Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6925-6928, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01421-3

Assignment of the Absolute Configuration of the Siphonarins and Baconipyrones. Enantiocontrolled Synthesis of a γ-Pyrone Subunit.

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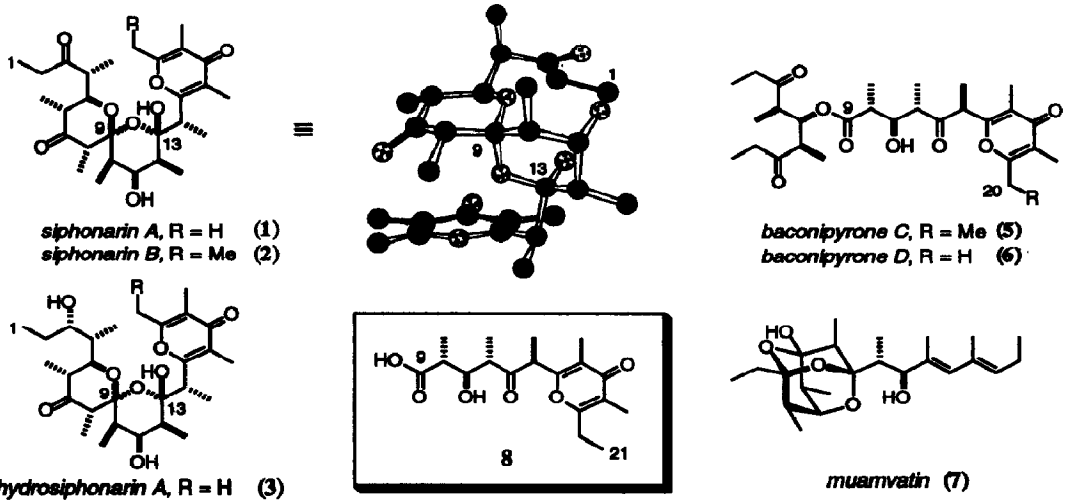
Abstract: Aldehyde **11** was prepared with >90% ds using a Sn(II)-mediated aldol reaction between (*S*)-**13** and (*S*)-**14**. Conversion into the γ-pyrone **8**, a known degradation product from dihydrosiphonarin B, established the absolute configuration as enantiomeric to that shown in **4**.

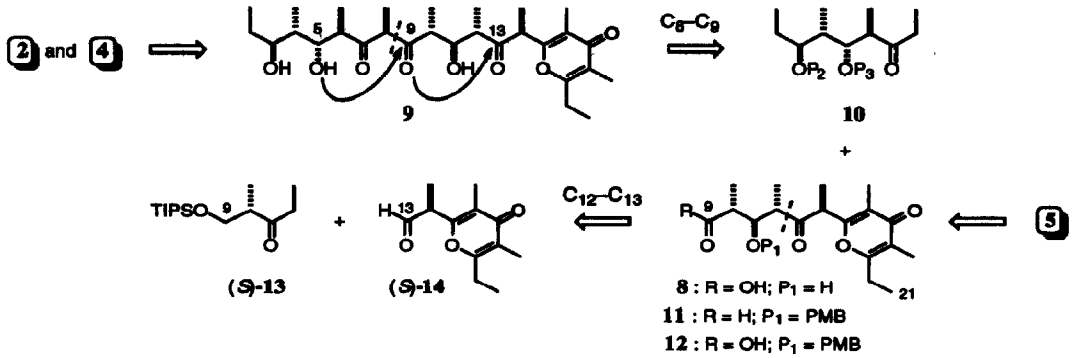
Marine pulmonates of the genus *Siphonaria* are limpet-like molluscs which produce characteristic polypropionate metabolites. Siphonarin A and B were first isolated by Faulkner *et al.* from *S. zelandica* collected in the intertidal zone along the coast of New South Wales, Australia.[1] Using spectroscopic and X-ray analysis, the γ-pyrone-containing structures **1** and **2** (**Scheme 1**) were determined for siphonarin A and B respectively. The analogous dihydrosiphonarin A (**3**) and B (**4**) were also isolated by Ireland *et al.* from *S. normalis* collected at Oahu, Hawaii. In this earlier work, the absolute configuration of the siphonarins was not determined and the *arbitrary* choice of the enantiomer shown was made. Other siphonariid metabolites subsequently reported include the related γ-pyrones baconipyrone C (**5**) and D (**6**),[2a] which lack the normal contiguous carbon skeleton of a polypropionate, and muamvatin (**7**),[2b] which has an unusual 2,4,6-trioxadamantane ring system.



