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Accounts

Synthetic Studies on Polypropionate-Derived 4-Pyrone-Containing Marine Natural Products

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Synthesis of 4-pyrone derivatives by employing the mild cyclization is described. The DMSO–$(COCl)_2$ and Ph_3P–CCl_4 conditions were appeared to accommodate a synthetic potential as proton equivalents. This study established the absolute configurations, and provided revisions of formerly proposed structures of highly oxygenated propionate derived 4-pyrones, such as ilikonapyrone, peroniatriols I and II, and onchitriols I and II.

Marine natural products derived from a variety of sources have attracted considerable interest of chemists for their unusual structures and concomitant biological activities.[1] Among marine invertebrates, molluscs include a variety of bioactive secondary metabolites exhibiting antimicrobiral activities and cytotoxicities. The original role of these bioactive substances has been considered to be a defensive function from predators; other possibilities might include prevention of fouling, inhibition of overgrowth, and protection from ultraviolet radiation.[2] This article will describe the chemistry of molluscs-derived 4-pyrones, biosynthetically classified as polypropionates that involve macrolide antibiotics derived from Streptomycetes as representative congeners. As can be seen in Figs. 1 and 2, the 4-pyrone family possessing a number of diverse structures consists of siphonarins, dihydrosiphonarins,[3] baconipyrones,[4] vallartanones,[5] placidene,[6] maurapyrones,[7] tridachiapyrones, isotridachiapyrones,[8] tridachiones,[9] crispatone, crispatene,[10] auripyrones,[11] cyercenes,[12] elysione,[13] caloundrin B,[14] ilikonapyrone,[15] peroniatriols I and II,[16] and onchitriols I and II.[17] Among them, ilikonapyrone (**1**), peroniatriols I and II (**2**, **3**), and onchitriols I and II (**4**, **5**), are a unique group, from the viewpoints of the highly oxygenated structures possessing two 4-pyrones linked via carbon chains carrying continuous stereogenic centers. In spite of such challenging characters, no synthetic studies have been reported, probably owing to chemically labile pyrone properties as well as no information about the absolute configuration, with the exception of onchitriols. The stereostructures had been proposed mainly by spectroscopic comparison with the data of **1**, whose relative stereochemistry had been determined by X-ray crystallographic analysis.[15] However, it should be noted that the determination of the relative stereochemical relationships of **2**, **3**, **4**, and **5** was undertaken without correlative evidence of the three isolated groups (**A**, **B**, and **C** in Fig. 2). Configuration of the methyl group in **B** had to be assigned only by its NMR chemical shift.[16,17] Accordingly, along with such spectroscopic evidence, synthesis of these substances in optically active forms would be required for the unambiguous determination of their stereostructures.

The Mild Synthesis of 4-Pyrone Derivatives. To accomplish syntheses of these 4-pyrone-containing natural products, two approaches were considered, as shown in Scheme 1. The first one is a biomimetic conversion of the triketides carrying chiral substituents into the target molecules (type **1**). Though general methods are known for the construction of the 4-pyrone derivatives,[18] they require drastic conditions such as strong acids or high reaction temperature, which might cause serious damage to adjacent stereogenic centers as well as their protective groups. The other approach is the attachment of carbon chains equipped with stereogenic centers to 4-pyrone skeletons (type **2**).[19] During extensive evaluation of possible approaches, we found effective proton equivalents [**I**: $(CH_3)_2S^+Cl$ from DMSO–$(COCl)_2$, **II**: $Ph_3P^+CX_3$ or Ph_3P^+X (X = Cl or Br) from Ph_3P–CCl_4] which promote the expected cyclization of the triketides to give 4-pyrones (type **1** in Scheme 1) in good yield even at room temperature or below.[20] The ^1H NMR studies indicated that the triketide in solution may exist as a tautomeric mixture of the corresponding acyclic and cyclic isomers, as can be seen in Scheme 2. A possibility of the latter isomers could be confirmed by X-ray crystallographic and spectroscopic analysis.[21] Accordingly, reaction of the active species **I** in Swern oxidation or phosphonium salt **II** may take

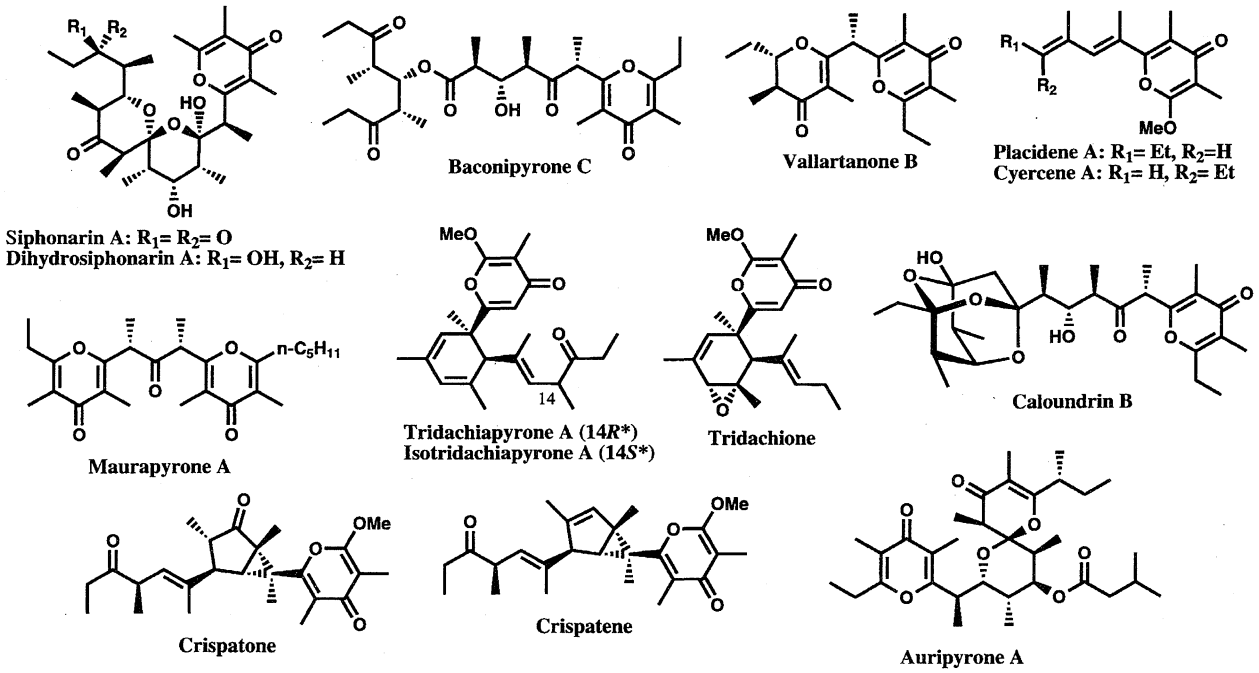


Fig. 1. Representative polypropionate derived 4-pyrone-containing marine natural products.

