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Marine prostanoids

M S Miftakhov, M E Adler, F A Akbutina, G A Tolstikov

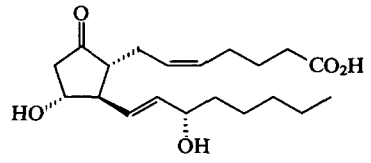
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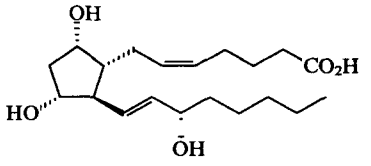
Abstract. The review describes the stages involving the isolation and the determination of the structures of marine prostanoids and their analogues, the problems of their biosynthesis, and their biological properties. The bibliography includes 76 references.

I. Introduction

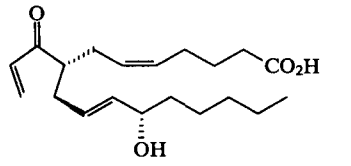
Prostaglandins (PG) were first discovered in the human seminal fluid by Kurzrok and Lieb[1] in 1930, but it was not until the beginning of the 1960s that Bergstrom and his coworkers[2–4] were able to isolate and identify a series of the main representatives of compounds of this class on the basis of the researches by Euler, who was Bergstrom's teacher. The structural formulae of the commonest series **2** prostaglandins are presented below.



PGE_2



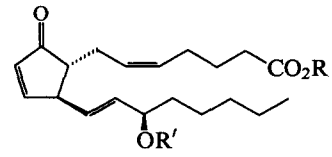
$PGF_{2\alpha}$



PGA_2

We may note that the content of total prostaglandins (more than ten prostaglandins of different types) in a rich source such as the plasma of human seminal fluid is only 300 μg ml^{-1}.[5] After the development of effective methods for the detection, isolation, and the determination of their structure, prostaglandins of different types and series as well as their derivatives were found at extremely low concentrations in virtually all mammalian organs and tissues and then in insects, plants, etc. (see the relevant reviews [6–10]).

Marine organisms, which are promising in this respect, did not prove an exception either. A major achievement of the period was the communication by Weinheimer and Sparings concerning the isolation of (15*R*)-PGA_2 (derivatives **1** and **2**) in 0.2% and 1.3% yields respectively from the coral *Plexaura homomalla*, which is common in the Caribbean Sea.[11] As can be seen from their structures, compounds **1** and **2** are the epimers of PGA_2 with respect to the allylic–alcoholic centre [C(15)] and they therefore lack the powerful hypotensive effects characteristic of PGA_2. Other workers[12] also isolated from corals of this species (15*R*)-PGE_2 and its ethyl ether in 0.1% – 0.2% yields. On the other hand, certain colonies of *Plexaura homomalla* contained only (15*S*)-prostaglandins identical to those isolated from mammals, while others contained approximately equal amounts of (15*R*)- and (15*S*)-PG.[13] Reasonable explanations of the lack of selectivity in the production of (15*R*)- and (15*S*)-PG by the coral were not proposed. Analysis of the lipids from both (15*R*)- and (15*S*)-prostaglandin-containing variants of *Plexaura homomalla* showed that 97% of the $C_{20:4}$ acid component comprises arachidonic acid. Therefore the formation of the (15*R*)-prostaglandins in some colonies of *Plexaura homomalla* and of (15*S*)-prostaglandins in other taxonomically identical colonies cannot be accounted for by the stereochemical differences between the initial $C_{20:4}$ acids.[14]



1, R = R′ = H
2, R = Me, R′ = Ac

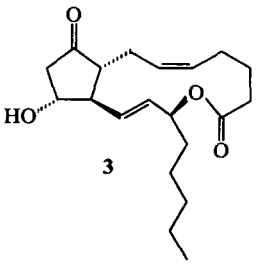
Schneider and coworkers[15,16] found 0.06% of PGE_2, traces of $PGF_{2\alpha}$, 13,14-dihydro-PGA_2, 5-*trans*-PGA_2, and other substances in Caribbean corals. Only insignificant amounts of (15*S*)-PG were discovered in specimens of *Plexaura homomalla* collected in the sea around Florida.[12] It was found that PGE_2 and $PGF_{2\alpha}$ are the most frequently encountered prostanoids in the marine organisms — coral, molluscs, seaweed, etc. Thus prostaglandin $F_{2\alpha}$, the 11-acetate of the methyl ester of $PGF_{2\alpha}$, and its 18-acetoxy-derivative were isolated from the soft

M S Miftakhov, M E Adler, F A Akbutina Laboratory for the Synthesis of Low-Molecular-Weight Bioregulators, Institute of Organic Chemistry
G A Tolstikov Institute of Organic Chemistry,
Ufa Scientific Centre, Russian Academy of Sciences, pr. Oktyabrya 71, 450054 Ufa, Russian Federation. Fax (7-347) 235 60 66

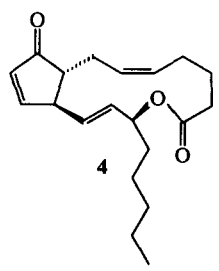
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coral *Lobophyton depressum*[17] and from the tissues of the molluscs *Tethys timbria* and *Aglisia californica*.[10] The content of PGE_2 in the Australian red seaweed *Gracularia lichenoides* is 0.05% – 0.07% of the dry mass.[18] $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ were isolated together with PGE_2 from the aqueous extracts of the sea sponge *Teprios zeteki*.[19]

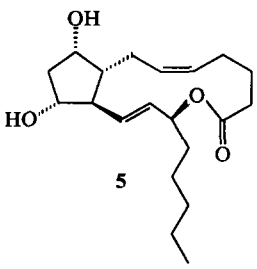
The 1,15-lactones of prostaglandins E_2, A_2, and $F_{2\alpha}$ (compounds **3**–**5**) and a series of their acyl derivatives, isolated from the tissues of the mollusc *Tethys timbria*, are of interest.[20] An unusual lactone **6**, related to prostanoids and called hybridalactone, was isolated from the red seaweed *Laurencia hybrida*. A mechanism of its biosynthesis from eicosapentaenoic acid has been postulated.[21] The structure of hybridalactone was confirmed by spectroscopic data and unambiguous synthesis.[22]



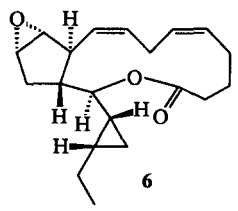
3



4



5

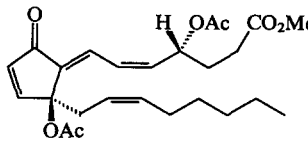


6

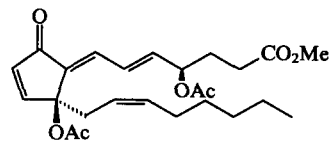
In order to identify the prostaglandins in the extracts from marine organisms, use was made of methods for their biological testing and their comparison with authentic specimens, immunochromatography and radioimmunology, thin-layer chromatography combined with biological testing for prostaglandin-like activity, etc.[10]

On the whole, it appears important that the above prostaglandins were detected and isolated in relatively large amounts from primitive nonmammalian sources (in contrast to mammals, in the tissues of which the content of prostaglandin does not exceed 1–2 ng g^{-1}, marine organisms are able to accumulate prostaglandins). The (15*R*)- and (15*S*)-PGA_2 substances produced by coral can be readily transformed chemically into prostaglandins of types E and F, which were used in its turn for the industrial manufacture of prostaglandins.[23] Several hypotheses concerning the biological functions of coral prostaglandins, including regulation of the ion and water transport in the coral as well as its protection against predators and parasites, have been put forward.

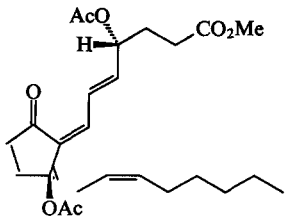
A group of Japanese scientists[24,25] published almost simultaneously in 1982 the results of studies devoted to the isolation from marine organisms and the determination of the structures of new prostanoids, which attracted attention because of their unusual structure and their antitumour activity. The prostanoids of this type detected in the corals of the Stolonifer *Clavularia virides* species were called clavulones by Yamada and coworkers.[24] Numerals ranging from I to IV were assigned, in order of decreasing polarity, to the related compounds **7**–**10** differing by the configuration of the double bonds at the C(5) and C(7) atoms. The names claviridenones D, C, B, and A, proposed for these structures by Kitagawa and coworkers[25] have not been widely used. Anticipating, we may note that clavulones and a series of similar structures — halovulones and punaglandins have been combined under the term marine prostanoids† in view of the unusual nature and uniqueness of their structures and this term also indicates the sources where they have been found and from which they have been isolated.



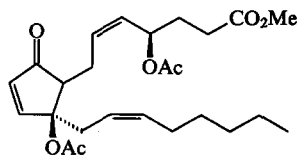
7, clavulone I



8, clavulone II



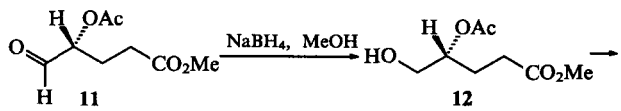
9, clavulone III



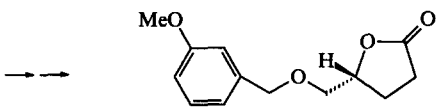
10, clavulone IV

The structure of the clavulones was established by thorough investigation of IR, UV, and ^1H and ^{13}C NMR spectroscopic data for these compounds, as well as of their chemical reactions. Additional evidence that compounds **7**–**10** are geometrical isomers was provided by the formation of the 1 : 6 : 12 : 2 mixture of all four compounds on UV irradiation of a benzene solution of any of these substances.[25] A similar result was achieved when one of the isomers was treated with a solution of oxalic acid in methanol (20 °C, 20 days).[26]

The absolute (*R*)-configuration of the C(4) chiral centre of clavulones was established by converting the aldehyde **11**, obtained by the ozonolytic cleavage of clavulone I, into the alcohol **12** and then into the lactone **13**, the enantiomer of which was obtained from the acetonide of D-glyceraldehyde.[26]



11 **12**

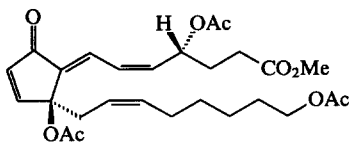


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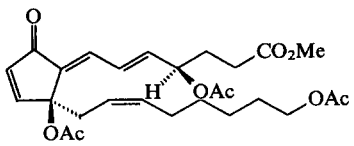
The study of ^1H NMR and circular dichroism spectra of the 9-(*p*-bromobenzoate) of clavulone I and its 12-deacetoxy-derivative established the (*S*)-configuration of the C(12) chiral centre.[26,27]

Subsequently three new C_{20}-acetoxyprostanoids **14**–**16** were isolated from the coral *Clavularia virides*.[28,29] Previously the C_{20}-hydroxyprostanoids were known as unstable prostaglandin metabolites detectable by gas–liquid chromatography or mass-spectrometrically. With the exception of the additional signal due to the CH_2OAc fragment, the spectroscopic characteristics of compounds **14**–**16** are identical with those of clavulones I–III, the absolute configuration of the chiral centres also remaining unchanged.

