along with lesser amounts of other forms. A similar mixture was obtained from **1b** in the presence of imidazole and the same set of minor tautomers appear to be present as impurities in the ^{1}H NMR spectrum of a natural sample of **1b**.[23] This constitutes the first enantioselective total synthesis of siphonarin B (**1b**) (cf. Paterson's[3] seminal diastereoselective synthesis).[16] Exposure of **1b** to neutral alumina in refluxing ethanol produced a mixture of **1b**, **3b**, **4b**, and **6**. Reaction of **6** under identical conditions gave a similar mixture in addition to **31** as the major product. These experiments clearly demonstrate that the baconipyrones are easily derived from **1b** or **6** under conditions that make them plausible isolation artifacts. Importantly, **3b** and **4b** do not interconvert under these conditions. These results suggests that **3b** is formed from **7a** in an unprecedented retro-Claisen/aldol cascade with the intermediates **A** and **B** accounting for the observed stereoselectivity, whereas **4b** results from ketonization of intermediate **A** (Scheme 1). The synthetic efficiency for production of **3b** and **4b** was substantially enhanced by executing the same chemistry on the 11-*O*-benzyl derivative **30b** followed by removal of the protecting group. This retro-Claisen synthetic route approach ("biomimetic") to baconipyrone C (**4b**) is necessarily less convergent than the previous approaches based on esterification.[6] Although the route is less efficient than Paterson's[6a] very concise synthesis of **4b** (and our own formal synthesis, vide supra), it compares favorably with the Hoveda[6b] and Yadav[6c] approaches.[16] The same route constitutes the first total synthesis of baconipyrone A (**3b**) (Scheme 4).

The ring−chain tautomerization of **6** is reversible, but retro-Claisen rearrangements are irreversible, at least under the conditions we examined.[27] Thus, the set of polypropionates **1b**−**4b** isolated from *S. zelandica* could, in principle, originate from an "acyclic" precursor like **6** or any of its ring−chain tautomers (e.g., **1b**, **2b**, **7**, etc.). The putative common precursor **6** readily forms hemiacetals **7a** and **32** that are stable to chromatography and undergo retro-Claisen rearrangement with similar propensity, but neither **7a**, **31**, **32**, nor 14-*epi*-**4b** have ever been found in siphonariid extracts. Therefore, if the baconipyrones are isolation artifacts, it is more likely that they are derived from the siphonarins rather than from an "acyclic" precursor like **6**. Similarly, if an incompletely folded precursor like **6** or **7** is the actual biosynthetic product, then we presume that it must have equilibrated (with or without catalysis) to the thermodynamically more stable **1b** prior to isolation. Alternatively, **1b** could be the biosynthetic product; it is commonly found in sipohanriid extracts and the above experiments establish that the **3b** and **4b** could be obtained as isolation artifacts from **1b**. However, the origin of caloundrin B (**2b**) remains a missing piece of the puzzle. We were unable to detect **2b** among the products of isomerization of **1b** or **6** under a variety of conditions. These results suggest that either **2b** is much less stable that **1b** or the energy barrier to reach **2b** is very high. Either scenario seriously challenges the hypothesis that **2b** is an artifact of isolation. It is plausible that **2b** is an unstable biosynthetic product from which the formation of **1b**, **3b**, and **4b** could be readily explained (Scheme 5). To explore that issue, we are currently pursuing the synthesis of **2b** by a different route, and our results will be reported in due course.

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Note Added after ASAP Publication. The structure of compound **28** in Scheme 4 was corrected on May 19, 2010.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all reported compounds; comparison of NMR data for natural and synthetic material; comparison of synthetic routes to **1b**, **3b**, and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) For an exception, see ref 10e.