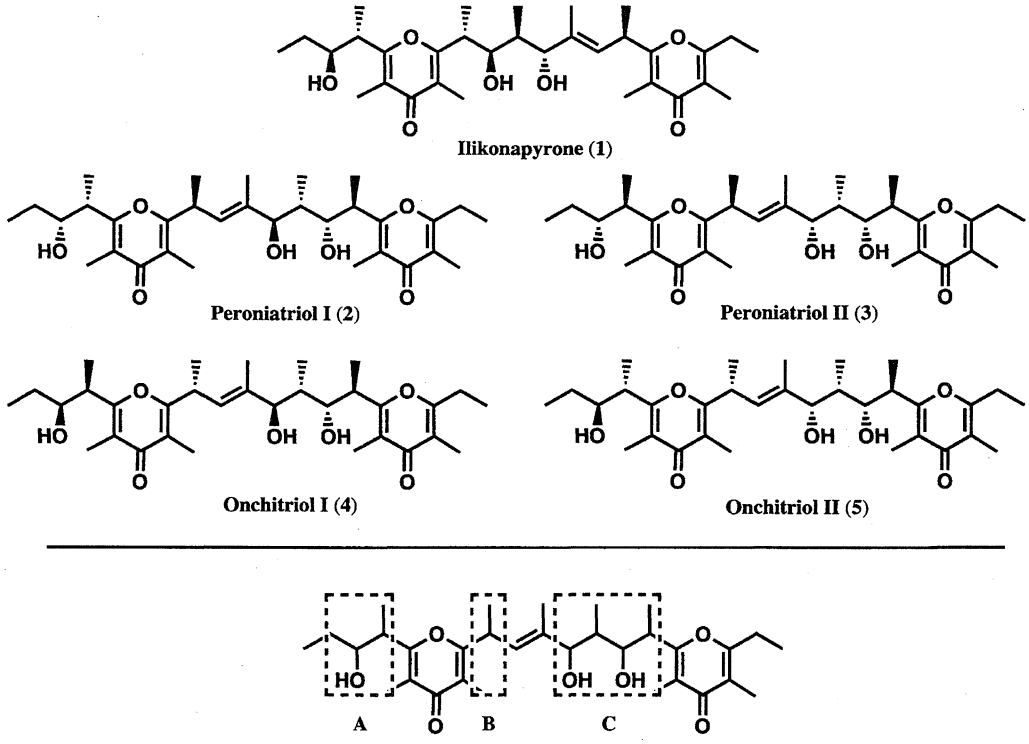
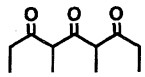
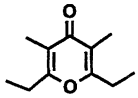
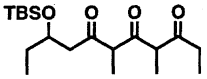
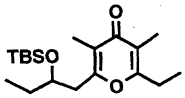
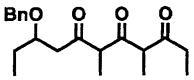
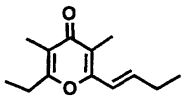
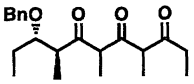
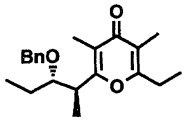


Fig. 2. Highly oxygenated marine natural products.

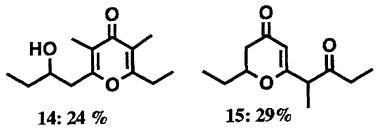
two kinds of pathway, Michael and dehydration processes, followed by final elimination of the substituents to afford the target 4-pyrone. Ultimately, the reagents are converted by the acquisition of one oxygen into DMSO (from **I**) and Ph_3PO (from **II**), respectively.

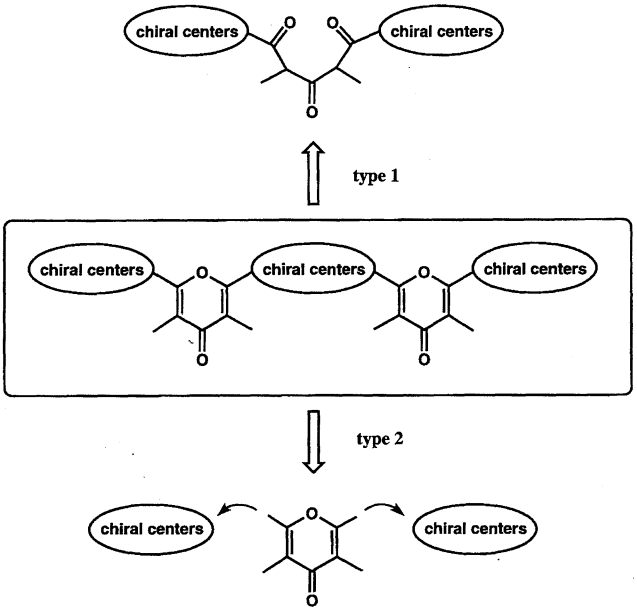
Table 1 scores the mild cylization reactions of triketides prepared by coupling of the corresponding carbonyl imidazolides with a dianione of 4-methylheptan-3,5-dione (LDA/THF, −78 °C),[20] compared with the acidic conditions (cat. TsOH/PhH, reflux temp).[18a] Although the simple triketide provided the desired 4-pyrone in good yields by both methods (Entries 1, 2, 3, and 4), the acidic conditions did not provide the expected cyclization in the cases of **8** and **10**, which possess functional groups (Entries 7 and 8). Contrary to these results, the mild conditions could provide the corresponding 4-pyrones in comparable yields to those of **7** except for Entry 6, where HBr generated probably induced abstraction of a protective group to **14**, followed by an an-

Table 1. 4-Pyrone Synthesis under the Mild Conditions

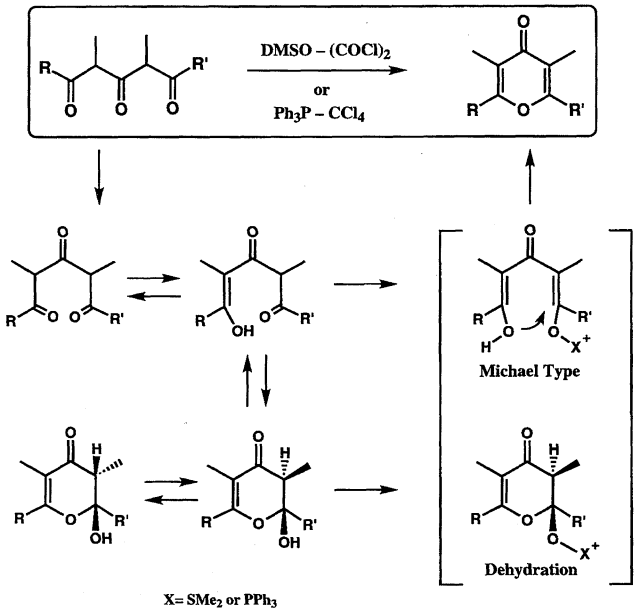
Entries	Starting materials	Conditions[a)]	Yields (%) and products
1		A	69
2		B	78
3		C	50
4	6	D	66
			 7
5		A	76
6		C	8[b)]
7	8	D	Decompose
			 9
8		D	48
	10		 11
9		A	68
10		B	79
	12		 13

a) Conditions: A. DMSO–$(COCl)_2$/CH_2Cl_2, −30 °C (Entry 9: −48——18 °C); B. Ph_3P–CCl_4/THF, room temp; C. Ph_3P–CBr_4/THF, room temp; D. Catalyst TsOH/benzene, refluxing with Dean–Stark trap. b) The following products were also obtained.