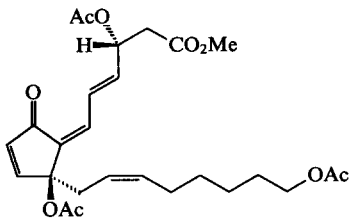
† As a consequence of a lack of appreciable structural differences from the classical prostaglandins isolated from mammals, it would be incorrect to combine the (15*R*)-PGA_2 and other prostaglandins (metabolites of C_{20} eicosapolyenoic acids) described previously with 'marine prostanoids' in terms of features defining this class. We shall therefore consider them only in terms of the historical aspect.



14

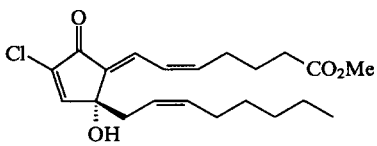


15

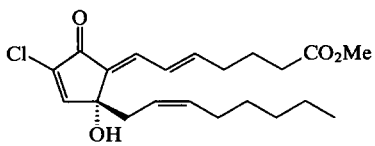


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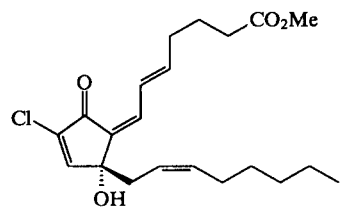
The next important stage of the studies on these lines was described in the communication published in 1985 concerning the isolation from *Clavularia virides* of 10-haloprostanoids exhibiting an anticancer activity—chlorovulones I–IV (compounds **17–20**).[30]



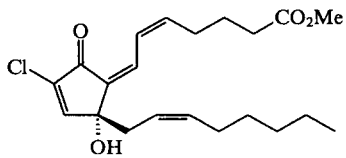
17, chlorovulone I



18, chlorovulone II



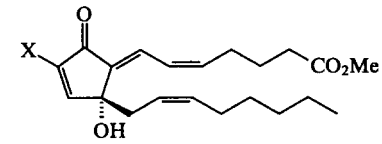
19, chlorovulone III



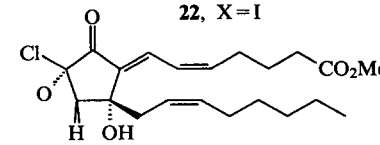
20, chlorovulone IV

The absolute configuration of the C(12) chiral centre in chlorovulones, determined from circular dichroism data of their derivatives and by comparing the spectroscopic characteristics as well as the specific angles of rotation of the natural chlorovulone II (compound **18**) and (−)-chlorovulone II obtained by enantioselective synthesis, was found to be the opposite of the configuration of the C(12) stereocentre of clavulones.[27]

In addition, prostanoids related to chlorovulones and containing Br and I atoms, which were called bromovulone I (compound **21**) and iodovulone I (compound **22**),[31,32] as well as the C(10,11)-epoxy-analogue **23**[33] were also identified among the series of compounds isolated from marine organisms. Like the parent chlorovulone I and clavulone I, they have the (5*Z*, 7*E*, 14*Z*)-configuration of the double bonds in the side chains.

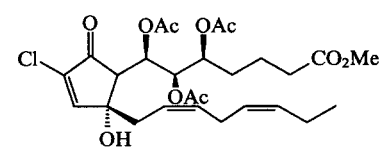


21, X = Br
22, X = I

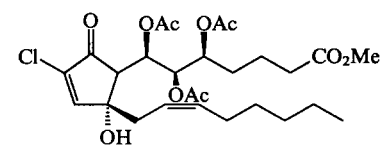


23

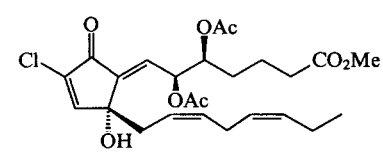
Representatives of halogenated eicosanoids with a more complex structure were isolated from the octocorals of the *Telesto riisei* species.[34,35] They have been called punaglandins I–IV (compounds **24–27**). The presence of vicinal acetate groups at the C(5) and C(6) atoms is characteristic of these compounds. The (*R*)-configuration of the C(12) chiral centre, refined by means of enantioselective synthesis, proved to be the opposite of that proposed initially and characteristic of clavulones.[35,36]



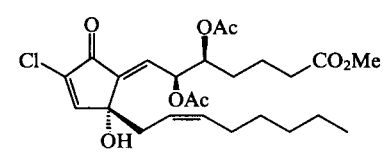
24, punaglandin I



25, punaglandin II



26, punaglandin III



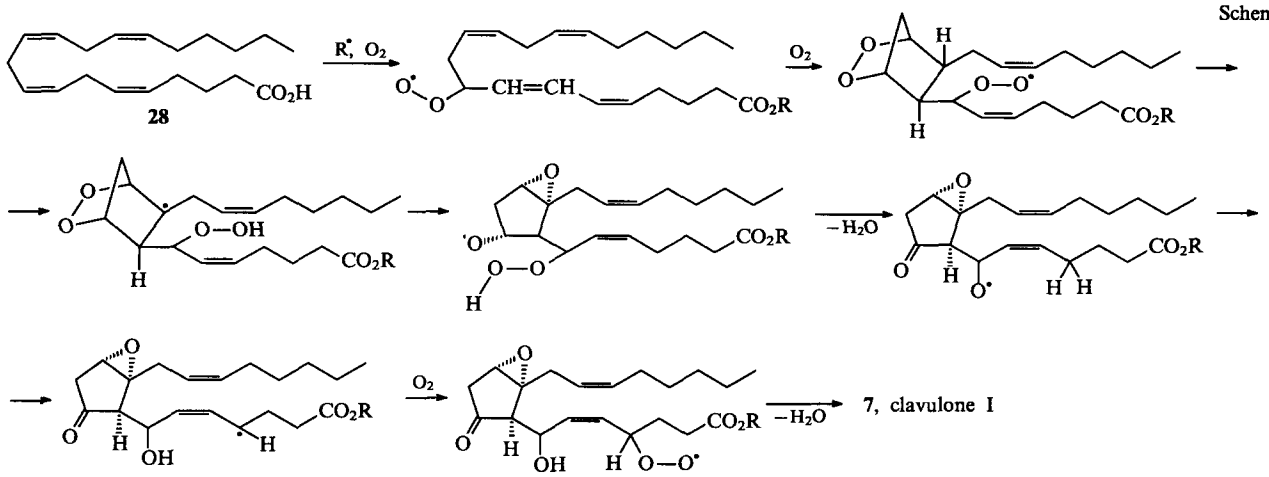
27, punaglandin IV

II. Biosynthesis of marine prostanoids

Arachidonic acid **28** is known to be synthesised by the 'endoperoxide pathway'. Initially Corey et al.[38] put forward the hypothesis that the biosynthesis of clavulones proceeds via a similar mechanism and that the key stage in this process is the ready transformation of the β-peroxyl radicals into cyclopentane epoxyketo-derivatives, which are formed as a result of the intramolecular attack by the radical on the nearest peroxide oxygen atom (Scheme 1, see over).

Somewhat later it was observed that, when arachidonic acid is treated with a homogenate of the coral of the *Clavularia virides* or *Pseudoplexaura porosa* species, the habitats of which are extremely remote from one another, a new eicosanoid **29**, called preclavulone A (PC-A), is formed.[35,39,40] Its structural similarity to 12-oxophytodienoic and *cis*-jasmonic acids suggested the similarity of the pathways leading to their biosynthesis, probably via a cationic mechanism through 8-hydroperoxyeicosatetraenoic acid [(8*R*)-HPETE] **30**, the allene oxide **31**, and the oxypentadienyl

Scheme 1

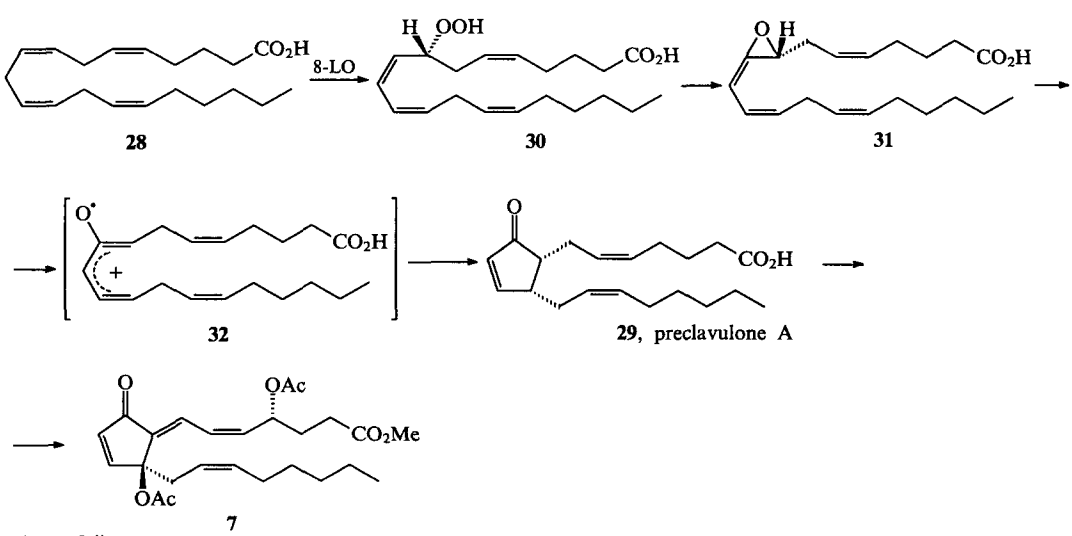


cation **32**.[40–42] Next, as a result of the successive enzymic hydroxylation of the C(4), C(7), and C(11) atoms, exhaustive acylation, and the elimination of the AcO group to the C(7) atom, preclavulone A is converted into clavulones (Scheme 2).

