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Studies in Marine Polypropionate Synthesis: Total Synthesis of (–)-Baconipyrone C

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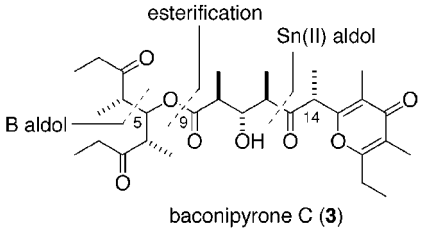
ABSTRACT

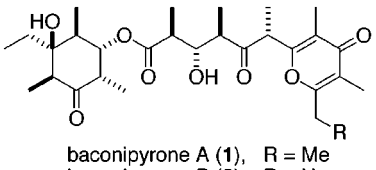


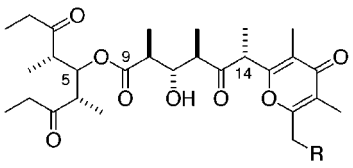
An asymmetric total synthesis of the unusual siphonariid metabolite, (–)-baconipyrone C (3), is described. Key steps included a tin(II)-mediated aldol coupling for the preparation of the carboxylic acid 17 and two different boron-mediated aldol additions leading to alcohol 8. Ester formation using modified Yamaguchi conditions gave 24, leading on PMB deprotection to (–)-baconipyrone C.

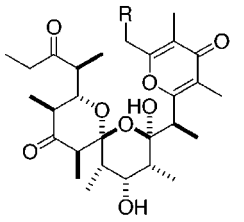
Siphonariids are pulmonate molluscs of the genus *Siphonaria*, which may represent an evolutionary link between marine and terrestrial gastropods. A diverse range of polyketides[1] have been isolated from siphonariids, and these appear to share a common biosynthetic origin to macrolide and polyether antibiotics.[2,3]

In 1989, Faulkner and co-workers reported the isolation of baconipyrones A−D (**1**−**4**) from *Siphonaria baconi* collected from intertidal rock platforms near Melbourne, Australia.[4] The structure of baconipyrone B (**2**) was established by X-ray analysis, while the structures of the other baconipyrones were determined by comparison of spectral data. The full absolute stereochemistry was not assigned.

The baconipyrones all contain a tetrasubstituted γ-pyrone with a characteristic polypropionate side chain. In contrast to other siphonariid metabolites, however, they do not contain a contiguous carbon skeleton as would be expected from regular polyketide biosynthesis. In baconipyrones A (**1**) and B (**2**), the γ-pyrone moiety is connected through an ester







linkage to a highly substituted β-hydroxy cyclohexanone, whereas in baconipyrones C (**3**) and D (**4**), it is connected through an ester to an acyclic β-hydroxy 1,5-diketone. It

(1) For recent reviews, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75. (b) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477.

(2) Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994**, *35*, 6929.

(3) (a) O'Hagan, D. *Nat. Prod. Rep.* **1989**, *6*, 205. (b) O'Hagan, D. *The Polyketide Metabolites*; Horwood, Chichester, 1991.

(4) Manker, C. D.; Faulkner, D. J.; Stout, J. T.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371.

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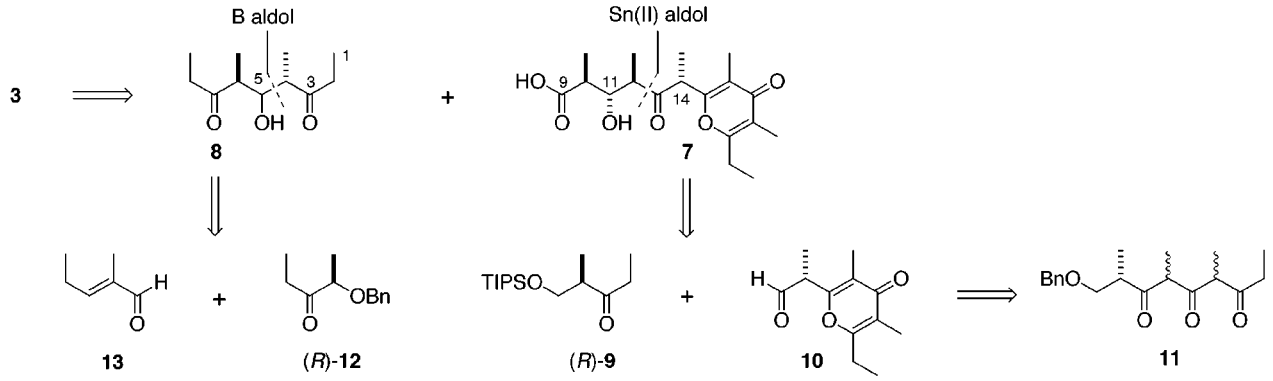
Scheme 1