Scheme 1

Previously, we have reported the first total synthesis of muamvatin,[3] leading to the assignment of the full stereostructure as **7**.[3,4] As part of synthetic studies on the siphonarins and baconipyrones, we now describe an enantiocontrolled synthesis of the γ-pyrone acid **8**. This is found to be antipodal to a degradation product obtained in the isolation of dihydrosiphonarin B.[1] Taken together with the X-ray analysis of a siphonarin A derivative by Garson *et al.*,[5] the absolute configurations of the siphonarins and baconipyrones are determined as *enantiomeric* to those indicated in structures **1–6**.

The siphonarin ring system contains a highly substituted spiroacetal with all its alkyl substituents equatorially oriented and both acetal oxygens axial with respect to the other ring. The X-ray crystal structure[1] of siphonarin A (**1**), reproduced in **Scheme 1**, shows this clearly. As outlined in **Scheme 2**, our synthetic plan for siphonarin B (**2**) and dihydrosiphonarin B (**4**) depends on attaining thermodynamic control in the cyclisation of an acyclic precursor such as **9**.[6] This triketone **9** (or a suitably protected derivative) should be available from an appropriate aldol coupling at C_8–C_9 between the two segments **10** and **11**, followed by careful oxidation at C_9 preserving the labile C_8 and C_{14} stereocentres.[7] Here, the derived acid **12** should also serve as a C_9–C_{21} subunit for the synthesis of baconipyrone C (**5**). Note that the unprotected form of this ketoacid, *i.e.* **8** (with undefined absolute stereochemistry), was reported to co-occur in the isolation of dihydrosiphonarin B and is probably a degradation product.[1,8] Our initial goal then was an enantiocontrolled synthesis of the C_9–C_{21} segments **8**, **11** and **12**. Using our general protocol for polypropionate synthesis,[9] these should come from a stereocontrolled aldol coupling at C_{12}–C_{13} between dipropionate reagent (*S*)-**13** and γ-pyrone aldehyde (*S*)-**14**.

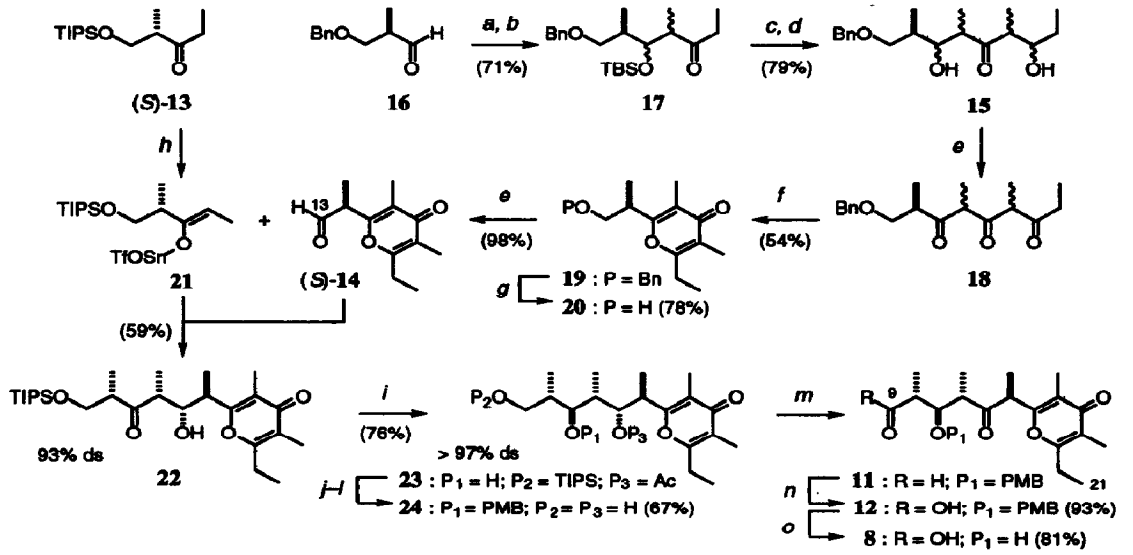


Scheme 2

The synthesis of the C_9–C_{21} segments **8**, **11** and **12** is shown in **Scheme 3**. The ketodiol **15** was prepared,[10] as a mixture of diastereomers, using a four-step sequence from diethylketone: (*i*) a titanium (IV)-mediated, syn aldol coupling[11,12] with aldehyde **16**, (*ii*) silyl protection of the resulting β-hydroxyl group, (*iii*) a similar aldol addition[11] on the other side of the ketone group in **17** to propionaldehyde, and (*iv*) HF deprotection. The γ-pyrone ring was prepared by cyclisation of the corresponding 1,3,5-triketone **18** under the conditions of Yamamura *et al.*[13] The efficiency of this process is determined by the oxidation method used in the preparation of the triketone.[14] Dess-Martin oxidation[15] of **15** gave the triketone **18** (as a mixture of tautomers by ^{1}H NMR), which without purification was directly cyclised by DMSO / oxalyl chloride[13] to form the γ-pyrone **19** in 54% yield. Hydrogenolysis of the benzyl ether and Dess-Martin oxidation of the resulting alcohol **20**[16], $[\alpha]_D^{20} = -31.0°$ (*c* 2.0, $CHCl_3$), then gave the aldehyde (*S*)-**14**. This aldehyde was prone to racemisation and could not be stored.