The formation of preclavulone A when the coral homogenate is kept in contact with tritium-labelled (8*R*)-HPETE confirms that the acid **30** is an intermediate in the biosynthesis of PC-A from arachidonic acid (radiochemical yield up to 13%).[42] The biosynthesis of PGA_2 in corals of the *Plexaura homomalla* species, which is known to be the richest source of prostaglandins (up to 2% of the dry residue), can take place via a similar chain of reactions (Scheme 3) from the acid **28** via the allene oxide **33**.[43] Thus, from the evolutionary point of view, the possibility of the biosynthesis of protanoids in mammals and marine organisms via different pathways is surprising.

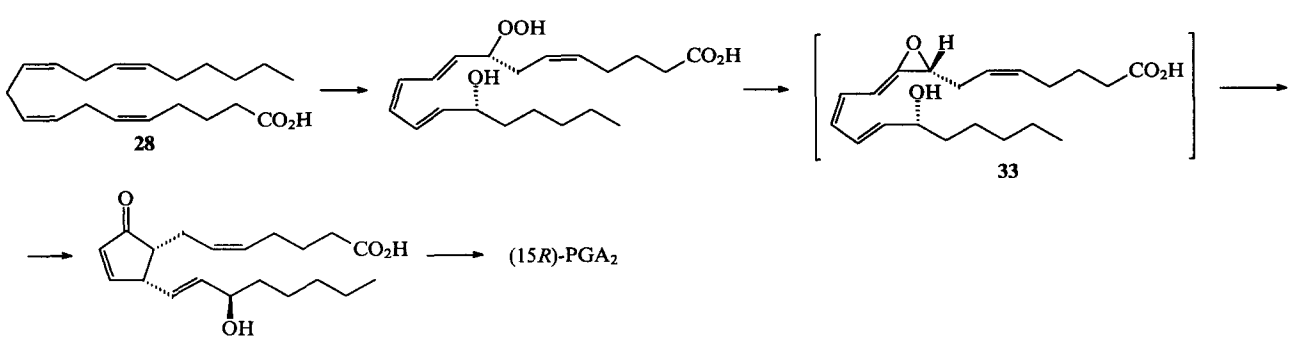
As already mentioned, the biomimetic synthesis of PC-A achieved by Corey[40] confirms the possibility, in principle, of the 'marine' pathway to the biosynthesis of prostanoids. The absolute configuration of the chiral centres of PC-A was established by the enantioselective synthesis of the methyl ester of (−)-preclavulone A.[44] The Cope rearrangement of the trimethylsilyl ether of the enone **34** undoubtedly constitutes a rational way of constructing the structures of the *cis*-joined tetrahydroindenes **35** and of achieving the synthesis of the key cyclopentanone derivative **36** with the required orientation and chemodifferentiation of the side substituents. The subsequent operations are standard and are well known from the chemistry of prostaglandins (Scheme 4).

Scheme 2

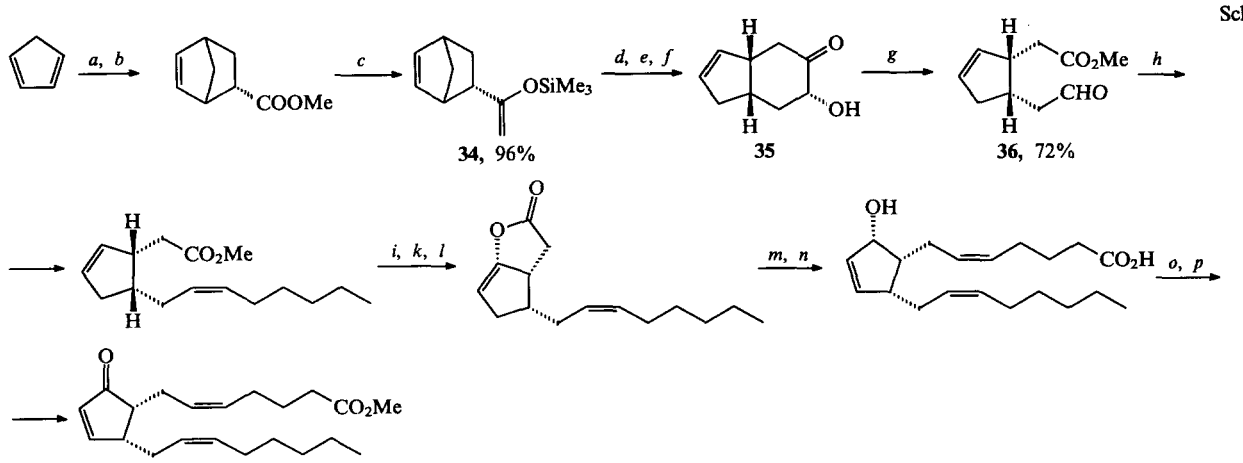


8-LO = 8-lipoxygenase.

Scheme 3



Scheme 4

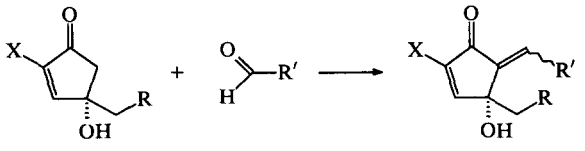


29a

(*a*) Acrylate of (*R*)-pentalactone, $TiCl_4$; (*b*) 3 equiv. of MeLi, from −25 to 0 °C, 1 h; (*c*) 2 equiv. of lithium diisopropylamide (LDA), 2.3 equiv. of Me_3SiCl, THF, −78 °C, 1.5 h; (*d*) 200 °C, toluene, 4 h; (*e*) 1.1 equiv. of *m*-$ClC_6H_4CO_3H$, 4 equiv. of $NaHCO_3$, CH_2Cl_2, −5 °C, 1 h; (*f*) 5 equiv. of 48% aqueous HF, 5 equiv. of NEt_3; (*g*) $Pb(OAc)_4$, MeOH, −5 °C, 1 h; (*h*) 1.6 equiv. of $Ph_3PC_6H_{13}Br$, 1.5 equiv. of sodio-derivatives of hexamethyldisilazane (HMDS-Na), THF, from −85 to 0 °C; (*i*) 1 M LiOH, H_2O–MeOH–THF (4 : 3 : 5), 23 °C, 24 h; (*k*) 3 equiv. of I_2, 5% aqueous $NaHCO_3$–THF, 0 °C, 2.5 h; (*l*) 2 equiv. of 1.5-diazabicyclo[5.4.0]undec-5-ene (DBU), dimethoxyethane (DME), refluxing for 12 h; (*m*) 2 equiv. of diisobutylaluminium hydride (DIBAH), CH_2Cl_2, −78 °C, 40 min; (*n*) $BrPPh_3(CH_2)_4CO_2H$, HMDS-Na, THF, 25 °C 2 h; (*o*) CH_2N_2, ether; (*p*) [O], CH_2Cl_2, 23 °C, 1 h.

III. Chemical syntheses of marine prostanoids

The stages involving the formation of the tertiary alcohol cyclopentane unit with a lower chain and the introduction of the polyoxygenated α-chain with an *exo*-methylene bond via the condensation of the enolate of the ketone **37** with the aldehyde **38** having the required structure are the most characteristic in the syntheses of marine prostanoids.



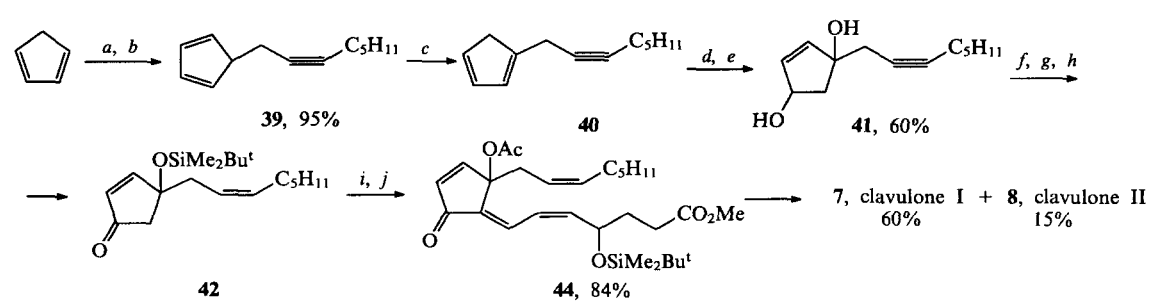
37, X = H, Cl **38**

Corey and coworkers[45] were the first to achieve the total synthesis of the racemic clavulone I. A synthetic scheme starting from cyclopentadiene is presented below.