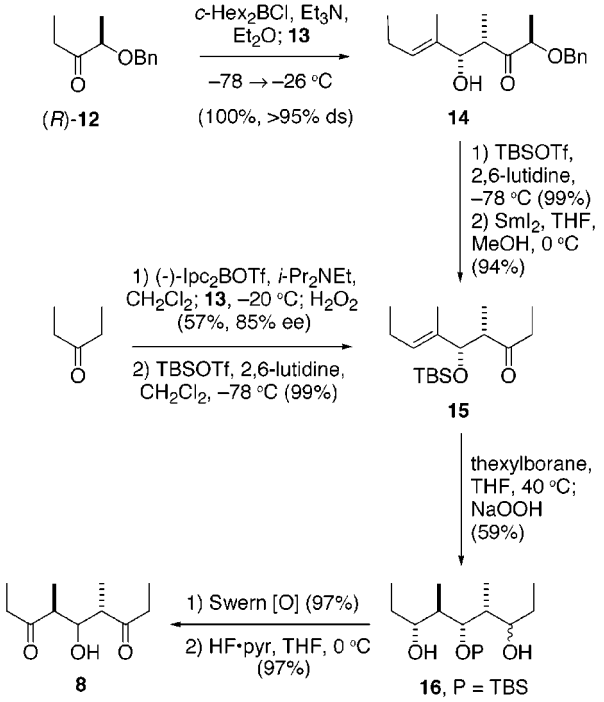


appears that **1** and **2** may be derived from **3** and **4**, respectively, by means of an aldol-type cyclization. A biosynthetic link with the structurally related siphonarins A (**5**) and B (**6**),[5a] which contain a spiroacetal moeity, has also been proposed.[4,5b] As part of our studies in the synthesis of such marine polypropionates,[6] we now report the first total synthesis of (−)-baconipyrone C (**3**), which also serves to firmly establish its absolute stereochemistry.

As outlined retrosynthetically in Scheme 1, disconnection of the ester linkage in **3** reveals the γ-pyrone carboxylic acid **7** and the C_2-symmetrical alcohol **8**. The antipode of acid **7** was previously synthesized in the course of investigations into the full stereostructures of the siphonarins and baconipyrones.[7] The key step in the preparation of the γ-pyrone-containing fragment **7** would be a syn aldol reaction between ketone (*R*)-**9** and aldehyde **10**, where the latter would be accessed via cyclization of the corresponding triketone **11**. The preparation of the alcohol **8** was envisaged using our boron-mediated, asymmetric aldol methodology from the ketone (*R*)-**12** and the commercially available (*E*)-2-methyl-2-pentenal (**13**).

As shown in Scheme 2, the synthesis of the C_2-symmetrical 1,5-diketone **8** began with a syn aldol reaction between the lactate-derived[8] ketone (*R*)-**12** and the enal **13**. Using our standard enolization conditions with $(c\text{-}C_6H_{11})_2BCl$ and Et_3N in Et_2O,[8a] the desired aldol adduct **14** was obtained with greater than 95% diastereoselectivity. Silyl protection (TBSOTf) of **14**, followed by reductive removal[8b,9] of the α-benzyloxy substituent using SmI_2, gave enantiopure ethyl ketone **15** in 88% overall yield. In this way, the ketone

Scheme 2



12 functions as an equivalent of 3-pentanone for performing asymmetric aldol reactions.

The syn-configured ketone **15** could also be accessed more rapidly (albeit in lower enantiomeric purity) by a reagent-controlled, asymmetric aldol reaction of 3-pentanone itself. Thus, an (−)-Ipc_2BOTf-mediated aldol reaction[10] with aldehyde **13**, followed by silyl protection, gave **15** in 85% ee and 56% yield. The remaining methyl-bearing stereocenter was introduced by hydroboration of the trisubstituted alkene in **15** using thexylborane.[11] This occurred with greater than 95% facial selectivity and concomitant reduction of the carbonyl group, giving the diols **16** (59%). Careful Swern oxidation[12,13] of **16**, followed by deprotection of the TBS ether, then completed the synthesis of **8** in 94% yield.

(5) (a) Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Zheng, Q.-T.; He, C.-H.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748. (b) A reexamination of *S. baconi*, as reported by Garson (ref 1b), failed to detect any baconipyrones, such that they may conceivably be artifacts of the isolation process rather than biosynthetically related metabolites to the siphonarins. This may also hold for other polypropionates obtained from siphonariids, as with muamvatin (ref 6b) and the denticulatins (ref 6c).

(6) (a) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801. (b) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608. (c) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811.

(7) Paterson, I.; Franklin, A. S. *Tetrahedron Lett.* **1994**, *35*, 6925.