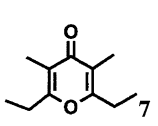
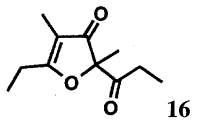
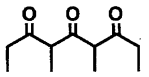
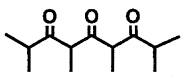
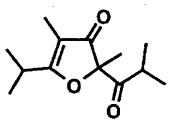
Scheme 1.

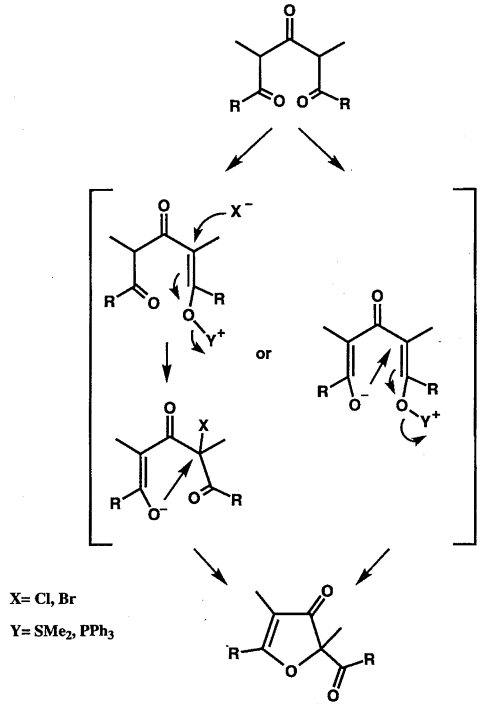


Scheme 2.

other cyclization to dihydropyrone **15**. Upon the addition of bases (**I**: Et_3N, **II**; pyridine) which means completion of the usual Swern oxidation and halogenation protocol, the mild cyclization methods opened an oxidation pathway, for example to **16** or **18** (Table 2) via a putative reaction mechanism (Scheme 3).[21] Based on these mild cyclization methodologies, we studied the chemistry of 4-pyrone-containing marine natural products.

Table 2. The Oxidation Reactions of Triketones

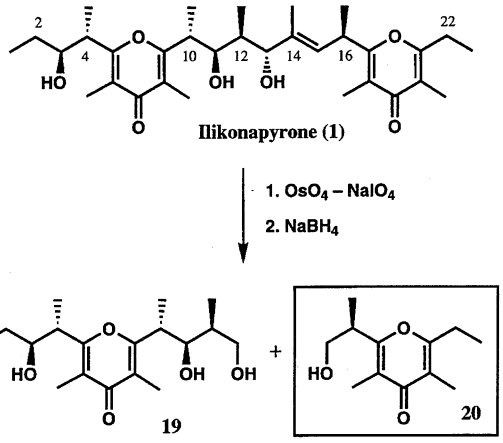
Entries	Starting materials	Conditions	Products	
			 7	 16
1		Ph_3P–CBr_4 / pyridine, 40–70 °C	19%	13%
2	6	DMSO–$(COCl)_2$ / CH_2Cl_2, then Et_3N, −30–−15 °C	33%	30%
3		DMSO–$(COCl)_2$ / CH_2Cl_2, then Et_3N, −65 °C		
	17		**18** (76%)	



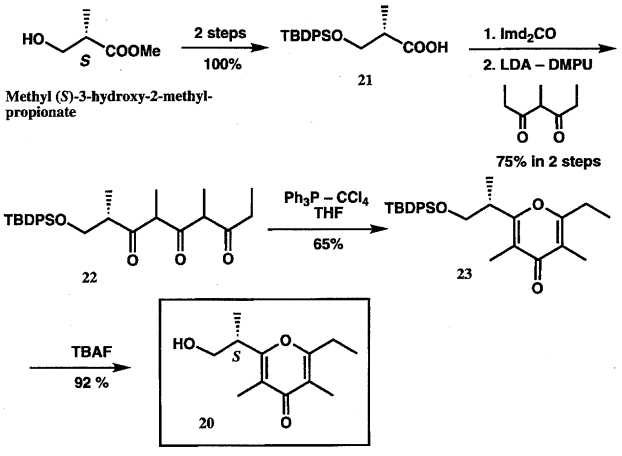
Scheme 3.

The Absolute Configuration of Ilikonapyrone (1). Ilikonapyrone (**1**) has a fundamental skeleton of esters which can be considered as probable defense allomones of the Hawaiian onchid *Onchidium verruculatum*.[15] Since the relative stereochemistry was confirmed by an X-ray crystallographic analysis, spectroscopic data of this compound had been utilized by structural determination studies of other related natural products. Chemical degradation of **1** has been known to afford two 4-pyrone derivatives **19** and **20** (Scheme 4).[15] Accodingly, assignment of the one stereogenic center of **20** would establish the absolute configuration of **1**.

Synthesis of 4-pyrone **20** was commenced by a usual protective group arrangement of commercially available methyl (*S*)-3-hydroxy-2-methylpropionate to carboxylic acid **21** (Scheme 5).[22] Compound **21** was transformed into the corresponding imidazolide, which was reacted with a dianione of 4-methylheptan-3,5-dione to give a tautomeric mixture of triketide **22**. The Ph_3P–CCl_4 conditions effected the desired cyclization to give 4-pyrone derivative **23** in 65% yield. After removal of the protective group, **20** was obtained in high



Scheme 4.



Scheme 5.

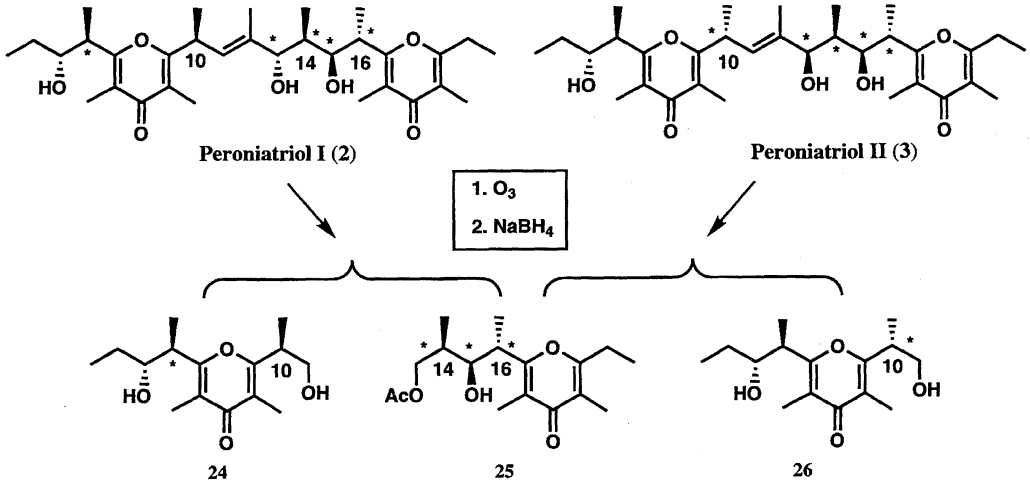
yield. While the ^{1}H NMR data of **20** was superimposable to that of the decomposition product, the optical rotations exhibited an opposite sign [$[\alpha]_D$ +32.8° (synthetic), $[\alpha]_D$ −16.7° (natural)].[23] These results indicated that the C16 position of **1** has *R*-configuration. Accordingly, the absolute configuration of ilikonapyrone (**1**) was unambiguously determined to be as depicted in Scheme 4.