The ethyl ketone (*S*)-**13**, $[\alpha]_D^{20} = +40.4°$ (*c* 1.0, $CHCl_3$), was prepared by a modification of our route to the corresponding benzyl ether.[9b,17] Suitable syn-syn stereocontrol in the aldol coupling of the dipropionate reagent (*S*)-**13** with aldehydes can be achieved *via* its tin(II) enolate **21**.[9c] Thus enolisation of (*S*)-**13** with $Sn(OTf)_2$ / Et_3N in CH_2Cl_2, followed by the addition of freshly prepared aldehyde (*S*)-**14**, gave the aldol adduct **22** as the major isomer[18] with 93% ds. Due to partial racemisation of the aldehyde, a small amount (7%) of aldol products from addition to (*R*)-**14** were also isolated. Using SmI_2 (1 equiv) and acetaldehyde, an Evans-Tishchenko reduction[19] of **22**, with concomitant C_{13} hydroxyl protection, gave acetate **23** with >97% ds in 76% yield. A three-step sequence of protecting group manipulations then led to diol **24** (67%).

Careful Swern oxidation of **24** gave the ketoaldehyde **11**, which corresponds to a C_9–C_{21} subunit for future use in the synthesis of siphonarin B and dihydrosiphonarin B. Using buffered sodium chlorite, further oxidation through to the C_9 acid **12**, $[\alpha]_D^{20}$ = +63.8° (*c* 1.0, $CHCl_3$), was achieved without any detectable epimerisation at the C_{12} stereocentre (93% from **24**). This compound corresponds to a C_9–C_{21} subunit for the synthesis of baconipyrone C. Finally, hydrogenolysis of the PMB ether in **12** gave the β-hydroxy acid **8** in 81% yield. This had ^{1}H NMR data in agreement[20] with that recorded by Ireland *et al.*,[1] while its ^{13}C NMR spectrum matched with the corresponding resonances (C_9 through to C_{21}) recorded for baconipyrone C.[2a] Similar homology was seen in the ^{1}H and ^{13}C NMR spectra of the methyl ester derived from **8** (CH_2N_2).[10] Synthetic **8** had $[\alpha]_D^{20}$ = +115.0° (*c* 0.5, CH_2Cl_2), while that reported for material isolated from *S. normalis* was $[\alpha]_D^{20}$ = –86.5° (*c* 0.052, CH_2Cl_2).[1,21] Thus the absolute stereochemistry of dihydrosiphonarin B and siphonarin B is enantiomeric[22] to that indicated in structures **4** and **2** in **Scheme 1**. This is also expected to hold for siphonarin A and dihydrosiphonarin A. In the case of the baconipyrones, which appear to be formed by rearrangement of the siphonarin skeleton,[2a] we have determined that baconipyrone D and siphonarin A are in the same enantiomeric series.[23]



Scheme 3 (*a*) Et_2CO, $TiCl_4$, CH_2Cl_2, -78 °C, 30 min; $^iPr_2NEt$, 90 min; **16**, 2 h; (*b*) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 2 h; (*c*) $TiCl_4$, CH_2Cl_2, -78 °C, 30 min; $^iPr_2NEt$, 90 min; EtCHO, 90 min; (*d*) HF, MeCN, 20 °C, 2 h; (*e*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 30 min; (*f*) $(COCl)_2$, DMSO, CH_2Cl_2, -20 °C, 2 h; (*g*) H_2, 10% Pd/C, EtOH, 20 °C, 2 h; (*h*) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, -78 °C, 90 min; (*S*)-**13**, 1 h; (*i*) SmI_2 (1 equiv), MeCHO (5 equiv), THF, -10 °C, 30 min; (*j*) $PMBOC(CCl_3)$=NH, TfOH (0.3 mol%), Et_2O, 20 °C, 45 min; (*k*) TBAF, THF, 20 °C, 90 min; (*l*) K_2CO_3, MeOH, 60 °C, 3 h; (*m*) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 1 h, Et_3N, → -30 °C, 30 min; (*n*) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, ^{t}BuOH/H_2O, 20 °C, 30 min; (*o*) H_2, 10% Pd/C, EtOAc, 20 °C, 16 h.

In summary, a full stereochemical assignment has now been made for the siphonarins, together with an analogous assignment for the baconipyrones. Their structural and stereochemical similarities with other siphonariid metabolites are considered in the following paper,[6] leading to a revised configurational model. Further work directed towards the total synthesis of siphonarin B and baconipyrone C is underway.

