# NEW MARINE PROSTANOIDS, CLAVULONES, HALOGENOVULONES, AND PUNAGLANDINS

**L. G. Lis and T. A. Zheldakova**

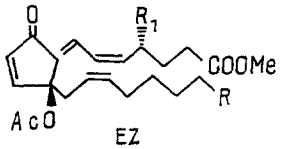
UDC 547.01

*In this review, questions of the isolation, biosynthesis, and total chemical synthesis of new marine prostanoids — clavulones, halogenovulones, and punaglandins — are considered.*

## NATURAL SOURCES, ISOLATION, AND BIOSYNTHESIS OF THE NEW MARINE PROSTANOIDS

In 1982, two groups of Japanese workers, independently of one another and practically simultaneously, reported the isolation of a series of new prostanoids from the Okinawa soft corals *Clavularia viridis* Quoy and Gaimard [1, 2]. The authors of one paper called these compounds clavulones [1], while the other group named these prostanoids claviridenones [2]. At the present time, the first name is used in the literature.

In the course of further investigations by the same authors, new compounds of this class were isolated, in addition, and at the present time, seven clavulones (1)-(7) are known [3, 4]. Characteristic for all the clavulones is the presence of a cyclopentenone fragment, as in the prostaglandins of the A series, and the presence of a seven-carbon $\alpha$- and an eight-carbon $\omega$-chain, and also a 12S-acetoxy function. In addition to this, the investigation of the more polar fraction after the isolation of the clavulones gave two 4-deacetyl products (8) and (9). Initially, all the clavulones were erroneously ascribed the 12R-configuration [4, 5], but this was later corrected [6]. One group was composed of four compounds (1)-(4) having a 4R-acetoxy function and differing by the geometry of the $\Delta^5$ and $\Delta^7$ bonds. A second group consisted of three 20-acetoxy derivatives, (5)-(7), and a third group of two 4-deacetyl derivatives, (8), and (9). An investigation of the absolute configurations of the clavulones was made independently by both research groups [4, 5], and the authors came to the same conclusion concerning the structures of these compounds. The results of IR, UV, PMR, $^{13}C$ NMR, and CD spectroscopy were used, together with those of some chemical methods — in particular, ozonization at the $\Delta^5$ bond and the study of the oxidation products.

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7. R = $CH_2OAc$, $R_1$=OAc
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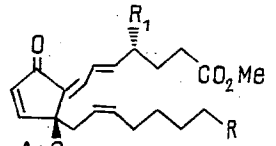


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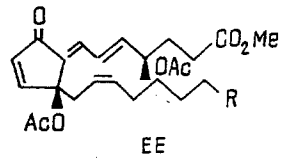


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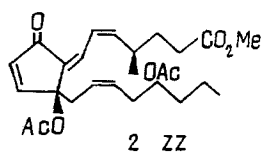


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Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Minsk. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 315-334, May-June, 1993. Original article submitted May 22, 1991.

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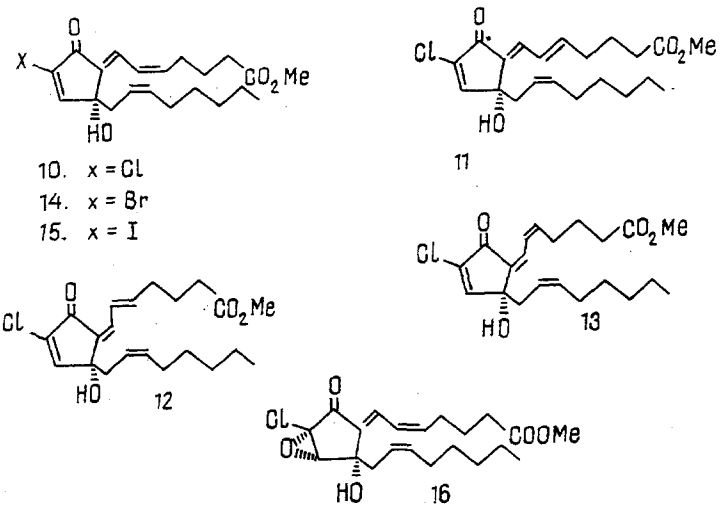
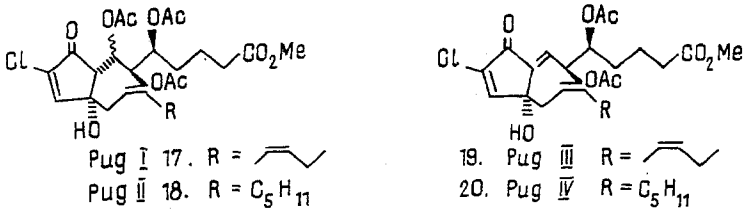
Further investigations of the Okinawa soft corals *Clavularia viridis* permitted the isolation of new prostanoids the structures of which included a halogen atom [6, 7]. Four compounds containing a chlorine atom were called chlorovulones I (10), II (11), III (12), and IV (13) [6], and two compounds containing bromine and iodine atoms were called bromovulone I (14) and iodovulone I (15), respectively [7]. In addition to this, an epoxy prostanoid (16) structurally close to chlorovulone I (10) was isolated from the same sources [8].