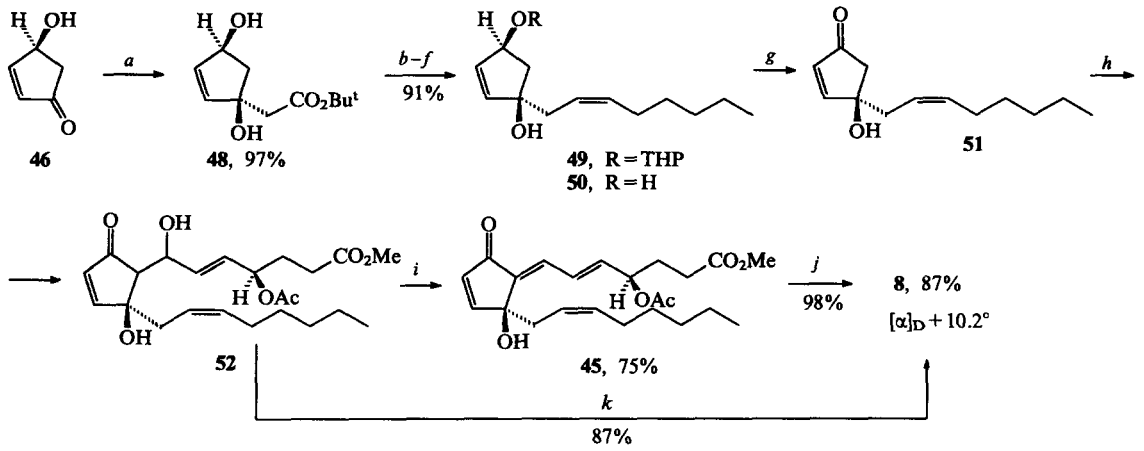
2-Alkylcyclopentadiene **40** was obtained by alkylating cyclopentadienyllithium with 1-iodooct-2-yne and subsequent 1,5-sigmatropic isomerisation of compound **39** under mild conditions. The key stage — photochemical oxidation of the diene **40** and the reduction of the intermediate endoperoxide by treatment with $NaBH_4$ — led to the diol **41**, which was converted by standard procedures into the synthon **42**. The second important stage — the condensation of the ketone enolate **42** with the aldehydoester **43** and the selective replacement of the Bu^tMe_2Si group protecting the tertiary hydroxyl by Ac — led to a mixture of the diastereoisomers **44** in proportions of 1 : 1, which was separated by column chromatography on SiO_2. The ^1H NMR spectrum confirmed the complete absence of the (7,8-*Z*) isomer. The less polar isomer was then smoothly transformed into a mixture of clavulones I and II, which were isolated by column chromatography on silica gel in 60% and 15% yields respectively and were identical as regards spectroscopic and chromatographic characteristics with the natural specimens.

The first enantioselective and stereoselective synthesis of clavulone II and of its 12-*O*-deacetyl derivative **45** has been described by Nagaoka et al.[46] The strategy of the synthesis is analogous to that presented above and consists in the successive introduction of the α-chain and of the chiral α,β-unsaturated aldehyde **47**, obtained from D-(+)-mannitol, into the structure of the optically active cyclopentenone **46** (Scheme 5).

The *cis*-diol **48** has been obtained with a high stereoselectivity by the interaction of (4*S*)-hydroxycyclopentenone **46** with the lithium enolate of *tert*-butyl acetate. The subsequent stages involving the blocking of the alcoholic groups, the conversion of the ester group into an aldehyde group, and the Wittig reaction, led to the alkene **49** in high yields. The oxidation of the diol **50** by Corey's reagent and condensation of the lithium enolate of the enone **51** with the aldehyde **47** afforded a diastereoisomeric



(*a*) BuLi, C_5H_{12}–THF; (*b*) 1.1 equiv. of $ICH_2C{\equiv}CC_5H_{11}$, from −78 to 30 °C, 3 h; (*c*) 23 °C, 4 h; (*d*) 0 °C, *hv*, MeOH, −40 °C, 2 h; (*e*) $NaBH_4$, MeOH; (*f*) pyridinium chlorochromate (PCC), CH_2Cl_2, 23 °C, 2 h; (*g*) H_2, $Pd/CaCO_3$, EtOAc–Py (9 : 1); (*h*) 2 equiv. of Bu^tMe_2SiCl, 3.5 equiv. of 2.6-lutidine, CH_2Cl_2, from 0 to 23 °C, 2.5 h; (*i*) LDA, THF, −78 °C, 5 min; (*j*) HOCCH=CHCH[OSi(Me$_2$)Bu^t]$CH_2CH_2CO_2Me$ **43**, from −78 to 10 °C, 6 h; (*k*) 5 equiv. of Bu_4^nNF, 20 equiv. of Ac_2O, 3 equiv. of 4-dimethylaminopyridine (4-DMAP), from 0 to 23 °C, 30 min; (*l*) column chromatography on SiO_2, Et_2O–C_6H_6 (6 : 4).



Scheme 5

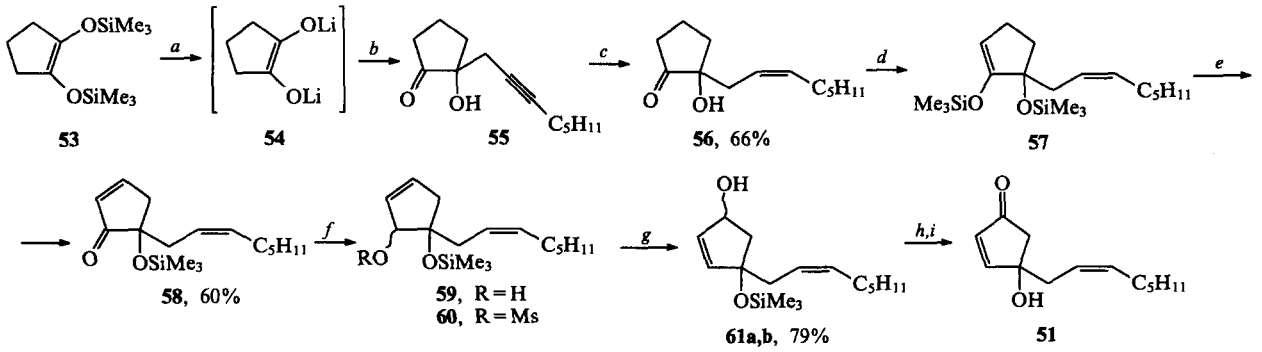
(*a*) $MeCO_2Bu^t$, LDA, THF, −78 °C; (*b*) dihydropyran (DHP), camphorsulfonic acid, Et_2O, 0 °C; (*c*) $LiAlH_4$, Et_2O, 20 °C; (*d*) DMSO–$(COCl)_2$, CH_2Cl_2, −78 °C, NEt_3; (*e*) $Ph_3PC_6H_{13}Br$, Bu^nLi, THF–HMPTA (hexamethylphosphoramide), −40 °C; (*f*) AcOH–H_2O (4 : 1); (*g*) PCC, molecular sieves (3 Å), CH_2Cl_2, 20 °C; (*h*) LDA, THF, −78 °C, HOCCH=CHCH(OAc)$CH_2CH_2CO_2Me$ **47**; (*i*) MsCl [Ms = methanesulfonyl (Translator)], NEt_3, CH_2Cl_2; (*j*) Ac_2O, Py, 30 °C; (*k*) Ac_2O, Py, 50 °C.

mixture of the alcohols **52**, the methanesulfonates of which are converted into 12-*O*-deacetylclavulone **45** on treatment with NEt_3. Standard acetylation of the latter afforded (+)-clavulone II, all the characteristics of which were identical with those of an authentic specimen of the natural product.

A fundamentally different pathway leading to the synthon **51** from the disilyl ether **53** has been proposed.[47] The key stage in this scheme—the interaction of the dilithium derivative of the 1,2-enediol **54** with 1-bromooct-2-yne, leading to a satisfactory yield of the hydroxyketone **55**, merits attention. Next, the ketoalcohol **56**, obtained by partial hydrogenation, is converted into the silyl ether of the enol **57**, which is oxidised by treatment with $Pd(OAc)_2$ in acetonitrile to the enone **58**. The boron hydride reduction of the latter, the methanesulfonation of the resulting allyl alcohol **59**, and subsequent hydrolysis of the methanesulfonate **60** afford a diastereoisomeric mixture of allyl alcohols **61a, b** in proportions of 1 : 1. The transformation of the enone **58** into an alcohol, formally regarded as 1,3-transfer of the oxygen-containing functional group, is possible as a consequence of the unidirectionality of the stages involving the hydrolysis and inversion of the sterically hindered allyl methanesulfonate **60**. The Collins oxidation of the alcohol **61** with subsequent hydrolysis of the protecting groups completes the synthesis of the enone **51**.

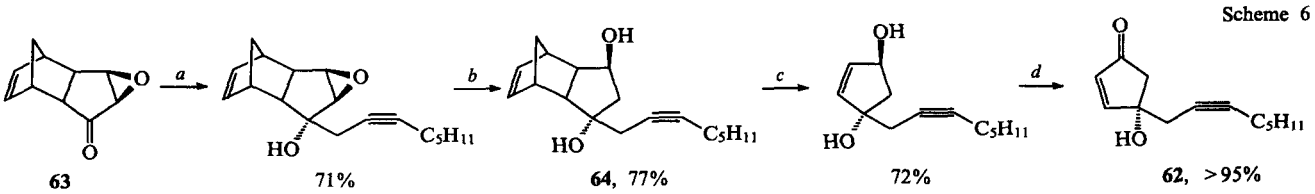
The acetylenic enone **62** described above, which is the equivalent of the synthon **51**, was obtained from the epoxyketone **63**, which is formed readily in its turn from *endo*-dicyclopentadiene.[48] The key stage in this scheme is the vacuum flash pyrolysis of the norbornene derivative **64** (Scheme 6).