The Absolute Configuration of Peroniatriols I and II (2 and 3). Peroniatriols I and II (**2**, **3**) are cytotoxic metabolites from saponified extracts of the mollusc *Peronia peronii*.[16] Both peroniatriols are stereochemical isomers, which accommodate closely related functional group distributions to those of ilikonapyrone (**1**). These similarities enabled the structural determination by spectroscopic data, employing oxidative degradation products (**24**, **25**, and **26**) as well as the mother molecule (Scheme 6). Some parts were spectroscopically compared with ilikonapyrone **1**. The configuration of the isolated methyl group at the C10 position was spectroscopically assigned on the hypothesis of a quasi-chair conformation supported by hydrogen bonding between the pyrone oxygen and the terminal hydroxy group of **24** and **26**, while ^{1}H NMR coupling constants of the C13—C16 positions involving a 1,3-diol system were compared with those of **1**. During synthetic investigation of the degradation products **24** and **26**, we envisaged an ambiguity of the assignment, which would be synthetically circumvented by the mild cyclization methodology.[24]

Synthesis of the epimeric isomers at the C-10 position (**24** and **26**) was started from the known alcohol **27**,[25] which was converted into the corresponding carboxylic acid **28** in four steps (Scheme 7). After conversion of **28** into triketide **12**, the DMSO–$(COCl)_2$ and Ph_3P–CCl_4 conditions effected the cyclization to **13** in good yields. Continuously, **13** was submitted to a C1 unit introduction procedure to produce the same carbon framework as those of the degradation products **24** and **26**, leading to the isomers at the C-10 position (**29a** and **29b**). At this stage, the synthesized **29a** and **29b** should be identical with the degradation products, although the stereochemistry at the C10 position could not be distinguished. While **29a** was indistinguishable from **26** by comparison of spectroscopic data as well as optical rotations, **29b** had a different structure from **24**. Therefore, the secondary hydroxy groups of both synthesized derivatives were epimerized to get further information of other isomers **30a**, **30b**. Comparison of the ^{1}H NMR spectra suggested that **30b** possessed the same structure as **24**, although the signs of the optical rotation showed an opposite relationship. Based on these observations, the degradation products have to possess the 3*R*,4*S*- (for **2**) and 3*R*,4*R*- (for **3**) configurations (Scheme 7). Additionally, they have the same stereochemistry at the C-10 position, although the absolute configuration could not be fixed at this stage.

In this context, synthesis of **31** bearing the 10*S*-configuration was undertaken to establish the absolute configuration of the C1—C11 portion of peroniatriol I (**2**).[22] As can be seen in Scheme 8, triketide **33** prepared by the tandem coupling of pentan-3-one successively with **21** and **32** was submitted to the cyclization (Ph_3P–CCl_4/THF, 75% yield), followed by removal of the protective groups to afford the desired **31**. Although no epimerized-products could be observed during the synthetic process, the 10*R* derivative **34** was also synthesized by essentially the same procedure to preclude a possibility of epimerization at this position. Ultimately comparison of the synthesized diastereomers **31** and **34** with the published data[16] indicated that **31** possess the same absolute configuration as that of the degradation product of **2**. Consequently, the stereochemistry at the C-10 positions was confirmed to be *S*-configuration in peroniatriols I (**2**) and II (**3**).

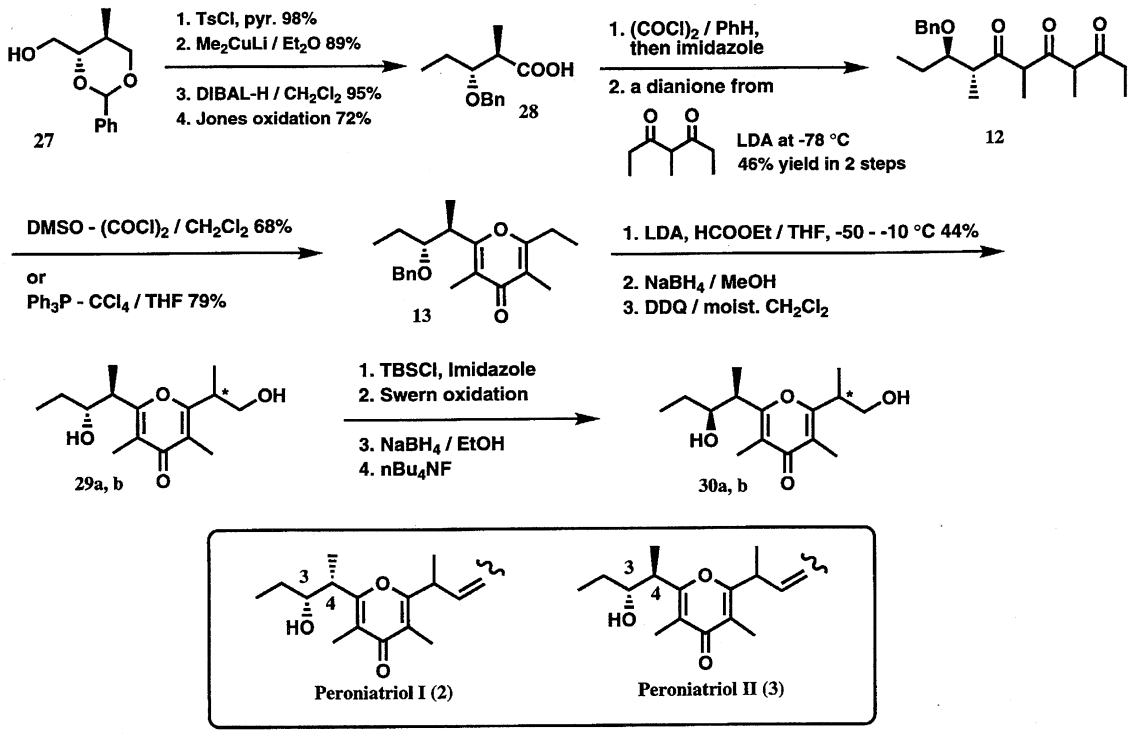
The structure of the C12—C16 portions of peroniatriols I and II was confirmed by the synthesis of **25**, which was obtained from both peroniatriols by an oxidative degradation. The stereochemistry of this compound seems reliable for two reasons: (1) as mentioned above, the continuous 1, 3-diol system at the C13—C15 positions of **2** and **3** would facilitate a spectroscopic analysis for a rather fixed conformation supported by hydrogen bondings. (2) This portion