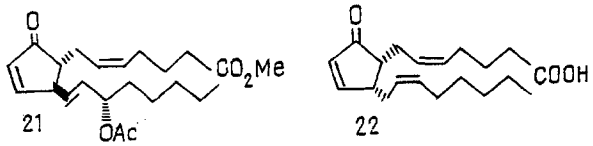

An investigation of the structures and absolute configurations of compounds (10)-(16) was carried out by the same methods as the study of the clavulones, using a whole complex of physicochemical methods of analysis [6-9]. This showed that compounds (10)-(13) differed by the configuration of the double bonds of the α-chain [6] while compounds (14)-(16) were structurally similar to chlorovulone I (10) [7, 8]. It was established that all the halogenovulones and epoxy prostanoids (16) had the 12R-configuration, i.e., the stereochemistries at the 12-centers in the halogenovulones and clavulones were opposite to one another [9]. In light of the fact that these classes of compounds are structurally close and were isolated from one and the same natural source, the question of the possible mechanisms of the biosynthesis of these compounds remains unclear.

In 1985, the first communication appeared on the isolation of chlorine-containing prostanoids from the Hawaiian corals *Telesto riisei* [10]. The compounds isolated were given the names of "punaglandins."

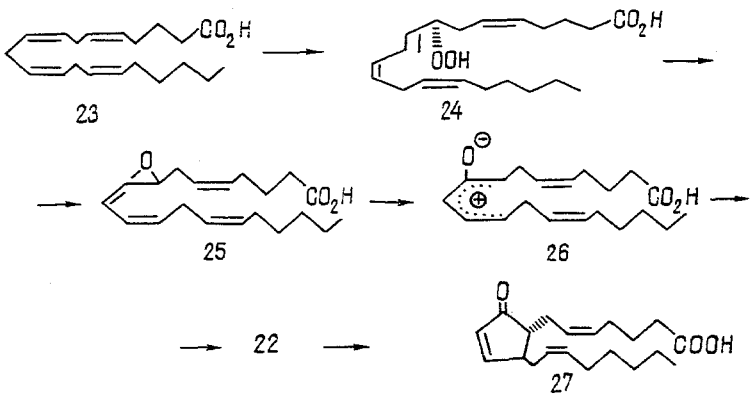
The compounds isolated were first ascribed incorrect structures [10], which were later corrected [11-13]. At the present time, punaglandins 1-4 have been assigned structures (17)-(20) with the (5S,6S,12R)-configuration. The *trans*-orientation of the side chains presupposes the R- configuration at C-8′ for punaglandins 1 (17) and 2 (18). However, the authors refrained from assigning a configuration to the acetoxy group at C-7 in compounds (17) and (18), and the stereochemistry at this center has not so far been elucidated [12].




The investigation of the biosynthesis of the new marine prostanoid has been carried out mainly in Harvard University, Cambridge, under the direction of Professor Corey. The authors of the corresponding papers on the investigation of the biosynthesis of the clavulones have put forward the hypothesis that the precursor of all the marine prostanoids, including the acetate of the methyl ester of $PGA_2$ (21) is compound (22), which has been called preclavulone A [14, 15].



The hypothesis has been put forward that the biosynthesis of the marine prostanoids, unlike that of the prostaglandins of animal origin, takes place not through an endoperoxide group but, by analogy with the biosynthesis of a plant growth regulator — cis-jasmonic acid — through the allene oxide (25) and the oxidopentadienyl cation (26) [16, 17]. The first stage of biosynthesis is the 8-lipoxygenation of arachidonic acid (23) leading to 8(R)-hydroperoxyeicosatetraenoic [8(R)-HPETE] (24) [15].