The effective stereospecific synthesis of clavulones from Corey's lactone—a synthon popular in the synthesis of prostaglandins—is of special interest.[49] The polyfunctionalised cyclopentane synthon **65** is an extremely rational starting compound for the construction of the of clavulone structure. The main problem in work involving this compound is the stereoselective introduction of the C(12)-hydroxy-group. For this purpose, Corey's lactone was converted via the α,β-unsaturated lactone **66** into the allyl alcohol **67** and then into the epoxide **68**



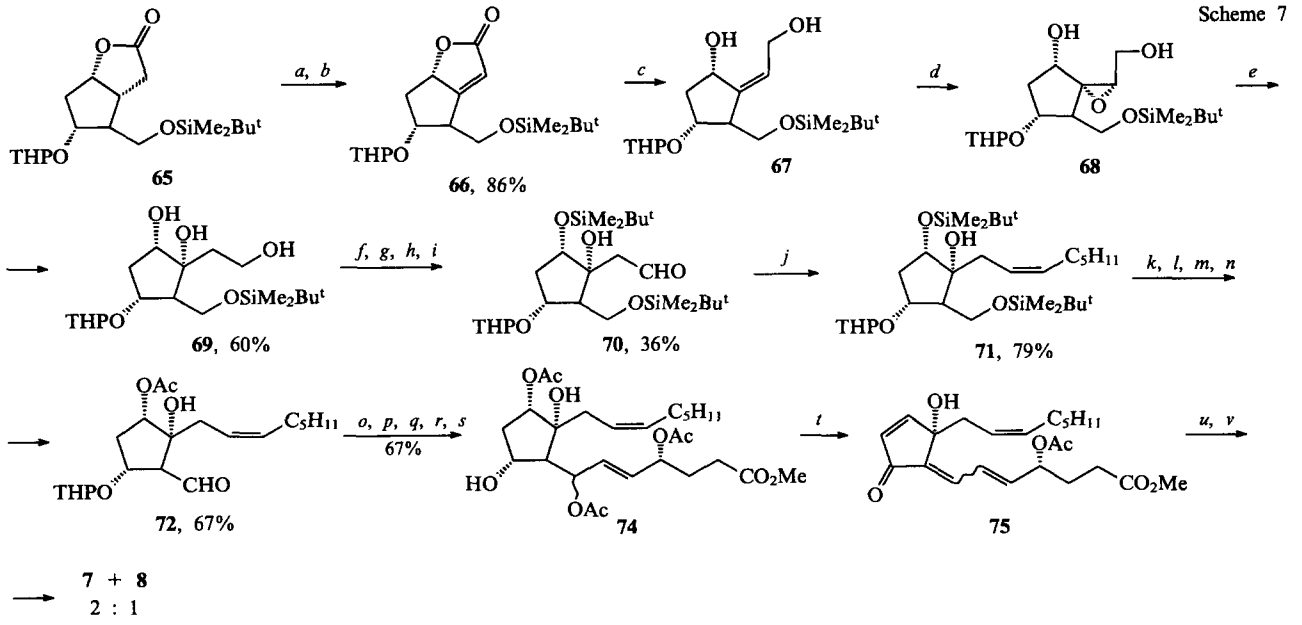
(*a*) MeLi, DME, Et_2O, −20 °C; (*b*) $BrCH_2C{\equiv}CC_5H_{11}$, HMPA, DME, −25 °C; (*c*) Lindlar H_2 catalyst, C_6H_{12}, 20 °C; (*d*) Me_3SiOTf [Tf = trifluoromethanesulfonate (Translator)], 2,6-Butidine, CH_2Cl_2, 25 °C; (*e*) $Pd(Ac)_2$, AcCN, 20 °C; (*f*) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, Ms_2O, Py, 4-DMAP, CH_2Cl_2, 0 °C; (*g*) H_2O, Me_2CO, 25 °C; (*h*) $CrO_3.2Py$, CH_2Cl_2, 0 °C; (*i*) AcOH–H_2O–THF, 25 °C.

Scheme 6



(*a*) $BrZnCH_2C{=}C(CH_2)_4Me$, THF; (*b*) $LiAlH_4$, THF, 25 °C; (*c*) 550 °C, 0.05 Torr; (*d*) PCC, CH_2Cl_2, 25 °C.

Scheme 7

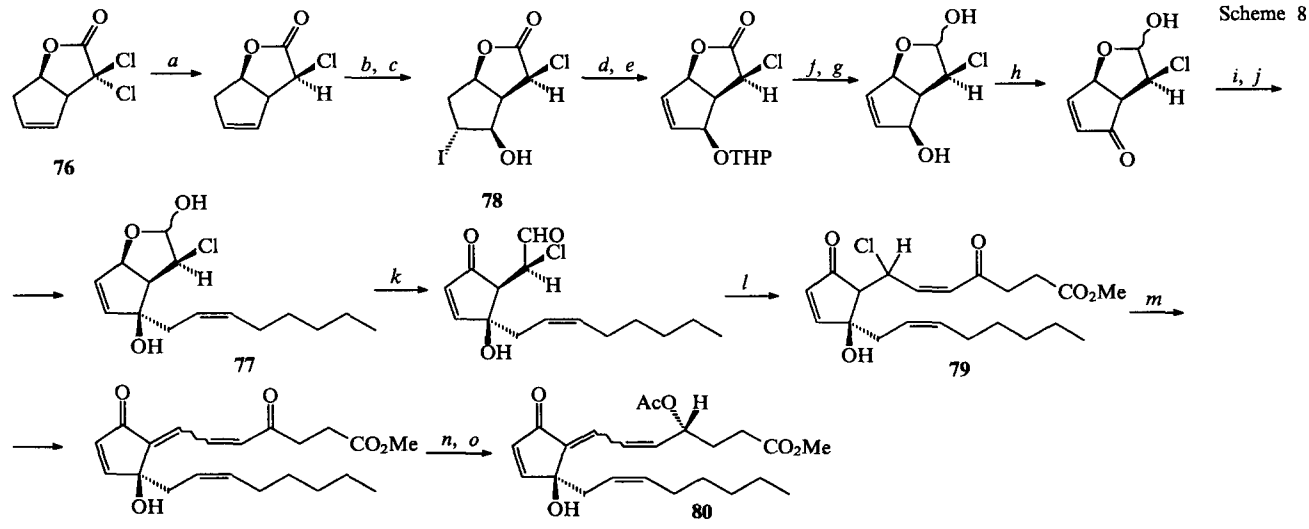


(*a*) LDA, PhSeCl, THF, −78 °C; (*b*) 10% aqueous H_2O_2, CH_2Cl_2, 1 h; (*c*) DIBAH, toluene, 0 °C, 30 min; (*d*) 2 equiv. of Bu^tOOH, $VO(acac)_2$; (*e*) 6 equiv of Red-Al, THF, 0 °C, 30 min; (*f*) PhCOCl, Py, CH_2Cl_2, −20 °C, 1 h; (*g*) Bu^tMe_2SiCl, Im (imidazole), DMF, 25 °C, 18 h; (*h*) K_2CO_3, MeOH, 40 °C, 1 h; (*i*) $CrO_3.2Py$, CH_2Cl_2, 0 °C, 15 min; (*j*) $PPh_3=CHC_5H_{11}$, THF− HMPTA (10 : 1), from −78 to 25 °C; (*k*) Bu_4NF, THF, 0 °C; (*l*) Ac_2O, Py, 25 °C; (*m*) Bu_4NF, THF, 0 °C; (*n*) $CrO_3.2Py$, CH_2Cl_2, 0 °C; (*o*) $LiCH=CHCH(OLi)(CH_2)_3OTHP$ **73** (THP = tetrahydropyran-2-yl), THF, −78 °C; (*p*) Ac_2O, Py, 25 °C, 18 h; (*q*) AcOH − H_2O (3 : 1), 80 °C, 8 min; (*r*) the Jones reagent, −20 °C, 30 min; (*s*) CH_2N_2, ether; (*t*) filtration through SiO_2; (*u*) Ac_2O, Py, 30 °C, 18 h; (*v*) high-pressure liquid chromatography.

(Scheme 7). On treatment with sodium bis(2-methoxyethoxy)-aluminium hydride (Red-Al), the epoxide afforded the tertiary alcohol **69** in 60% yield. The construction of the ω-chain from the triol **69** via the aldehyde **70** by the Wittig reaction does not present difficulties. Manipulation of the protecting groups in the resulting unit made it possible to arrive at compound **71**, the Collins oxidation of which led to the corresponding aldehyde **72**, which was then condensed with the dilithium intermediate **73**. By performing on the intermediate aldol the operations: acylation, hydrolysis of the protecting groups, the Jones oxidation, and methylation, the ketoester **74** was obtained. During the slow filtration of the latter through a layer of silica gel, the labile C(7)- and C(12)-acetoxy-groups were smoothly split off, which led to the thermodynamically favourable conjugated polyene structure **75** in the form of a mixture of isomers. Acylation of the tertiary alcoholic functional group at the C(12) atom in compound **75** gave rise to a mixture of clavulones I and II in proportions of 2 : 1, which were separated by high-pressure liquid chromatography (HPLC).

The initial compound in another effective scheme for the stereospecific synthesis of clavulones is the readily available *gem*-dichlorolactone **76**.[50,51] The key synthon **77** with a tertiary alcoholic group was obtained by a ten-stage sequence of reactions including the selective dechlorination of the lactone **76**, the preparation of the iodohydrin **78**, dehydroiodination with formation of a double bond, reduction to the lactol, the Jones oxidation, introduction of the ω-chain, and the selective hydrogenation of the triple bond (Scheme 8). In order to form the α-chain, the lactol **77** was converted into the corresponding aldehyde and was subjected

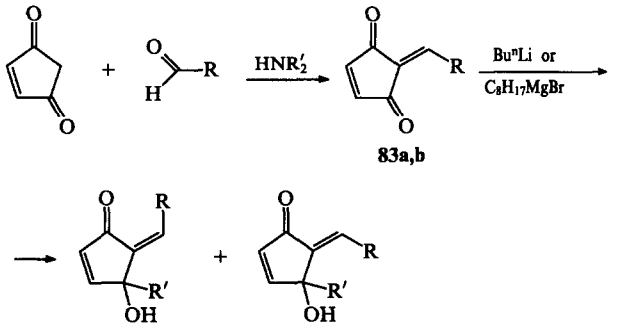
Scheme 8



(*a*) Zn, AcOH, 15–20 °C, 0.5 h; (*b*) 5% Na_2CO_3, 25 °C, 0.5 h; (*c*) 5 N AcOH, KI, 25 °C, 3 h; (*d*) DHP, *p*-TsOH, CH_2Cl_2, 1.5 h; (*e*) DBU, THF, 25 °C, 15 h; (*f*) diisobutylphosphorus hydride (DIBPH), toluene, −70 °C, 0.5 h; (*g*) $BF_3.Et_2O$, MeOH, 0.5 h; (*h*) Jones reagent, 25 °C, 0.5 h; (*i*) $Me(CH_2)_4C\equiv CCH_2Li$, THF–$Et_2O$, from −78 to 15 °C; (*j*) H_2, $Pd/BaSO_4$, 25 °C; (*k*) Jones reagent, 60 °C, 1 h; (*l*) $(MeO)_2POCH_2CO(CH_2)_2Me$, NaH, THF; (*m*) OH^-; (*n*) $Zn(BH_4)_2$; (*o*) Ac_2O.

to Wittig condensation with dimethyl 4-methoxycarbonyl-2-oxobutylphosphonate. In conclusion, the diketone **79** obtained was converted into a mixture of clavulones **80** by dehydrochlorination, selective reduction of the keto-group in the α-chain, and exhaustive acylation.