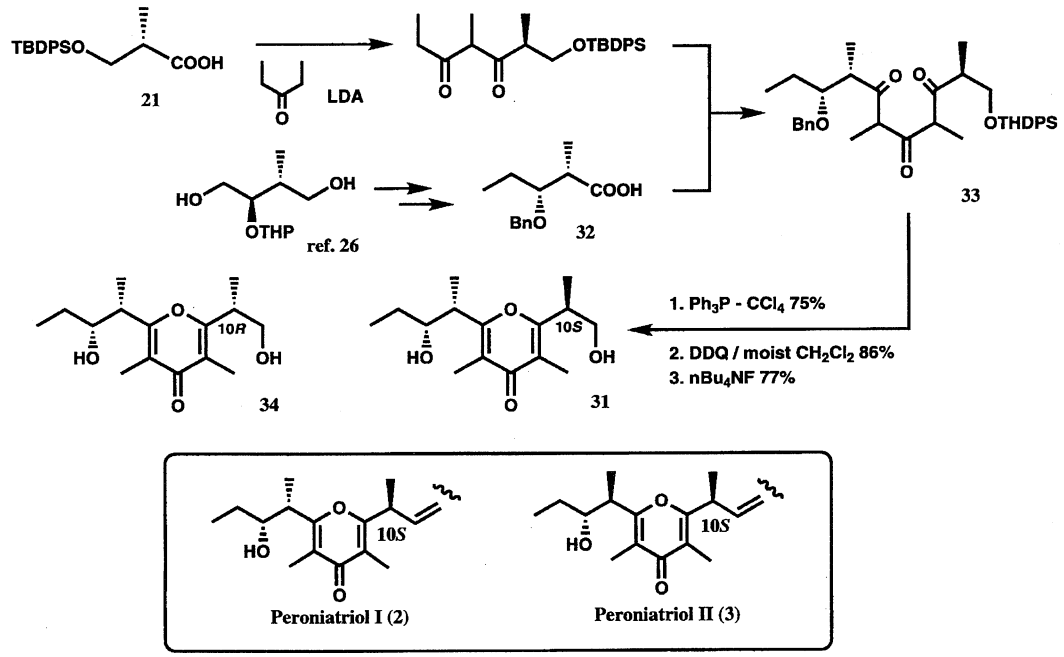
* The stereochemistry of this position was revised.

Scheme 6. The proposed structures of peroniatriols I and II (**2** and **3**), and the degradation products.

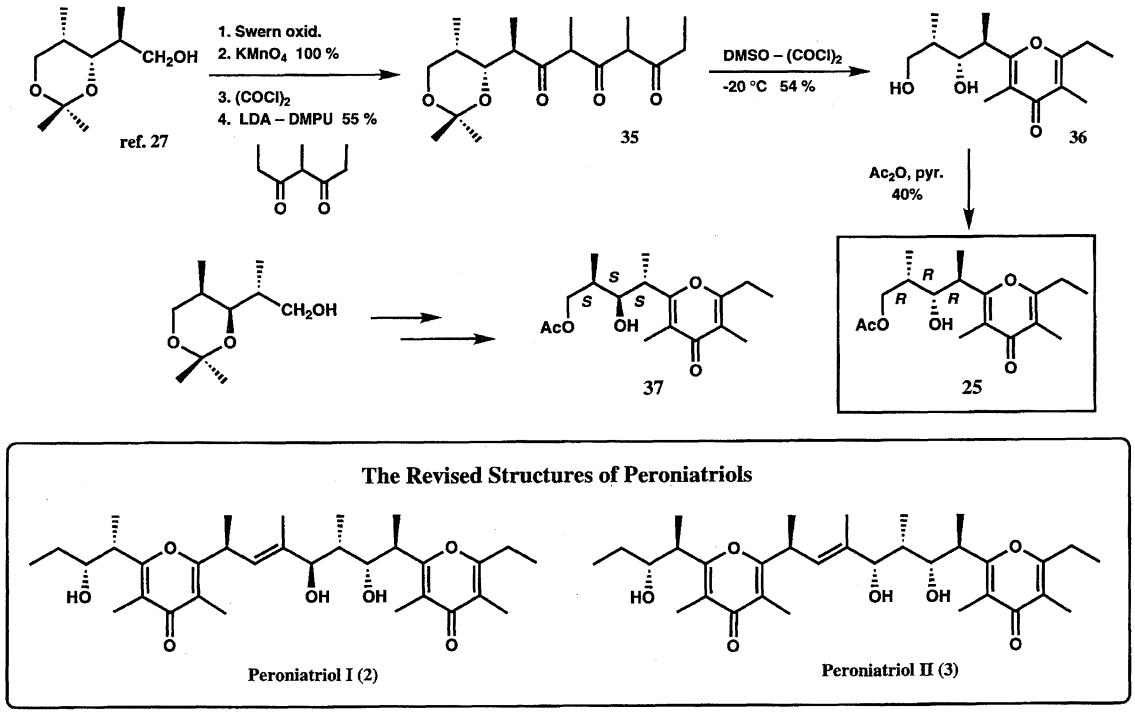
is a constituent of closely related onchitriols, whose structures were determined by the combination of spectroscopic and chemical results.[16] Thus, the appropriately functionalized triketide **35** prepared from the known alcohol[27] was cyclized under the DMSO–$(COCl)_2$ conditions involving removal of an acetonide group to give 4-pyrone **36** in 54% yield (Scheme 9). The product was sequentially submitted to selective acetylation, leading to the desired **25**. In addition **37**, which is an enantiomer of **25**, was synthesized starting from the corresponding enantiomer. As expected, the ^{1}H NMR spectra of **25** and **37** were identical with the reported data,[16] and the optical rotation of **25** showed the same sign as that of the degradation product. These results established a 14*R*, 15*R*,16*R*-configuration of **2** and **3**. Although no information pertinent to the C13 position was obtained from this synthesis, the stereochemical relationship to onchitriols suggested 13*R* (**2**) and 13*S* (**3**) configurations, which will be discussed later. Based on these investigations, the stereostructures of



Scheme 7.



Scheme 8.

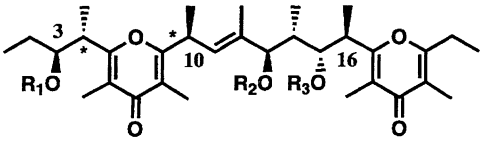


Scheme 9.

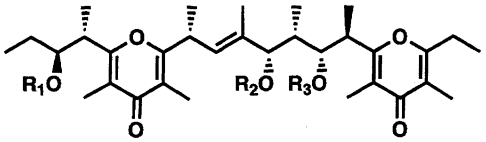
peroniatriols I and II (**2**, **3**) should be revised as shown in Scheme 9.