The subsequent keeping of the 8(R)-HPETE with an enzyme isolated from the corals *Pseudoplexaura porosa* leads through the allene oxide (25) and the pentadienyl cation (26) to preclavulone A (22) by antarafacial ring closure [15, 18]. Subsequently, the authors showed that the Caribbean corals *Plexaura homomalla, Plexaura nina, Plexaura flexuoso, Pseudopterogia americana, Mureciopsis flavida,* and *Eunicea asperula,* convert arachidonic acid (23) into 8(R)-HPETE (24) and both of them into preclavulone A (22), thereby showing the generality of the biosynthesis of the marine prostanoids and in particular, a common route for the biosynthesis of clavulones in the corals *Clavularia viridia* and of prostaglandin $A_2$ in *Plexaura homomalla* [19].

It must be mentioned that the *cis*-cyclopentenone derivative (22) formed is racemic [19], and the authors, in explaining this fact, put forward the hypothesis that the enzyme present in a homogenate is incapable of controlling the chirality in the cyclization of the oxidopentadienyl cation (26) probably because of the substantial changes in the tertiary structure of the extracted enzyme in comparison with the structure of the enzyme existing "*in vivo.*"

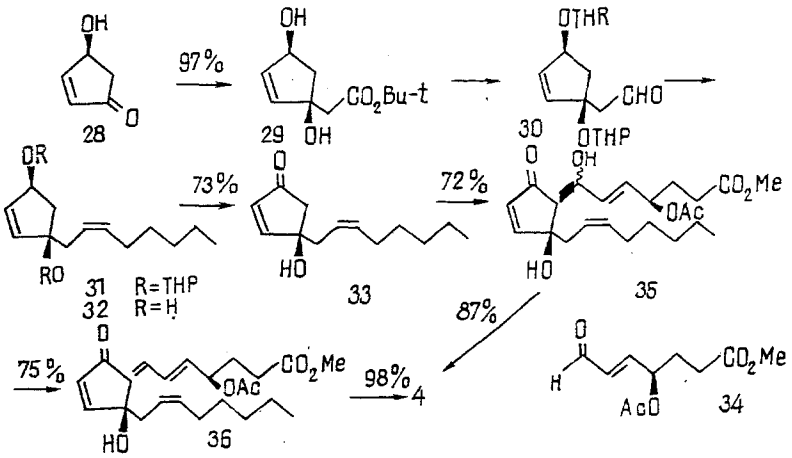
Brash et al. [20], studying the mechanism of the "noncyclooxygenase synthesis of the prostanoids" in corals came up against the same problem. A similar question arises in the study of the cyclization of the (13S)-hydroperoxide from linolenic acid into 12-oxo-cis-phytodienoic acid — the first cyclic precursor of jasmonic acid [21, 22]. The same authors [20] left open the question of the reasons for this phenomenon, suggesting the hypothesis that, possibly, the racemic products were subsequently subjected to enantiospecific cyclization into chiral derivatives.

Brash [23] has also shown that the allene oxide (25) is formed from (8R)-HPETE (24) and retains the (8R)-configuration, it being assumed that the subsequent pathway for the biosynthesis of the PGs must include the cyclization of the allene oxide with the formation of the configuration at C-8 and then, either in the course of cyclization or on subsequent isomerization, the product with the *trans* orientation of the side chains (27) (as in $PGA_2$) must be formed. This work [23] thus cast doubt on the mechanism of the formation of $PGA_2$ from 8(R)-HPETE via 8,15-DiHPETE by the 15-lipoxygenase route suggested by Corey [15].

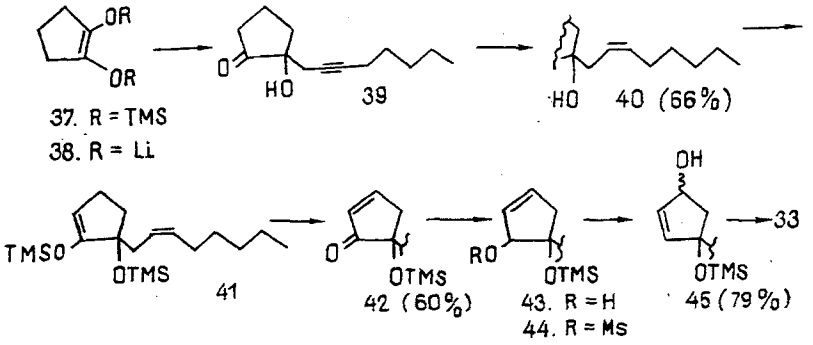
Thus, the mechanism for the biosynthesis of the clavulones based on the endoperoxide route suggested in earlier publications by Corey [24] was rejected by him on the basis of experiments with labeled arachidonic acid, which was metabolized by 8-lipoxygenase into preclavulone A [16]. In this situation, although many important questions of the biosynthesis of the marine prostanoids remain unelucidated, the mechanism of the biosynthesis of the halogenovulones and punaglandins has scarcely been studied, although available literature reports permit the statement that the mechanisms of the biosynthesis of marine prostanoids and plant cyclopentanoid acids (jasmonic acid, dicranenones, cucurbic acid, etc.) are similar. It is obvious that the marine prostanoids and prostaglandins of animal origin are formed by completely different biosynthetic pathways, and this is extremely important from the evolutionary point of view [15].