A convergent approach to the synthesis of clavulone-like compounds **81a–d** and **82a–d**, fundamentally different from those described above, has been proposed by Tolstikov et al.[52] The scheme is based on the initial construction of a new synthon — cyclopentene-1,3-dione **83a,b** with an exocyclic double bond in the side chain — and the subsequent introduction of the ω-chain with the simultaneous generation of a tertiary hydroxy-group via the condensation of the enone with the corresponding organometallic reagents.



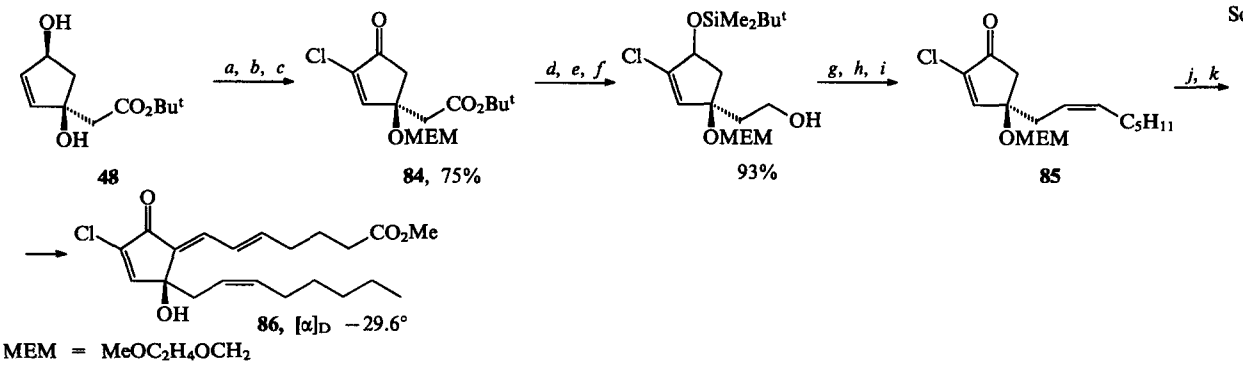
The enantioselective synthesis of (−)-chlorovulone II was undertaken by Yamada and coworkers[27] in order to establish the absolute configuration of the chiral centres in this natural product. The scheme for the synthesis reflects to an appreciable extent the strategy used by the same workers in the synthesis of clavulones.[46] The initial compound in this case is the optically active diol **48** obtained from (4*S*)-hydroxycyclopenten-2-one, which was converted in three stages into α-chlorocyclopentenone **84** and further into the key intermediate **85**. The subsequent transformation of this synthon led to (−)-chlorovulone II (compound **86**), identical in terms of all its spectroscopic characteristics, except for the sign of the angle of rotation, with a specimen of the natural product (Scheme 9).

Punaglandins II and IV have been obtained mainly in accordance with schemes similar to those described above for clavulones and chlorovulones.[27,46]

Thus, according to Nagaoka et al.,[35] the lithium enolate of the chiral cyclopentenone **87** is condensed with the chiral aldehyde **88**, synthesised from 2-deoxy-D-ribose via the acetonide **89** and the (*S*)-aldehyde **90**, which readily isomerises to compound **88** on treatment with catalytic amounts of K_2CO_3 in methanol (Scheme 10). The key condensation reaction and the subsequent standard transformations yielded a set of clavulones with different configurations of the chiral centres. The structures of punaglandins III and IV, which have the (5*S*, 6*S*, 12*R*)-configuration, were refined by comparing the spectroscopic (^{1}H NMR, IR, UV, and CD) as well as optical rotation data and the chromatographic characteristics of the synthetic and natural specimens.

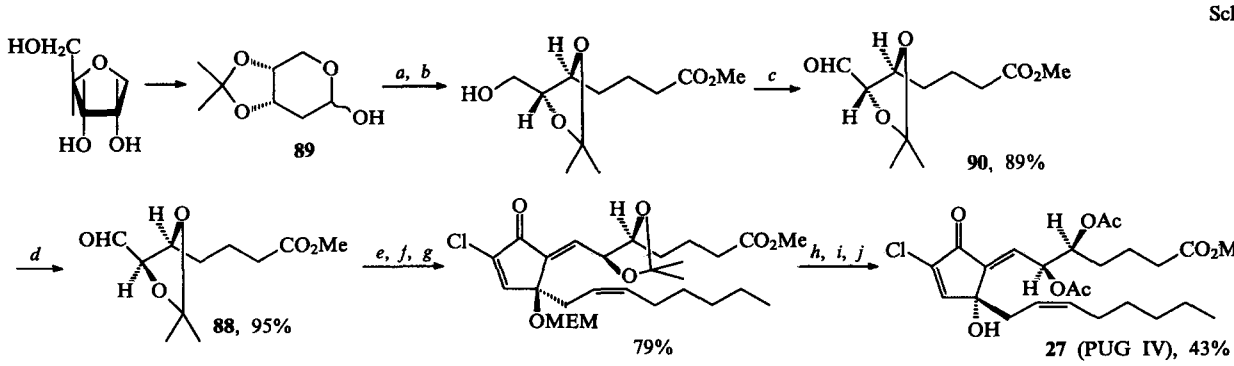
Another scheme for the preparation of punaglandins (IV) is based on the use of 1,2-bistrimethylsilylcyclopentene **53**, which was used earlier in the synthesis of clavulones.[53] The intermediate **91**, obtained by chlorinating the synthon **56**, was reduced after

Scheme 9



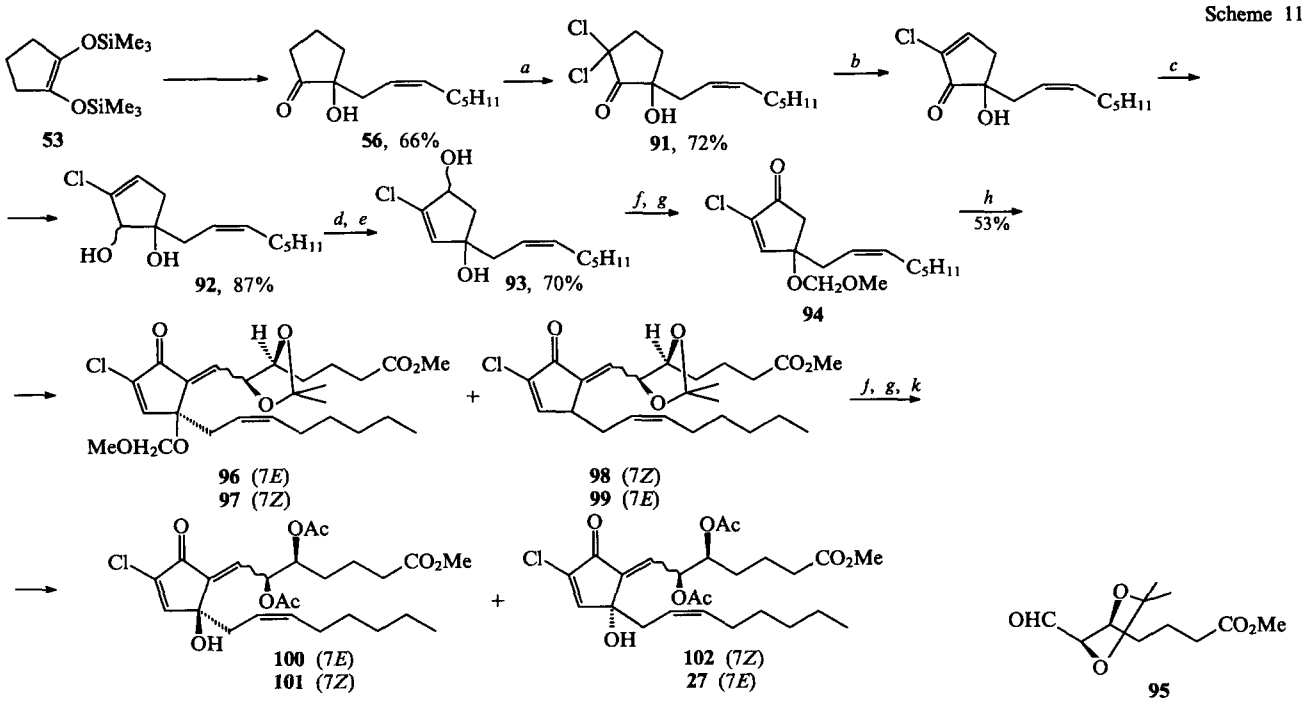
(*a*) Jones reagent, 0 °C; (*b*) $ClCH_2OMe$, Pr^i_2NEt, $(CH_2Cl)_2$, 60 °C; (*c*) Cl_2, Et_2O, 25 °C, NEt_3; (*d*) $NaBH_4$, $CeCl_3$, MeOH, 25 °C; (*e*) Bu^tMe_2SiCl, Im, DMF, 25 °C; (*f*) $LiAlH_4$, Et_2O, 0 °C; (*g*) $(COCl)_2$, DMSO; (*h*) $Ph_3P{=}CHC_5H_{11}$, THF–HMPTA, 42 °C; (*i*) H^+; (*j*) 1 equiv. of LDA, $OHC(CH{=}CH)_2CH_2CO_2Me$, THF; (*k*) conc. HCl–AcOH (1:50).

Scheme 10



(*a*) 1.1 equiv. of $Ph_3PCH{=}CHCH_2CO_2Me$, DME, refluxing, 6 h; (*b*) H_2, 10% Pd/C, EtOAc, 23 °C, 4 h; (*c*) 1.1 equiv. of $(COCl)_2$, 2 equiv. of DMSO, CH_2Cl_2, −78 °C, 10 min, NEt_3; (*d*) K_2CO_3–MeOH, 23 °C, (*e*) 1.2 equiv. of LDA, **87**, THF, −78 °C, 10 min; (*f*) Ac_2O, Py, 4-DMAP, 60 °C, 40 min; (*g*) SiO_2; (*h*) AcOH–H_2O (4:1), 60 °C, 1 h; (*i*) Ac_2O, Py, 70 °C, 40 min; (*j*) conc. HCl–AcOH (1:50), 40 °C, 15 min.