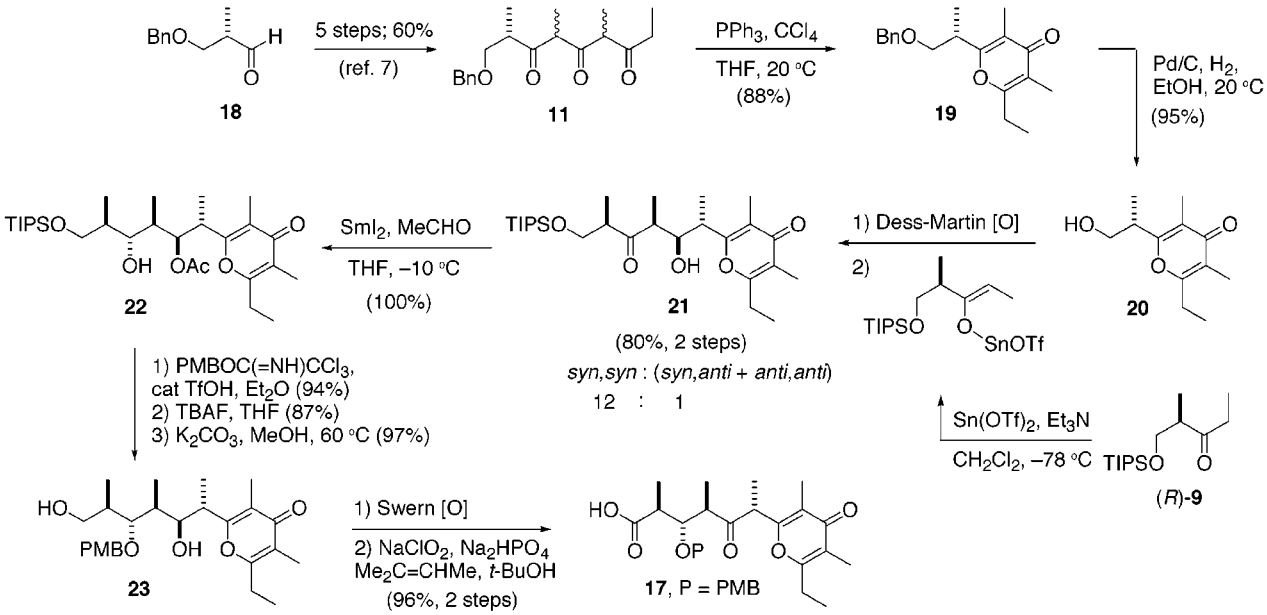
(8) (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (b) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087. (c) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

(9) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

(10) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(11) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

Scheme 3



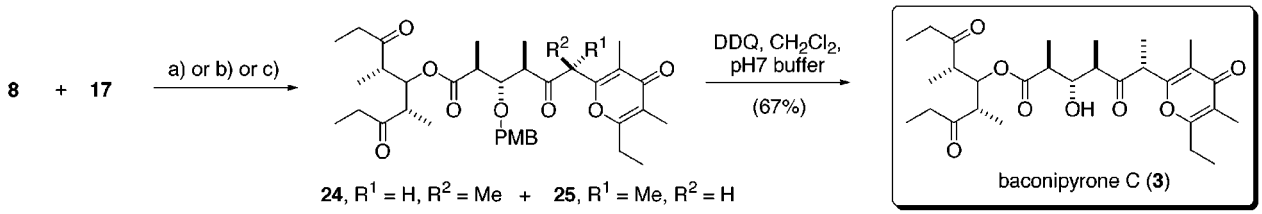
As shown in Scheme 3, the corresponding acid fragment **17** having a PMB ether at C_{11} was prepared by adaptation and improvement of our earlier route.[7] Cyclization of triketone **11** (accessible in five steps from aldehyde **18**) employing the DMSO/$(COCl)_2$ protocol of Yamamura and co-workers[14] gave γ-pyrone **19** in only moderate yield (54%). However, the use of the alternative PPh_3/CCl_4 cyclization conditions[14] gave **19** in a much improved 88% yield.[15] Debenzylation, followed by Dess−Martin oxidation[16] of the resulting alcohol **20**, gave the sensitive chiral aldehyde **10**, which was reacted immediately with the preformed Sn(II) *Z*-enolate of (*R*)-**9**.[17] This gave a 74% yield of the desired syn-syn aldol adduct **21**, together with 6% of a mixture of syn-anti and anti-anti isomers. A SmI_2-promoted, Evans−Tishchenko reduction[18] with MeCHO then gave the acetate **22** as a single isomer. A three-step sequence of protecting group manipulation then gave diol **23**. Finally, careful Swern oxidation[12] of **23**, followed by further oxidation with $NaClO_2$,[19] led to the desired ketoacid **17** (96%).

