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Total Synthesis of Siphonarin B and Dihydrosiphonarin B

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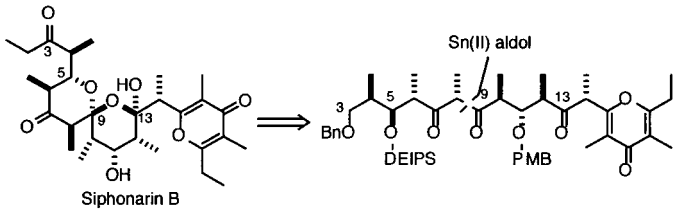
ABSTRACT



The spirocyclic core of the siphonarins was constructed by a directed cyclization of a linear triketone, prepared using a Sn(II)-mediated aldol coupling and Swern oxidation at C9 and C13. To circumvent a facile retro-Claisen pathway generating a baconipyrone-type ester, a Ni(II)/Cr(II)-mediated coupling reaction with vinyl iodide was used to complete the first synthesis of siphonarin B and dihydrosiphonarin B. A stable isomeric spiroacetal was also prepared which could not be equilibrated to the siphonarin skeleton.

Siphonarins A (**1**) and B (**2**) are unusual γ-pyrone polypropionates,[1−3] containing a characteristic spiroacetal ring system, which were first isolated by Faulkner and Ireland and their co-workers[2a] from the marine molluscs, *Siphonaria zelandica* and *S. atra*, collected on the coast of New South Wales, Australia, while the C3 dihydro congeners **3** and **4** were obtained from a siphonariid collection made in Hawaii. Their highly substituted spiro-bis-acetal core is proposed to be determined by the oxidation state of the carbons and the configuration of the hydroxyl- and methyl-bearing stereocenters in an unstable linear polyketide-derived precursor, such as **5**, that participates in a thermodynamically driven cyclization cascade.[3,4]

As part of studies on these and related siphonariid-derived polypropionates,[2c,5,6] we have previously synthesized baconipyrone C (**6**),[5a,7] which lacks a normal contiguous carbon skeleton. By controlling the cyclization mode of an open-chain precursor, we now report the first total synthesis of siphonarin B (**2**) and dihydrosiphonarin B (**4**), as well as the formation of a stable isomeric spiroacetal ring system, along with experimental support for the occurrence of a retro-Claisen reaction leading to baconipyrone-type structures under mild conditions.

As outlined in Scheme 1, unravelling of the spirocyclic core of siphonarin B (**2**) suggested the triketones **7** (C1−C21) and **8** (C3−C21) as protected acyclic precursors. For synthetic purposes, the introduction of the elaborate oxy-

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(3) For modeling studies supporting this proposal, see: Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994**, *35*, 6929.

(4) An alternative cyclization mode is available to 8-*epi*-**5** to produce the trioxaadamantyl ring system of caloundrin B (**28**, Scheme 3). Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. *Aust. J. Chem.* **1994**, *47*, 2255.

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(6) For recent synthetic work on other siphonariid-derived compounds, see: (a) Perkins, M. V.; Sampson, R. A. *Org. Lett*. **2001**, *3*, 123. (b) Arjona, O.; Menchaca, R.; Plumet, J. *Org. Lett*. **2001**, *3*, 107. (c) DeBrabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169. (d) Yamamura, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025. (e) Hoffmann, R. W.; Dahmann, G. *Liebigs Ann. Chem.* **1994**, 837. (f) Andersen, M. W.; Hildebrandt, B.; Dahmann, G.; Hoffmann, R. W. *Chem. Ber.* **1991**, *124*, 2127.

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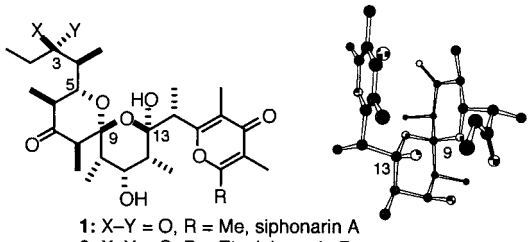
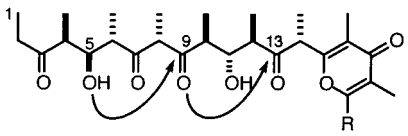
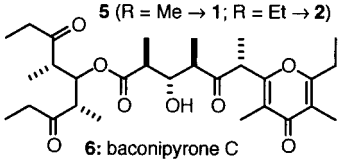


1: X–Y = O, R = Me, siphonarin A
2: X–Y = O, R = Et, siphonarin B
3: X = OH, Y = H, R = Me, dihydrosiphonarin A
4: X = OH, Y = H, R = Et, dihydrosiphonarin B