Scheme 11



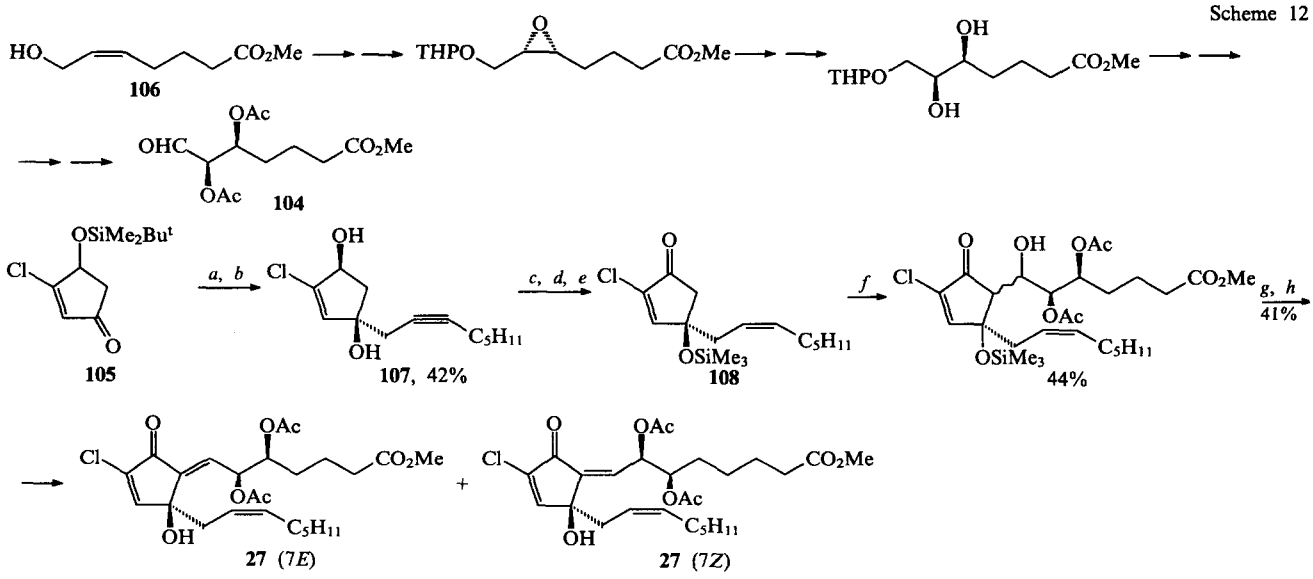
(*a*) *N*-chlorosuccinimide (NCS), NaOAc, dioxane, 25 °C; (*b*) LiCl, DMF, 120 °C; (*c*) $NaBH_4$, $CeCl_3$; (*d*) 1.3 equiv. of 4-DMAP, Py–CH_2Cl_2, 0 °C, 50 min; (*e*) 80% aqueous DMSO; (*f*) dipyridinium chromate (DPC), DMF; (*g*) $MeOCH_2Cl$, Pr^i_2NEt $(CH_2Cl)_2$, 60 °C; (*h*) LDA, **95**; (*i*) 80% aqueous AcOH, 100 °C.

dehydrochlorination to the diol **92**, which was converted into a secondary methanesulfonate and solvolysed in 80% aqueous DMSO (Scheme 11). The solvolysis of methanesulfonate proceeds with the allyl rearrangement and affords the alcohol **93** [a 1 : 1 mixture of the epimers at C(9)]. Oxidation of the crude mixture yielded a cyclopentanone derivative, which was converted into the corresponding methoxymethyl-blocked ketone **94**. The lithium enolate of the latter was treated with the aldehyde **95** and a mixture of the four diastereoisomers **96**–**99** obtained in equal amounts was separated by column chromatography. Their absolute configurations were determined by comparing the spectroscopic and optical rotation characteristics with those for authentic specimens. Selective hydrolysis of the isopropylidene protecting group in each of the products followed by acylation and acid hydrolysis afforded compounds **27** and **100**–**102** in 30%–40% yields, compound **27** being identical with the natural punaglandin IV.

A similar strategy (introduction of the ω-chain into the corresponding cyclopentenones, chlorination of the cyclopentane ring, and addition of a chiral aldehyde — the equivalent of the α-chain — by means of aldol condensation) has been used in the synthesis of 6-*epi*-14,15-dihydropunaglandin IV.[54]

Noyori's group[36] described a convergent synthesis of the natural (7*E*)- and (7*Z*)-punaglandins IV by means of the successive introduction of precursors of the ω-chain (compound **103**) and the α-chain (compound **104**) into (4*S*)-cyclopentenone **105**.

Scheme 12



(*a*) 1 equiv. of $H_2C{=}C{=}C(C_5H_{11})SnBu^n_3$ **103**, BuLi, THF, −78 °C; (*b*) Bu_4NF; (*c*) the Lindlar catalyst, MeOH; (*d*) $Py.2CrO_3$, DMF; (*e*) $MeSO_3SiMe_3$, Pr^i_2NH, CH_2Cl_2; (*f*) **104**, LDA, THF, −78 °C; (*g*) Ac_2O, 4-DMAP, CH_2Cl_2; (*h*) AcOH–THF–H_2O (6 : 3 : 1).

Tributylstannylallene **103** was obtained by the S_N2 reaction of 3-chloro-1-tributylstannylpropyne with tributylphosphine-pentylcopper at −78 °C in solution in THF. The chiral aldehydoester **104** was synthesised by the enantioselective Sharpless epoxidation of the unsaturated alcohol **106**. In the concluding stage of the synthesis, the crystalline diol **107** was obtained by condensing the stannyl derivative **103** with the enolate of the ketone **105**. The structure of the diol was confirmed by X-ray diffraction. The sequence of selective hydrogenation, oxidation and silylation reactions led to a satisfactory yield of the synthon **98**, in which the α-chain **104** was formed by standard methods (Scheme 12).

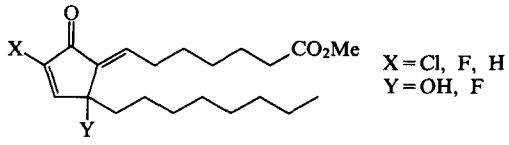
Overall, all the possible diastereoisomers with different configurations of the C(5), C(6), and C(12) chiral centres were obtained from the set of synthons **103**–**105** and their enantiomers. The involvement of the enantiomer **105** and compounds **103** and **104** in the above sequence of reactions led to a product all the characteristics of which (NMR, CD) agreed with those of the natural punaglandin IV having the (5*S*, 6*S*, 12*R*)-configuration. Thus the configuration of the C(12) chiral centre in punaglandins is identical with that in chlorovulones and is the opposite of the configuration of the C(12) centre in clavulones.

IV. Analogues of marine prostanoids

Immediately after the discovery of this class of prostanoids, studies were published on the synthesis and biological activity of their modified derivatives. Thus a group of Japanese investigators took out a series of patents[55–58] describing the isolation from *Clavularia virides* of clavulones and related compounds exhibiting anti-inflammatory and antitumour activities.

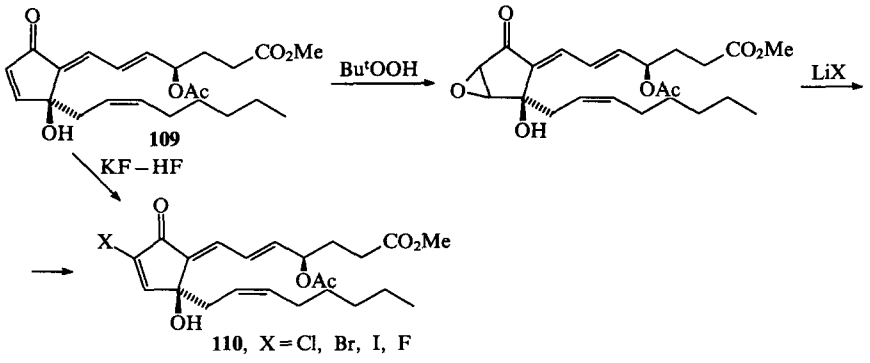
A patent[59] described the synthesis of analogues of clavulones by means of elimination reactions of sulfo-derivatives of 7-hydroxy-PGE_2. They exhibit anticancer and antiviral properties (IC_{50} = 0.4–1 μg ml^{-1}). The same workers[60] used the 7,8-dehydro-analogues of PGA to obtain the corresponding 1-chloro-derivatives, which can be regarded as modified clavulones. The compounds synthesised possessed antitumour, antibacterial and antiherpes activities.

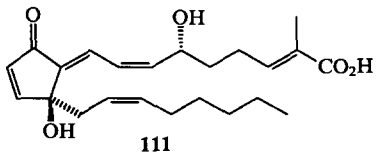
Derivatives of punaglandins have been patented[61] as effective anticancer and antiviral compounds. An attempt has been made[62] to modify the cyclopentane ring in prostaglandins by introducing powerful electronegative substituents—fluorine atoms—in the C(10) and C(12) positions. Unfortunately, comparative data on the biological activities of these compounds are not presented.