The Absolute Configuration and Total Synthesis of Onchitriols I and II (4, 5). Onchitriols I and II (**4**, **5**) are saponified products of the cytotoxic 4-pyrone-containing metabolites, isolated from the New Caledonian pulmonate mollusc *Onchidium* sp.[17] In addition to the saponified derivatives, Riguera reported the first isolation of natural esters, as depicted in Fig. 3. The ID_{50} values of **4** and **5** were 10 and 20 $\mu g\,ml^{-1}$ against P388, A-549, and HT-29 cell lines. These compounds also exhibited antiviral activities against HSV-1 (10 $\mu g\,ml^{-1}$) and VSV (20 $\mu g\,ml^{-1}$) cell lines. The esters also exhibited a growth inhibition (90—98%) in vitro against KB cells. The closely relevant structures of **4** and **5** to those of peroniatriols I and II indicated by the spectroscopic comparison (^1H, ^{13}C NMR chemical shifts and coupling constants) were reported, although the two stereogenic centers have been corrected by the following investigation (Fig. 3). The stereochemistry of the C13—C16 positions was also supported by the agreement of experimentally observed coupling constants of the corresponding acetonide derivatives with those obtained by MM calculations for the corresponding models. The absolute configuration of **4** and **5** was established by employing the Trost–Mosher method[28] which inspects the chirality with chemical shift difference between *R*- and *S*-O-methyl mandelate derivatives. According to the above investigation, **4** and **5** were determined to have the configurations 3*S*,4*S* (revised later), 10*S* (revised later), 13*R*, 14*R*, 15*R*, 16*R* and 3*S*, 4*S*, 10*R*, 13*S*, 14*R*, 15*R*, 16*R*, respectively (Fig. 3).[29]

Based on these results, we initiated total synthesis of onchitriols. Reliable and challenging stereostructures can be synthesized by employing the 4-pyrone construction



Onchitriol I (4): R_1=R_2=R_3=H
Onchitriol IA: R_1=H, R_2=R_3=Ac
Onchitriol IB: R_1=H, R_2=COEt, R_3=Ac
Onchitriol IC: R_1=H, R_2=Ac, R_3=COEt
Onchitriol ID: R_1=Ac, R_2=R_3=COEt

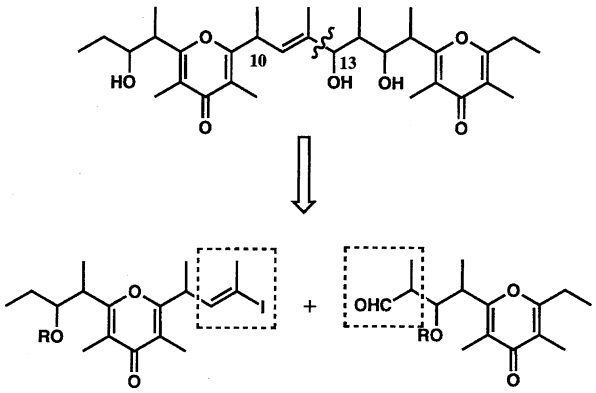


Onchitriol II (5): R_1=R_2=R_3=H
Onchitriol IIA: R_1=R_2=H, R_3=Ac
Onchitriol IIB: R_1=R_2=H, R_3=COEt
Onchitriol IIC: R_1=R_2=R_3=Ac
Onchitriol IID: R_1=R_3=Ac, R_2=H

* The stereochemistry of this position was revised.

Fig. 3. The proposed structures of onchitriols I and II and their esters.

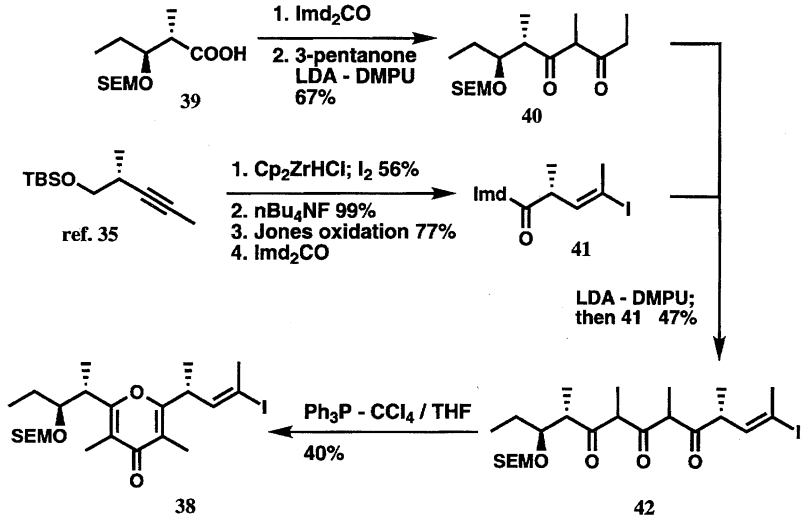
methodology.[30,31] To achieve the total synthesis of onchitriols, retrosynthetic analysis indicated the two pyrone segments would be coupled in a final stage of the synthesis. The $NiCl_2$–$CrCl_2$ reaction[32] between a vinyl iodide and an aldehyde would be a method of choice for coupling of the segments involving the chemically sensitive 4-pyrone units (Scheme 10).[33]



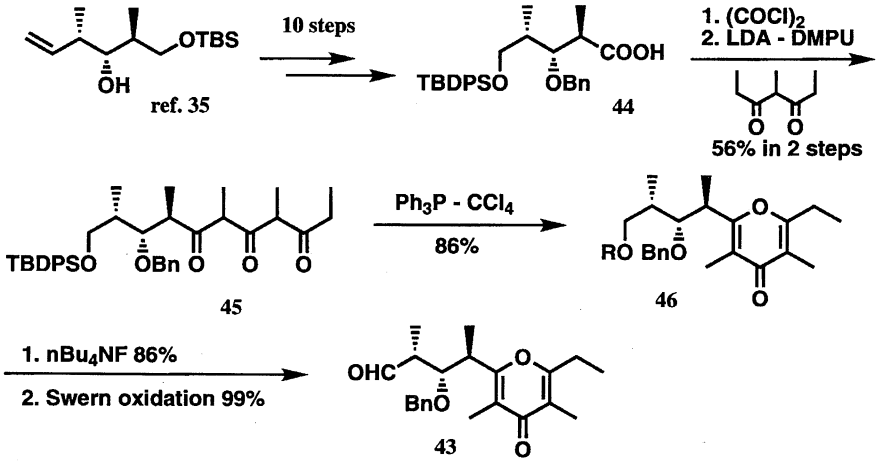
Scheme 10.

Construction of the C1—C12 segment **38** carrying a vinyl iodide function was accomplished by coupling of diketone **40** prepared from **39**[34] with **41**, to triketide **42**. The Ph_3P–CCl_4 cyclization of **42** provided the desired segment **38** (Scheme 11).