## CHEMICAL SYNTHESIS OF THE CLAVULONES

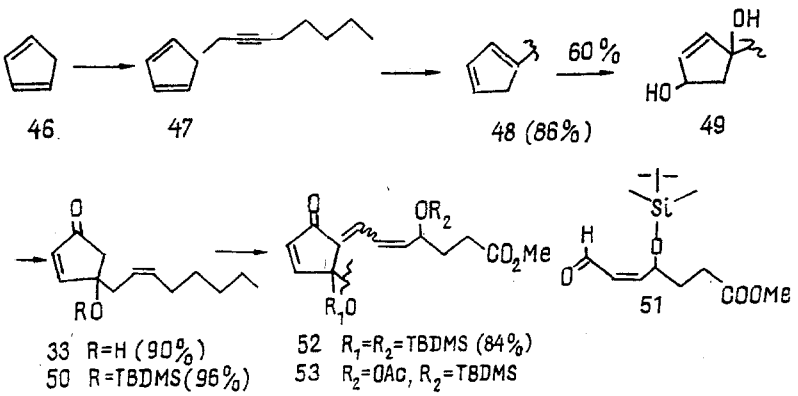
The first enantio- and stereoselective synthesis of clavulone II (4) and its 12-O-deacetyl analog (6) was achieved by Japanese researchers in 1984 [25].




The interaction of (S)-4-hydroxycyclopentenone (28), obtained from *L*-(+)-diethyl tartrate with the lithium enolate of *t*-butyl acetate led with high stereoselectivity to the *cis*-diol (29). After protection of the hydroxy groups in the form of THP ethers, the ester function was reduced with lithium tetrahydroaluminate to an alcohol function, and subsequent oxidation by Swern's method gave the aldehyde (30), which was treated with $Ph_3P = CHC_5H_{11}$, giving the olefin (31) with a yield of 91% [calculated on the (29)]. Elimination of the THP-protective groups under acid conditions led to the diol (32), which, after oxidation by pyridine chlorochromate gave the enone (33). The interaction of the lithium enolate of (33) with the $\alpha,\beta$-unsaturated aldehyde (34) (obtained from D-mannitol in 10 stages) gave the aldol (35) in the form of a diasteromeric mixture. Without being separated, this diasteromeric mixture was treated with methanesulfonyl chloride, giving 12-O-deacetylclavulone II (36). The acetylation of this product led to clavulone II (4). The direct treatment of the aldol (35) with acetic anhydride in pyridine also led to clavulone II (4).