5 (R = Me → **1**; R = Et → **2**)

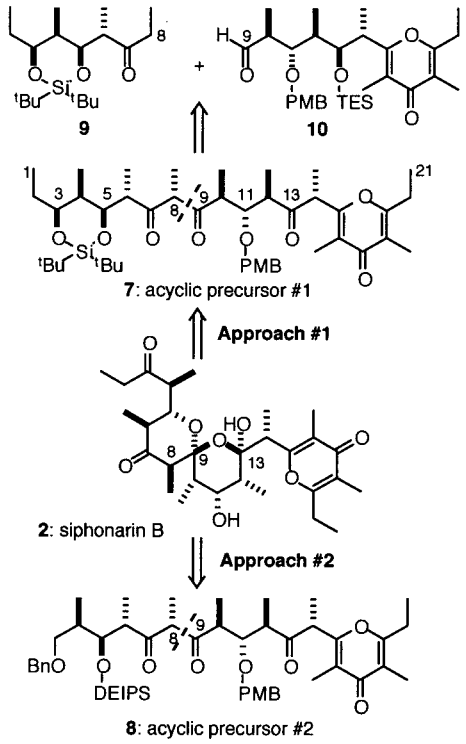


6: baconipyrone C

genation and methylation pattern, together with avoiding alternative modes of cyclization, were challenging and required the careful selection of protecting groups and oxidation conditions throughout. The readily epimerizable C8 and C14 stereocenters were also of concern.

Inspired by our earlier denticulatin synthesis,[5b] the 7,9,13-triketone **7**, incorporating a silylene-protected 3,5-diol and a PMB-protected 11-OH, was selected initially as a potential cyclization precursor. We envisaged a C8−C9 aldol coupling between ketone **9** and aldehyde **10**, followed by oxidation of the 9-OH and 13-OH and then release of the 5-OH to initiate a cyclization cascade to deliver the spiro-bis-acetal ring system.

Scheme 1



The preparation of ketone **9** (Scheme 2) began with an asymmetric aldol reaction between 3-pentanone and (*E*)-2-methyl-2-pentenal using (−)-Ipc$_2$BOTf.[8] Narasaka-type reduction[9] of the resulting adduct **11** (^{n}Bu$_2$BOMe; LiBH$_4$) gave 1,3-*syn* diol **12** (52%, ≥97:3 ds, 90% ee). Following silyl protection, hydroboration[10] of the allylic ether with thexylborane (90:10 ds), and then Dess−Martin oxidation, gave ketone **9** (67%). The aldehyde component **10** was obtained in 89% yield from the diol **13**,[2c,5a] having the γ-pyrone ring already installed, by a sequence of bis-TES protection, selective cleavage, and Dess−Martin oxidation.

The key aldol coupling between **9** and **10** was best performed using Sn(OTf)$_2$/Et$_3$N,[11] leading to a mixture of adducts **14** (94%; ca. 60:40 ds in favor of the 6,8-*syn*-8,9-*syn* isomer). After separation of the major *syn* isomer, selective cleavage of the TES ether, followed by careful Swern oxidation to preserve the C8 configuration,[5b] gave the triketone **7** (74%). Exposure to buffered HF·py deprotection then induced cyclization. However, rather than the required spirocyclization, hemiacetal formation between the 3-OH and C7 ketone gave **15** (69%). Oxidative removal of the PMB ether (DDQ) then led to the spiroacetal **16** (56%) engaging the 11-OH, accompanied by epimerization at C8. Notably, this acetal ring system (assigned by extensive NMR analysis and diagnostic NOE correlations) is stabilized by a double anomeric effect, as well as having all but one of the alkyl substituents in equatorial positions. Despite numerous attempts, using a variety of acidic conditions, spiroacetal **16** could not be isomerized to generate 3-*epi*-dihydrosiphonarin B (**17**). After succumbing to this alternative thermodynamically favored cyclization mode, a revised strategy using the modified acyclic precursor **8** shown in Scheme 1 was adopted. This now employed orthogonal protection, with DEIPS and benzyl ethers at C5 and C3, respectively, and required the late introduction of the terminal ethyl group.