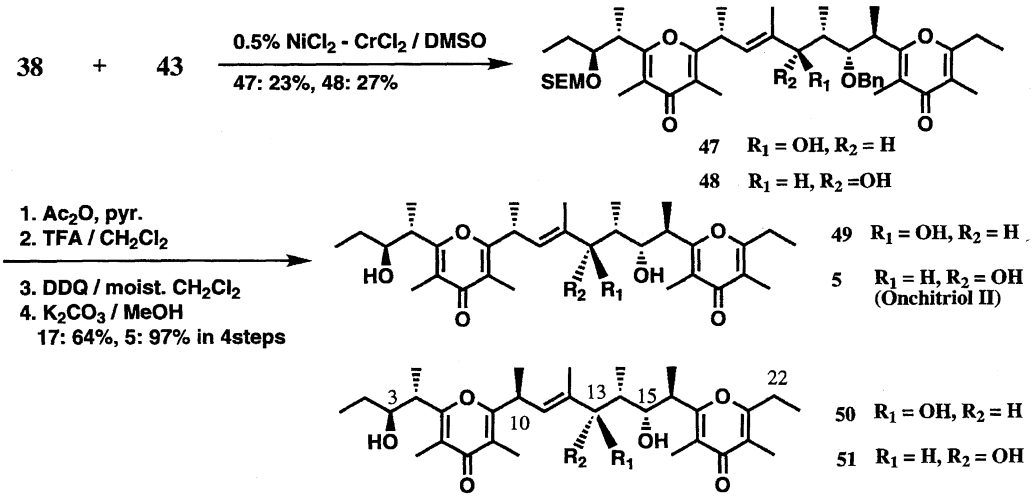
To synthesize the C13–C23 segment **43**, the continuous stereogenic centers of the C14—C16 positions were obtained from the known alcohol,[34] which was converted into the corresponding carboxylic acid **44** (Scheme 12). After chain elongation of **44** with 4-methylheptan-3,5-dione, **45** was submitted to the Ph_3P–CCl_4 reaction to the 4-pyrone derivative **46**. Deprotection and oxidation provided aldehyde **43**. As shown in Scheme 13, treatment of **38** with **43** under the $CrCl_2$–$NiCl_2$ conditions[37] employing DMSO as a solvent effected the desired coupling to give a chromatographically separable mixture (ca. 1 : 1) of **47** and **48**, while no reaction was observed in a DMF solution.[32] In the next stage, removal of the benzyl protective group under DDQ oxidative conditions resulted in a complex mixture, probably owing to participation of the C13 hydroxy group. Accordingly, after protection as an acetyl ester, **47** and **48** underwent the manipulation to give the expected **49** and **5**. The synthetic **5** was identical in all respects of spectroscopic data and optical rotation with the reported data of onchitriol II.[17] The isomers **50** and **51** possessing the 10*S*-configurations were also synthesized by essentially the same procedure as mentioned above.[38] Although **50** had the proposed structure for onchitriol I, comparison with the reported data of **4** indicated that both had different structures. In addition to the reliability of the stereochemistry at C13—C16 positions which



Scheme 11.



Scheme 12.

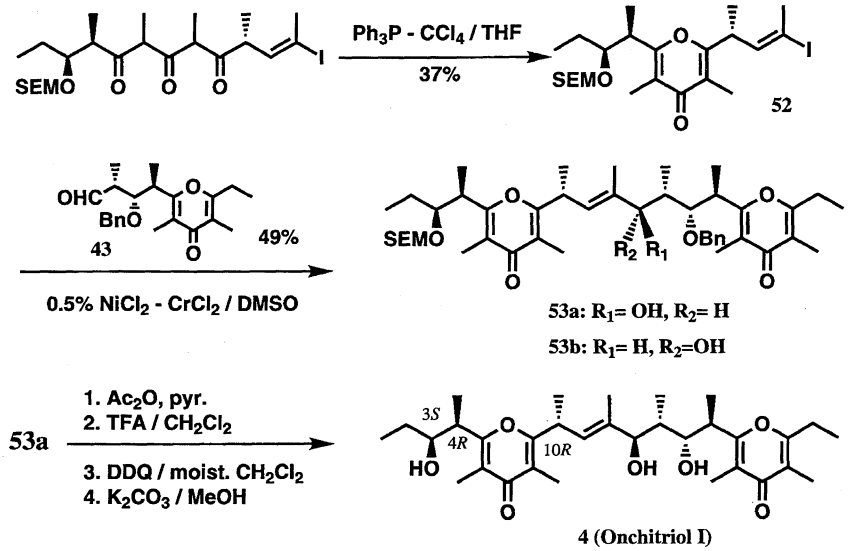


Scheme 13.

was verified by several methods, detailed inspection of the reported data as well as our results indicated onchitriol I would have a 3*S*,4*R*,10*R*-configuration. Based on this consideration, synthesis of **4** was undertaken by the coupling of vinyl iodide **52** with aldehyde **43** under the $NiCl_2$–$CrCl_2$ conditions (Scheme 14).[31] Deprotection of the major isomer **53a** provided **4**, exhibiting the identical spectroscopic data and optical rotation with those of natural onchitriol I. The total synthesis of **4** established the structural revision of the proposed stereochemistry at the C4 and C10 positions as 4*R*, 10*R*-configuration.

Through these investigations, onchitriols and peroniatriols have been found to exhibit an interesting stereochemical relationship. The C13—C16 positions of peroniatriol I (**2**) and onchitriol I (**4**), and those of peroniatriol II (**3**) and onchitriol II (**5**) have the same absolute configurations. Contrary to the identified structures in the right units, the C3—C10 positions of **2** and **4**, and those of **3** and **5** have enantiomeric relationships. As Reguera pointed out,[17] the stronger biological activity of **4** compared to that of **5** might require a *trans* 1, 3-diol system at the C13 and C15 positions. Contribution of such structural features to their biological activities as a defensive allomone, as well as cytotoxicities and antiviral activities will open a new bioscientific field.

Related Synthesis. Synthesis of the 4-Pyrone Derivatives Related to Siphonarins, Dihydrosiphonarins, and Baconipyrones. Siphonarins A and B (**54**, **55**) (from *Siphonaria zelandica* and *S. atra*), and dihydrosiphonarins A and B (**56**, **57**) (from *S. normalis* and *S. laciniosa*) are pulmonate mollusc-derived polypropionates.[3a] The structures were determined by spectroscopic comparison with siphonarin A (**54**), whose relative stereochemistry was defined by X-ray crystallographic analysis. Recently, the absolute configuration of siphonarin B (**55**) was established as shown in Fig. 4, by re-X-ray analysis of the corresponding *p*-bromophenylboronate derivative,[3b] along with the synthesis of the degradation product **58**.[3c] The latter investigation also showed that the absolute configuration of baconipyrone D (**59**) (from *Siphonaria baconi*), which could be derived from **55** via retro-aldol process,[4] is the same as that of **58**. A



Scheme 14.