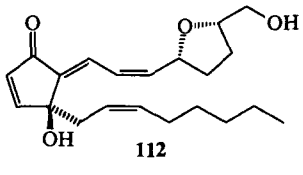


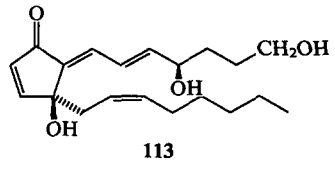
10-Haloclavulones **110** have been obtained from the cross-conjugated trienone **109**.[63]

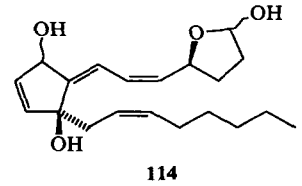
Modifications of the natural clavulones have been achieved.[64,65] Thus α-homologues of type **111**, γ-lactols **112**, the triols **113** and **114**, the lactone **115**, and derivatives **116** involving the modification of the carboxy-group have been synthesised from clavulone II.[64]

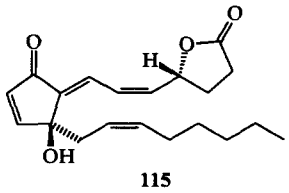


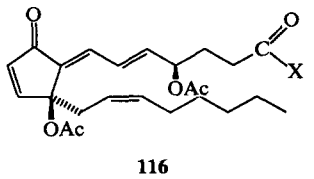






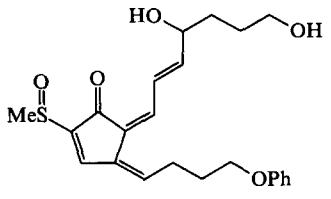




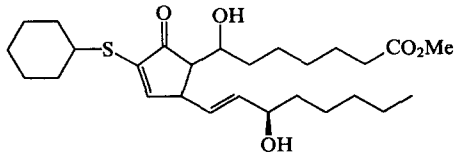


X = OH, OCH_2Ph, Bu^tO, Bu^iNH

Considerable attention has been devoted to the synthesis of the 10-thio-analogues of marine prostanoids.[66,67] In vitro experiments designed to test the activity against L-1210 cells demonstrated that the 10-methanesulfonyl derivative **117** had IC_{50} = 0.1 mg ml^{-1}, while compound **118** had IC_{50} = 0.02–2.30 mg ml^{-1}.



117



118

A series of other modifications have been achieved in order to investigate in detail the 'structure–activity' relation for this series of compounds.[68] This will be considered in detail in the next Section.

V. Biological properties of marine prostanoids

The antitumour activity of prostaglandins of types A and E was discovered as early as 1972. Subsequently, Suzuki et al.[62] found that the growth of cancer cells is also inhibited by PGD_2 and PGI_2 (9-deoxy-Δ^9-PGD_2), the activity of the latter exceeding by a factor of 3 that of PGA and PGE. Among the known prostaglandins, the most powerful antitumour agents are Δ^7-PGA_1 and Δ^{12}-PGI_2 and their derivatives. It was shown that the cyclopentane ring containing the α,β-unsaturated ketone fragment is responsible for this type of biological activity. Thus a promising field of study of prostaglandins concerns prostanoids with an alkylidenecyclopentane ring, which exhibit specific cytotoxic and antitumour activities. Clavulones (acetoxy-derivatives of Δ^7-PGA_2), discovered in 1982, and then the related punaglandins proved to be the most striking representatives of this class of prostaglandins. Tests on fertilised chicken eggs (30 μg ml^{-1}) showed that clavulones I–III possess anti-inflammatory properties.[69]

Clavulone I exhibited a distinctive antiproliferation activity in relation to HL-60 cells (ED_{50} = 0.4 μmol $litre^{-1}$), it is cytotoxic[70] at concentrations in excess of 1 μM, and it inhibits the synthesis of DNA.[71] Clavulone II manifested effective cytotoxic properties on L-1210 cells (IC_{50} = 0.6 μmol $litre^{-1}$)[71] and exhibited an antiviral activity in relation to the vesicular stomatitis virus in mice (IC_{50} = 1–1.5 μmol $litre^{-1}$).[72] Depending on the dose, punaglandins inhibit the growth of L-1210 cells in vitro (0.01–0.2 mg ml^{-1}), for which IC_{50} = 0.02 mg ml^{-1}; this is less than for vincristine and doxorubicin—the most powerful anticancer agents.[63,73,74] For clavulones, IC_{50} = 0.3 mg ml^{-1}, which is close to data for Δ^7-PGA_1.

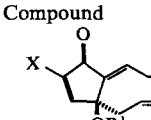
In vitro experiments showed[73] that, when mice infected with the L-1210 strain are administered punaglandins III and IV for five days using a dose of 5 mg per kilogram per day, their survival time increases by 50.5% and 78.9% respectively, while for clavulone II (10 mg per kilogram per day) the increase is by 50.8%; similar results are attained for Δ^7-PGA_1 using a dose of 20 mg per kilogram per day. Overall, the relative activities of the prostanoids in vitro and in vivo are correlated. It was also found that these compounds inhibit the synthesis of macromolecules containing leucine or thymidine: punaglandin IV causes 90% inhibition at a concentration of 5 mg ml^{-1} (L-1210), while clavulone II gives rise to a similar result at a concentration which is five times greater. It may be that these processes lead to the inhibition of the growth of tumours. The facts obtained also permit the hypothesis that one of the functions of eicosanoids in the vital activity of marine organisms may be the regulation of the growth of corals and other organisms growing in the immediate vicinity.

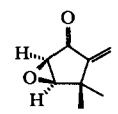
Yamada and coworkers[75,76] reported the results of biotests and elucidated certain features of the 'structure–activity' relation for a series of marine eicosanoids.

The decisive factor, necessary for the compounds to possess cytotoxic and antitumour (anti-HL-60 cells) activities, is the presence of an alkylidenecyclopentenone fragment in the structure. Comparison of the data in Table 1 for clavulone II and of its 10,11-dihydro-analogue shows that the presence of the C(10)–C(11) double bond is essential for the manifestation of cytotoxic activity. An exception to this rule is epoxyclavulone, which has no cross-conjugated cyclopentene system but which does exhibit a high activity. The epoxyketone fragment is probably a biological isostere of the enone system in this case (Table 1).

Table 1. The inhibiting effect of prostanoids of the clavulone type on the growth of HL-60 cells.[76]

Compound	X	R^1	R^2	IC_{50}/μmol $litre^{-1}$ (μg ml^{-1})	Cytotoxic effect/μmol $litre^{-1}$ (μg ml^{-1})
Clavulone II	H	MeCO	MeCO	0.40 (0.2)	>1.0 (0.5)
4-*O*-Deacetylclavulone II	H	MeCO	H	0.24 (0.1)	>1.2 (0.5)
12-*O*-Deacetylclavulone II[36]	H	H	MeCO	0.15 (0.06)	>0.5 (0.2)
4,12-*O*-Deacetylclavulone II	H	H	H	0.07 (0.025)	>0.3 (0.1)
10-Chloro-12-*O*-deacetylclavulone II	Cl	H	MeCO	0.03 (0.015)	>0.3 (0.15)
10,11-Epoxyclavulone II[a]	—	MeCO	MeCO	0.43 (0.2)	>1.08 (0.5)
10,11-Dihydroclavulone II[b]	—	MeCO	MeCO	2.23 (1.0)	>11.2 (5.0)
12-*O*-Methoxymethylclavulone II	H	$MeOCH_2$	MeCO	2.00 (0.90)	>4.5 (2.0)



a 

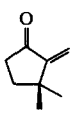
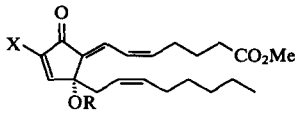
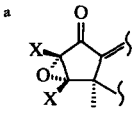
b 

Table 2. The inhibiting effect of prostanoids of the chlorovulone type on the growth of HL-60 cells.



Compound	X	R	IC_{50}/ μmol litre^{-1} (μg ml^{-1})	Cytotoxic effect/ μmol litre^{-1} (μg ml^{-1})
Chlorovulone I	Cl	H	0.03 (0.01)	>0.3 (0.1)
Bromovulone I	Br	H	0.06 (0.025)	>0.9 (0.4)
Iodovulone I	I	H	0.06 (0.03)	>0.9 (0.4)
12-*O*-Acetyl-chlorovulone I	Cl	Bu^{t}O	0.19 (0.08)	>1.18 (0.5)
10,11-Epoxy-chlorovulone I[a]	Cl	H	0.10 (0.04)	>0.76 (0.3)

[a] 

The introduction of a halogen atom in the C(10) position increases the biological activity (Cl = F > Br = I > H) (Table 2).

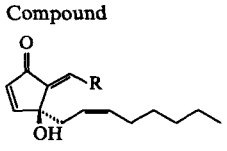
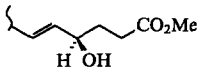
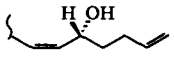
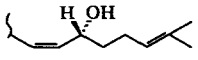
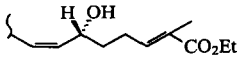
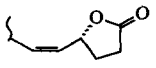
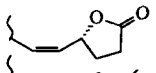
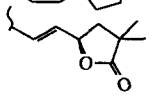
The introduction of a hydroxy-group at the C(12) atom increases the activity and the stereochemistry of the hydroxy-group does not exert an appreciable influence on the latter. The 12-hydroxy-group greatly increases the antiproliferation and cytotoxic activities. Thus the weak antiproliferation activity of PGA_2, Δ^7-PGA, PGI, and Δ^{12}-PGI has been explained precisely by the absence of the C(12)–OH group. When it is replaced by an acetyl group, the cytotoxic effect is diminished. Epoxidation decreases the activity compared with chlorovulone I, although it is nevertheless higher than that of clavulone II.

The introduction of groups blocking the β-oxidation of the α-chain does not induce an appreciable increase in activity. As shown in Table 3, the introduction of a cyclic γ-lactone or a hemiacetal group (d, e, f) does not have much influence on the β-oxidation process. On the basis of the data presented, one may note that the activity diminishes with increase in the length of the α-chain (chlorovulone I > a > b > c). The presence of eight carbon atoms is probably optimal, since the shortening of the chain also diminishes the activity.

The presence of the dienone fragment [C(5,6), C(7,8)] leads to an increase in activity.

Overall, the observed features of the 'structure–activity' relation in the series of marine prostanoids are undoubtedly important and necessary for studies directed specifically to the creation of a new class of anticancer medicinal preparations.

Table 3. The inhibiting effect of clavulones with a modified α-chain.

Compound 	R	IC_{50}/μmol litre^{-1} (μg ml^{-1})	Cytotoxic effect/μmol litre^{-1} (μg ml^{-1})
4,12-Deacetylclavulone II		0.07 (0.025)	>0.3 (0.1)
a		0.10 (0.033)	>0.6 (0.2)
b		0.11 (0.04)	>0.6 (0.2)
c		0.36 (0.15)	>1.2 (0.5)
d		0.09 (0.03)	>0.3 (0.1)
e		0.12 (0.04)	>0.6 (0.2)
f		0.11 (0.04)	>0.6 (0.2)

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