As shown in Scheme 3, assembly of **8** was initiated by preparation of ketone **18** and aldehyde **19**, having a labile TMS ether at C13, enabling later discrimination from the C5 DEIPS ether. Here, a boron-mediated aldol reaction ((*c*-Hex)$_2$BCl, Et$_3$N) between (*R*)-**20**[12] and propionaldehyde, with in situ reduction (LiBH$_4$),[5b] gave 1,3-diol **21** cleanly (86%; >95:5 ds). Bis-DEIPS protection, followed by hydrolysis of the less hindered silyl ether, released the 7-OH, which was oxidized to give ketone **18** (49%). Similarly, bis-TMS protection of the previously described diol **13**,[5a] followed by selective cleavage of the primary TMS ether (K$_2$CO$_3$, MeOH) and buffered Dess−Martin oxidation, gave the

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(10) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.
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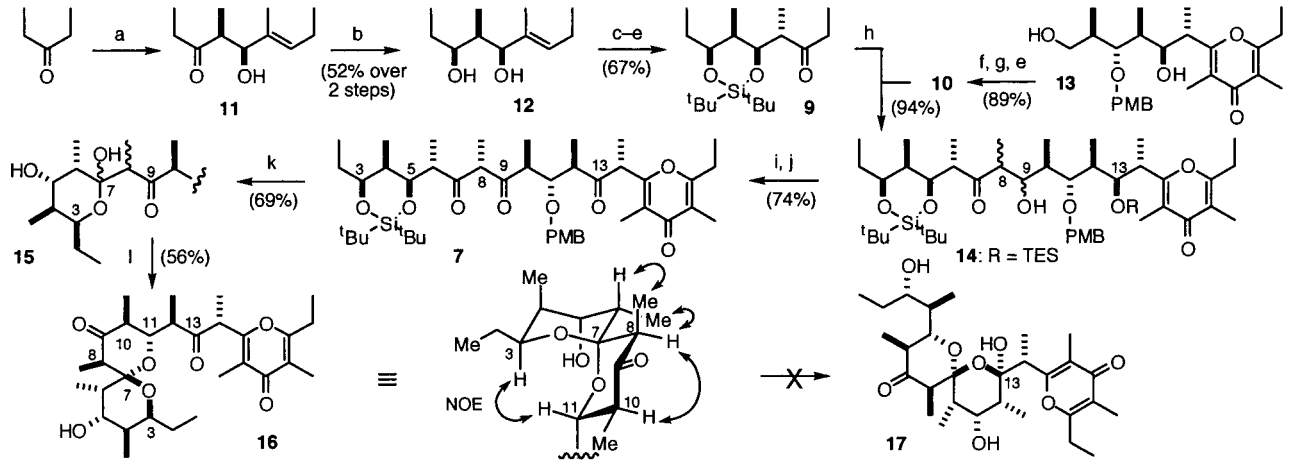
(12) (a) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.
(13) The configuration was determined by NMR analysis of the derived PMP acetal obtained on exposure of **22** to anhydrous DDQ.