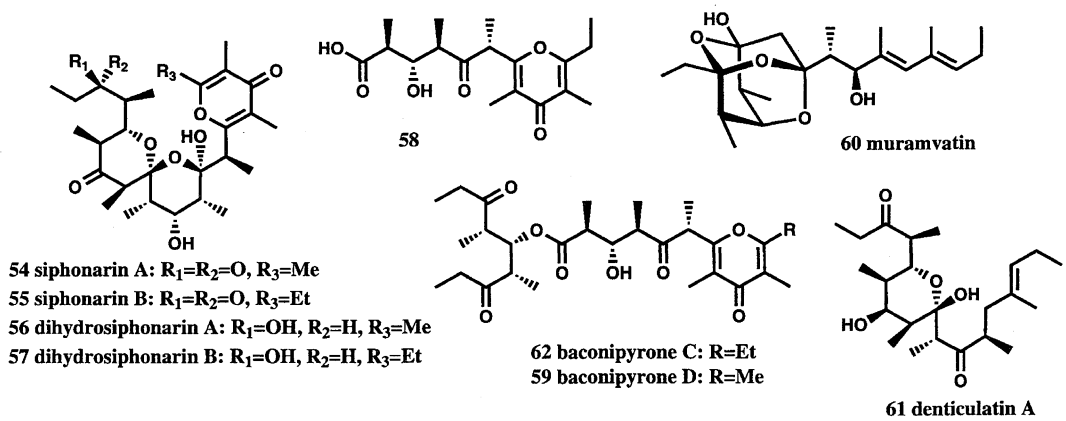
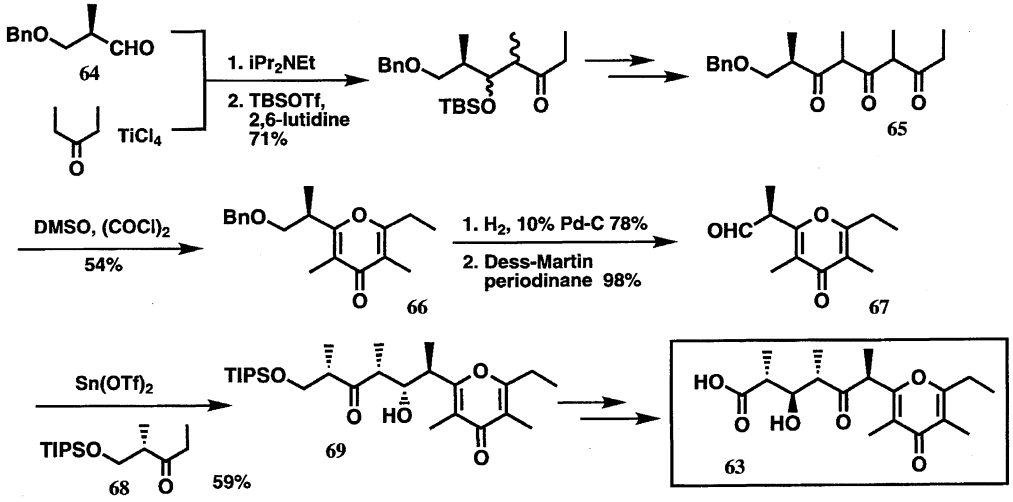


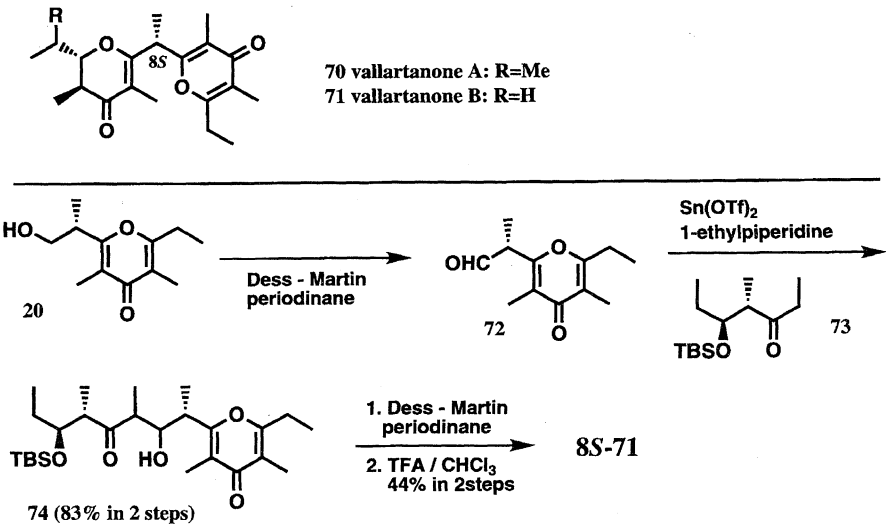
Fig. 4. Siphonarins and biogenetically related polypropionate-derived marine natural products.

joint research project by Garson and Paterson[3b,3c] proposed a biosynthetic pathway including propionate homologation and final cyclization, based on the stereochemical relationship of **54** with muramvatin (**60**) bearing a trioxaadamantanyl structure,[39] and tetrahydropyanyl-type denticulatin A (**61**).[40] As part of these investigations, Paterson synthesized the 4-pyrone **63**, an epimer of **58**, involving the stereocontrolled aldol reaction and the cyclizaiton to 4-pyrone (Scheme 15).[3c] Successive carbon chain elongation of aldehyde **64** under the Lewis acid conditions followed by oxidation provided a tautomeric mixture of the triketone **65**. Treatment of **65** with DMSO–$(COCl)_2$ effected the expected cylization to 4-pyrone **66**, which underwent deprotection and oxidation to yield the labile aldehyde segment **67**. Coupling reaction of **67** with tin enolate of **68**[41] afforded **69** with 93% ds. The following manipulation involving Evans–Tishchenco reduction[42] to a 1,3-*syn* diol system gave the target 4-pyrone **63**, which is identical in all respects of the spectroscopic data with the natural one, with the exception of the optical rotation, which exhibited an opposite sign. Consequently, the absolute configurations of siphonarin B (**55**) and its rearranged derivative baconipyrone C (**62**) were determined as shown in Fig. 4. It was also appeared that siphonarin A (**54**), dihydrosiphonarin A (**56**), and baconipyrone D (**59**) have the same stereochemical relationships.

Synthesis of Vallartanone B(71) and its Structural Revision. Vallartanones A and B (**70**, **71**),[5a] produced by the Mexican pulmonate mollusc *Siphonaria maura*, share a 4-pyrone linked with an optically active dihydro-4-pyrone via a C1 unit. While **70** has an inducing activity for larval settlement in the tube worm *Phragmatopoma californica*, **71** possesses deterrent activities of feeding of the fish *Thallasoma lunare*. The structural determination including the absolute configuration was accomplished by NMR techniques, along with circular dichronic spectrum employing the exciton coupling theory[43] which suggested 3*R*,4*R*,8*R*-configuration of **70**. The structure of vallartanone B (**71**) was elucidated by comparison of spectroscopic data, to have the same 3*R*,4*R*,8*R*-configuration as **70**. The synthesis of **71** by Arimoto et al. is summarized in Scheme 16.[5b] The 8*S*-4-pyrone **20** produced by the Ph_3P–CCl_4 reaction[21] was converted into aldehyde **72**, which was connected with ethyl ketone **73** under the aldol conditions to give **74**. Upon oxidation, **74** underwent simultaneous deprotection and cyclization, leading to 8*S*-**71**, which was contaminated with ca. 13% of 8*R*-**71**. The same feature was also observed in the synthesis of 8*R*-**71**. After chromatographic separation, ^1H and ^{13}C NMR, and CD spectral data of both compounds



Scheme 15.



Scheme 16.

indicated that natural vallartanones A and B (**70**, **71**) must be revised to have the 8*S*-configurations.

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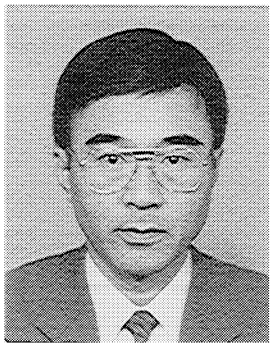

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