Acknowledgement: We thank the EPSRC and Pfizer Central Research for support, Corpus Christi College for a research fellowship (ASF), Dr M. J. Garson (Queensland) for helpful discussions, Professor C. M. Ireland (Utah) for kindly making available the ^{1}H NMR spectrum of compound **8**, and Dr J. A. Channon (Cambridge) for some preliminary experiments.

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6. Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994**, *35*, 6929 (following paper).
7. A similar strategy was successfully used to achieve a stereocontrolled synthesis of denticulatin B, see: Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801.
8. Acid hydrolysis of dihydrosiphonarin A (3) is reported to give the corresponding acid to 8, where a methyl replaces the ethyl group on the γ-pyrone ring (ref. 1).
9. (a) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821. (b) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (c) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233. (d) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (e) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797.
10. All new compounds gave spectroscopic data in agreement with the assigned structures. **8** had $[\alpha]_D^{20}$ = +115.0° (*c* 0.5, CH_2Cl_2); ^1H NMR δ ($CDCl_3$, 400 MHz) 4.17 (1H, q, *J* = 6.8 Hz), 3.60 (1H, dd, *J* = 9.7, 1.9 Hz), 2.86 (1H, dq, *J* = 9.7, 6.7 Hz), 2.71 (1H, qd, *J* = 7.2, 2.0 Hz), 2.58 (2H, q, *J* = 7.6 Hz), 2.14 (3H, s), 1.93 (3H, s), 1.36 (3H, d, *J* = 6.8 Hz), 1.35 (3H, d, *J* = 7.2 Hz), 1.14 (3H, t, *J* = 7.6 Hz), 0.89 (3H, d, *J* = 6.7 Hz); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 209.6, 180.6, 177.6, 166.1, 162.0, 120.7, 118.6, 77.6, 51.4, 48.5, 40.4, 24.8, 15.1, 13.9, 12.7, 11.3, 10.2, 9.7; IR (Thin film) 3600 – 2400 (br), 3423 (br), 2934, 1720, 1649, 1591; HRMS (CI, NH_3) calc for $C_{18}H_{27}O_6$ (MH^+) 339.1808 found 339.1808. The methyl ester from **8** had $[\alpha]_D^{20}$ = +174.4° (*c* 0.35, $CHCl_3$); ^1H NMR δ ($CDCl_3$, 400 MHz) 4.05 (1H, q, *J* = 6.8 Hz), 3.68 (3H, s), 3.61 (1H, ddd, *J* = 9.2, 9.2, 3.1 Hz), 3.33 (1H, d, 9.2 Hz), 2.75 (1H, dq, *J* = 9.0, 6.8 Hz), 2.67 (1H, qd, *J* = 7.1, 3.1 Hz), 2.55 (2H, m), 2.07 (3H, s), 1.94 (3H, s), 1.36 (3H, d, *J* = 6.8 Hz), 1.28 (3H, d, *J* = 7.2 Hz), 1.15 (3H, t, *J* = 7.6 Hz), 0.87 (3H, d, *J* = 6.8 Hz); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 210.0, 180.6, 175.9, 164.9, 160.5, 120.3, 118.4, 77.4, 52.0, 51.2, 48.3, 40.9, 24.7, 15.1, 14.1, 12.8, 11.3, 10.0, 9.5.
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16. Alcohol *ent*–**20** has recently been prepared by a different route as a fragment of ilikonapyrone, see: Arimoto, H.; Cheng, J.-F.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 5781.
17. Ethyl ketone (*S*)-**13** was prepared in 86% overall yield from (*S*) methyl 2-methyl-3-hydroxypropionate (Aldrich) by (*i*) $^iPr_3SiCl$, imidazole, DMAP (10 mol%), CH_2Cl_2, 20 °C, 2 h (100%); (*ii*) Me(MeO)NH.HCl, Me_3Al, PhMe, 0 → 70 °C, 3 h (97%); (*iii*) EtMgBr, THF, 0 → 20°C, 2 h (89%).
18. The stereochemistry was established as shown by ^1H NMR analysis of the (*R*)- and (*S*)-MTPA esters. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
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20. The original ^1H NMR spectrum of compound **8** obtained in the isolation work (ref. 1) was made available for comparison by Professor Ireland.
21. The higher rotation obtained for synthetic **8** is probably due to the availability of larger amounts of pure material (only 0.9 mg was available to Ireland *et al.*).
22. Dihydrosiphonarin A has been converted into siphonarin A by oxidation (ref. 1), which indicates that they have identical configuration. We assume that this also holds for dihydrosiphonarin B and siphonarin B.
23. Paterson, I.; Franklin, A. S., unpublished results.

(*Received in UK* 13 *June* 1994; *revised* 18 *July* 1994; *accepted* 22 *July* 1994)