Scheme 2

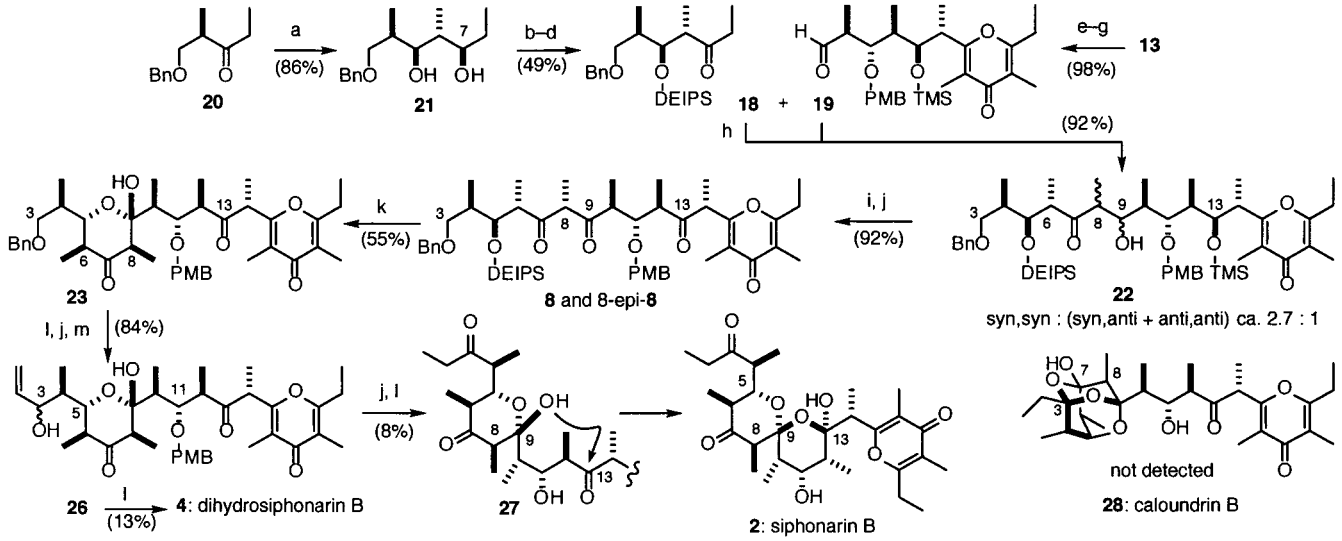


[a] (−)-Ipc$_2$BOTf, ^{i}Pr$_2$NEt, CH_2Cl_2. [b] ^{n}Bu$_2$BOMe, THF/MeOH; $LiBH_4$. [c] ^{t}Bu$_2$Si(OTf)$_2$, 2,6-lutidine, CH_2Cl_2. [d] Thexylborane, THF; H_2O_2, NaOH. [e] Dess−Martin periodinane, CH_2Cl_2. [f] TESOTf, 2,6-lutidine, CH_2Cl_2. [g] AcOH/THF/H_2O. [h] $Sn(OTf)_2$, Et_3N, CH_2Cl_2. [i] PPTS, MeOH/CH_2Cl_2. [j] $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N. [k] HF·py/py, THF. [l] DDQ, CH_2Cl_2/pH 7 buffer.

γ-pyrone aldehyde **19** (98%). This was immediately subjected to reaction with the Sn(II) enolate[11] derived from ketone **18** to give a mixture of aldol adducts **22** (92%; ca. 73:27 ds in favor of the 6,8-*syn*-8,9-*syn* isomer[13]). Selective deprotection of the TMS ether (PPTS, MeOH/CH_2Cl_2), followed by double Swern oxidation, then gave the sensitive triketone **8** (and its C8 epimer, ca. 2.7:1; 92%). In this case, desilylation (HF·py/py) led to the formation of the required six-membered hemiacetal ring **23** (55%), having all alkyl substituents equatorially oriented (where an NOE correlation between H6 and H8 indicated that the major C8 configuration had been preserved).

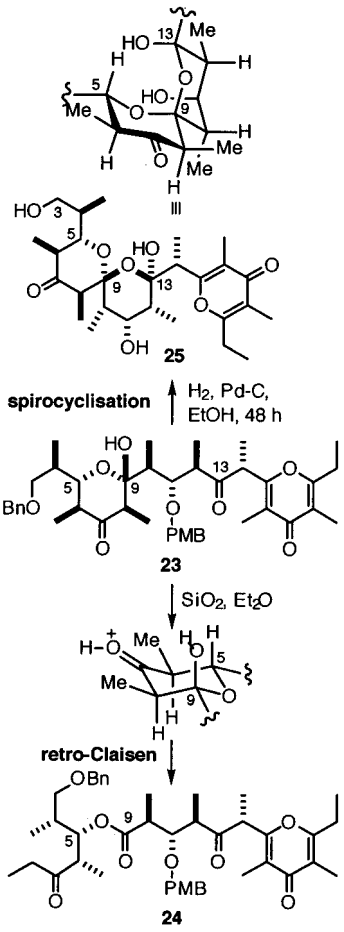
With hemiacetal **23** in hand, attention was now focused on generating the spirocyclic core of the siphonarins. However, exposure of the delicate hemiacetal **23** to mildly acidic (e.g., extensive SiO_2 chromatography) or basic conditions resulted in a facile retro-Claisen reaction, producing the baconipyrone-type ester **24** (Scheme 4), which had a diagnostic resonance for H5 (5.35 ppm, dd, J = 8.3, 3.4 Hz). A similar rearrangement has been proposed by Faulkner[7] for the biosynthetic interconversion of the siphonarins and baconipyrones. The present finding suggests that this could easily occur on chromatographic purification, lending support

Scheme 3



[a] (c-Hex)$_2$BCl, Et_3N, Et_2O, EtCHO; $LiBH_4$. [b] DEIPSCl, Imidazole, DMF. [c] PPTS, MeOH/CH_2Cl_2. [d] Dess−Martin periodinane, CH_2Cl_2. [e] TMSOTf, 2,6-lutidine, CH_2Cl_2. [f] K_2CO_3, MeOH. [g] Dess−Martin periodinane, py, CH_2Cl_2. [h] $Sn(OTf)_2$, Et_3N, CH_2Cl_2. [i] PPTS, MeOH/CH_2Cl_2. [j] $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N. [k] HF·py/py, THF. [l] Pd/C, H_2, EtOH. [m] $NiCl_2/CrCl_2$ (5% $NiCl_2$), $H_2C{=}CHI$, DMF.