Completion of the synthesis of baconipyrone C required a challenging esterification to be accomplished between fragments **8** and **17** (Scheme 4). Initial attempts to form **24** employing the Steglich esterification protocol[20] gave exclusively the undesired *N*-acylurea derivative of **17**. The Keck modification[21] of the Steglich method resulted in a 52% yield of coupled products (entry a). However, this generated an inseparable mixture of diastereomers, which appeared to be in favor of the undesired C_{14}-epimer **25**. Similar results were observed with the Yonemitsu variation[22a] of the Yamaguchi esterification procedure (entry b).[22b] However, further investigations revealed that by modifying the Yonemitsu−Yamaguchi protocol, the extent of epimerization could be significantly reduced (entry c). By warming the reaction mixture from −78 to 0 °C over a period of 10 min, followed by rapid quenching with $NaHCO_3$ solution, the desired ester **24** was obtained in 73% yield with less than 10% epimerization detected. Finally, oxidative removal of the PMB ether with DDQ in wet CH_2Cl_2 gave a 67% yield of baconipyrone C (**3**) after chromatographic separation from a small amount of diastereomer.

The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) obtained for synthetic (−)-baconipyrone C were in agreement with that recorded for natural material.[4] The specific rotation was measured as $[\alpha]^{20}_D = -73.3$ ($c = 0.77$, MeOH), while an authentic sample provided by Professor Faulkner had $[\alpha]^{20}_D = -82$ (*c* 0.16, MeOH).[4,23] The full absolute stereochemistry of baconipyrones A−D (**1**−**4**) is therefore assigned

(12) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(13) The double Swern oxidation was routinely performed by employing oxalyl chloride (5 equiv), DMSO (10 equiv), and triethylamine (15 equiv). After warming from −78 to −20 °C, the reaction mixture was quenched with a mixture of anhydrous hexane/toluene (3:1), followed by filtration through Celite, to obtain spectroscopically pure diketone. Other procedures (Dess−Martin, TPAP) led to undesired cyclisations of mono-oxidized products.
(14) (a) Yamamura, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025. (b) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5491. (c) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619.
(15) This also avoided the presence of sulfur residues in the subsequent hydrogenolysis of the benzyl group, which proved to be problematic due to catalyst poisoning.
(16) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(17) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.
(18) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
(19) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(20) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(21) Keck, G. E.; Boden, E. P. *J. Org. Chem.* **1985**, *50*, 2394.
(22) (a) Hikotam, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367. (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Scheme 4



24, R^1 = H, R^2 = Me + **25**, R^1 = Me, R^2 = H

	24	:	**25**
a) DCC, DMAP, DMAP•HCl, CH_2Cl_2, 20 °C, 16 h (52%)	1	:	2.5
b) DMAP, Et_3N, 2,4,6-$Cl_3(C_6H_2)COCl$, PhMe, 20 °C, 10 min (74%)	1	:	2
c) DMAP, Et_3N, 2,4,6-$Cl_3(C_6H_2)COCl$, PhMe, −78 → 0 °C, 10 min (73%)	10	:	1

as represented in this paper, which is in agreement with that established independently for the siphonarins.[7,24]

In conclusion, the first total synthesis of the unusual siphonariid metabolite, (−)-baconipyrone C (**3**), has been achieved in 17 steps with 13.9% overall yield from **18**. The efficient construction of the polypropionate skeleton using the ketones (*R*)-**9** and (*R*)-**12** and appropriate aldol chemistry, together with the special conditions required for esterification to generate **24**, are noteworthy.

(23) We repurified Professor Faulkner's sample of natural baconipyrone C and obtained a consistently higher specific rotation than that reported in ref 4 ($[\alpha]^{20}_D = -19.0$ (*c* 0.90, MeOH)). It is possible that the original measurement was adversely affected by an impurity or residual solvent. Our measured $[\alpha]^{20}_D$ values for baconipyrone C are now also quite similar to that recorded for the normethyl compound, baconipyrone D (**4**).

(24) Garson, M. J.; Jones, D. J.; Small, C. J.; Liang, J.; Clardy, J. *Tetrahedron Lett.* **1994**, *35*, 6921.

Acknowledgment. We thank the EPSRC, the Cambridge Commonwealth Trust, the Sim Foundation, King's and Corpus Christi Colleges, Ministerio de Educación y Cultura (Spain), the European Commission (Marie Curie Fellowship to J.L.A.), and Merck, Sharp & Dohme for support. We also thank Professor John Faulkner (Scripps Institution of Oceanography) for his assistance in kindly providing an authentic sample of baconipyrone C, along with copies of NMR spectra, and Dr. Mary Garson (Queensland) for valuable discussions.

Supporting Information Available: Copies of NMR spectra and experimental procedures for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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