Scheme 4



to the suggestion by Garson that the baconipyrones may be isolation artifacts.[1a,14]

While hemiacetal **23** resisted all attempts at further cyclization due to this competing retro-Claisen pathway, hydrogenolysis of the benzyl and PMB ethers (H_2, Pd/C, EtOH, 48 h) led to isolation of the desired thermodynamically favorable spiro-bis-acetal core **25** (32%), where all the alkyl substituents are equatorially oriented with anomeric stabilization at the C9 and C13 acetal centers. Recognizing that mild reaction conditions and workup procedures (with minimal chromatography) were crucial for the remainder of the synthesis, this observation suggested that reductive removal of the PMB ether might be used in the last step as a convenient trigger for the spirocyclization.

Thus debenzylation of hemiacetal **23** under controlled conditions (H_2, Pd/C, EtOH, 30 min) with retention of the PMB ether (Scheme 3), followed by Swern oxidation of the resulting primary alcohol (the 5-OH is internally protected here as a hemiacetal),[5c] gave a labile aldehyde that was immediately subjected to Kishi−Nozaki[15] coupling conditions ($CrCl_2$, 5% $NiCl_2$, DMF) with vinyl iodide, leading to an ca. 2.5:1 mixture of allylic alcohols **26** in 84% yield. Notably, attempted addition of more common organometallic reagents (EtMgBr, EtLi. Et_2CuLi, etc.) led only to decomposition by the retro-Claisen pathway, emphasizing the mildness of the Ni(II)/Cr(II)-mediated protocol.

A further Swern oxidation performed on **26** then gave the corresponding enone, which was submitted to catalytic hydrogenation (H_2, Pd/C, EtOH, 16 h) to provide the ethyl group with concomitant removal of the PMB ether. Gratifyingly, this final step also triggered the desired spirocyclization through hemiacetalization between the 9-OH and the C13 ketone in **27**, leading to isolation of (+)-siphonarin B (**2**).[16] The spectroscopic data (^1H, ^{13}C, IR, HRMS) and specific rotation, $[\alpha]^{20}_D$ +10.5 (*c* 0.12, $CHCl_3$), were in excellent agreement with that reported[2a] for the natural material ($[\alpha]^{20}_D$ +13.2 (*c* = 0.014, $CHCl_3$) and by NMR comparison with an authentic sample, thus confirming the absolute configuration.[2b,c] Notably, we did not detect any formation of caloundrin B (**28**), an isomeric siphonariid-derived compound that might have been produced by an alternative cyclization mode via 8-*epi*-**27**.[4] Similarly, dihydrosiphonarin B (**4**) could also be obtained by catalytic hydrogenation of the major epimer at C3 in **26** and this had spectroscopic data in accord with that reported.[2a,16]

In conclusion, the first total synthesis of the unusual marine polypropionates siphonarin B (**2**) and dihydrosiphonarin B (**4**) has been accomplished.[17] The successful generation of the highly substituted spiro-bis-acetal core of the siphonarins from the acyclic triketone precursor **8** required the careful orchestration of delicate intermediates. In contrast, the more elaborate precursor **7** was easily converted into a particularly stable spiroacetal ring system **16** that resisted isomerization into the siphonarin skeleton. Conceivably, this novel ring system might even be found in siphonariid-derived extracts.[4] In general, these findings lend support to the proposal that such siphonariid-derived compounds are thermodynamic, i.e., non-enzymic, cyclization products of unstable acyclic polypropionate metabolites.[1a,3,4,5b,14]

Acknowledgment. We thank the EPSRC, the Cambridge Commonwealth Trust, the Sim Foundation, King's and Corpus Christi Colleges, Merck, and Pfizer for support. We are grateful to Dr. José Luis Aceña (Cambridge) and Dr. Mary J. Garson (Queensland) for helpful discussions and to Dr Garson for kindly providing us with an authentic sample of siphonarin B.

Supporting Information Available: Tabulated NMR and spectroscopic data for compounds **2**, **4**, and **16**, along with spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) A reexamination of *S. baconi*, as reported by Garson (ref 1a), failed to detect any baconipyrones, such that they may conceivably be artifacts of the isolation process rather than biosynthetically related metabolites to the siphonarins. See also: Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497.

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(16) Due to the small quantity of dihydrosiphonarin prepared, an accurate specific rotation could not be measured.

(17) Siphonarin B (**2**) was obtained in 25 steps (0.9% overall yield) from (*S*)-3-(benzyloxy)-2-methylpropanal (ref 5a). The low yield obtained for the final step is due to competing decomposition encountered under the prolonged reaction time (16 h) needed to remove the PMB ether.