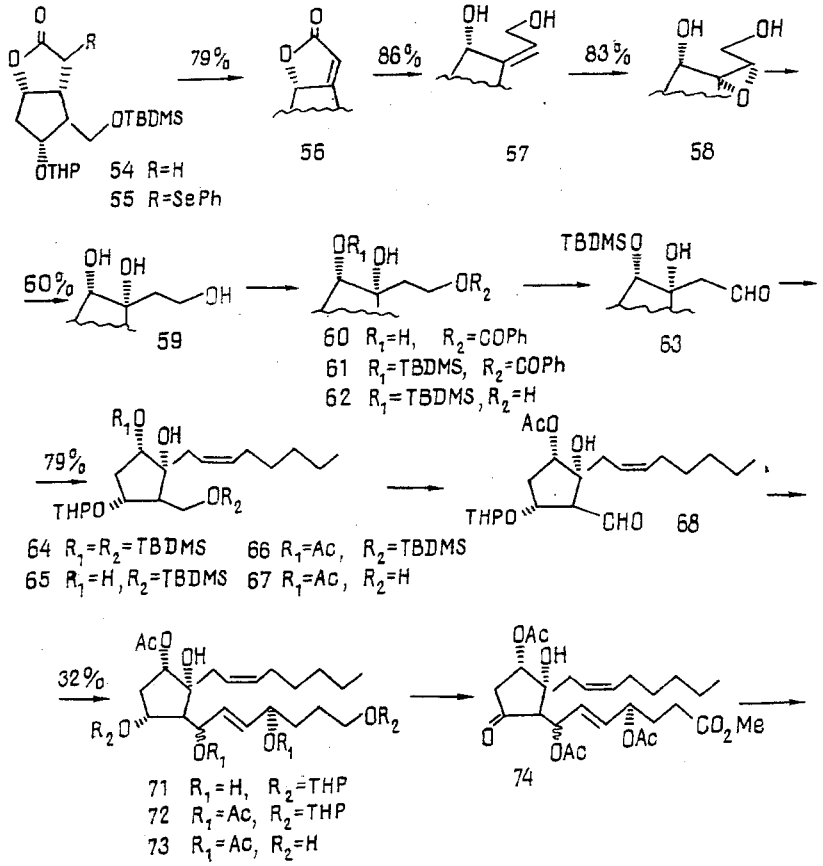

An analogous strategy in the synthesis of clavulone II (4) was used by other authors [26], but their method of obtaining the key intermediate — the enone (33) — differed from that given above. The enediol dilithium derivative (38), obtained from 1,2-bis(trimethylsilyloxy)cyclopentene (37) was brought into reaction with 1-bromooct-2-yne. The hydroxyketone (39) obtained was reduced over Lindlar catalyst, giving the Z-olefin (40). The interaction of the hydroxyketone (40) with a silylating agent gave the enol ether (41), the treatment of which with $Pd(OAc)_2$ led to the enone (42). The transformation of the latter into the allyl alcohol (45) formed the most important part of the synthesis. Reduction of the enone (42) with sodium tetrahydroborate in the presence of a cerium salt gave the allyl alcohol (43), which, by treatment with methanesulfonic anhydride, was converted into the mesylate (44). Hydrolysis of the mesylate took place with the addition of a molecule of water in the $\gamma$-position, giving a diastereomeric mixture of allyl alcohols (45). The Collins oxidation of the latter led to the enone (33) in quantitative yield. The subsequent conversion of the enone (33) into clavulone II (4) and its 12-epi- analogue was carried out by the method described in [25].

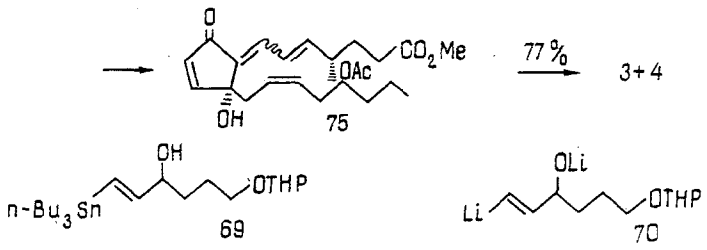



The synthesis of the racemic clavulone I (1) was undertaken by Corey in 1984 and was based on the same strategy of three-component coupling as that described above [27]. In this case the key synthon — the enone (33) — was obtained from cyclopentadiene (46).

The alkylation of the lithium derivative of cyclopentadiene with 1-iodooct-2-yne led to the diene (47), which, at 23°C, underwent a 1,5-prototropic shift, giving the isomeric diene (48). Photooxidation of the latter with oxygen followed by the action of sodium tetrahydroborate (to reduce the endoperoxide) led to the diol (49). Oxidation of the diol with pyridine dichromate formed a γ-hydroxycyclopentenone which, after reduction over Lindlar catalyst, gave the hydroxydienone (33). Silylation of the latter led to the tert-butyldimethylsilyl ether (50). The subsequent condensation of compound (50) using lithium diisopropylamide and the aldehyde (51) gave a mixture of two diastereomers (52).

The subsequent action of acetic anhydride in the presence of tetra-*n*-butylammonium fluoride and 4-dimethylaminopyridine led to the selective replacement of the TBDMS group by an acetyl group, giving a mixture of two diastereomeric mono-TBDMS ethers/monoacetates (53) which were easily separated by chromatography. The less polar isomer, after prolonged (6 h) treatment with acetic anhydride in the presence of tetra-*n*-butylammonium fluoride and 4-dimethylaminopyridine, followed by chromatography, gave 60% of clavulone I (1) and 15% of clavulone II (4).

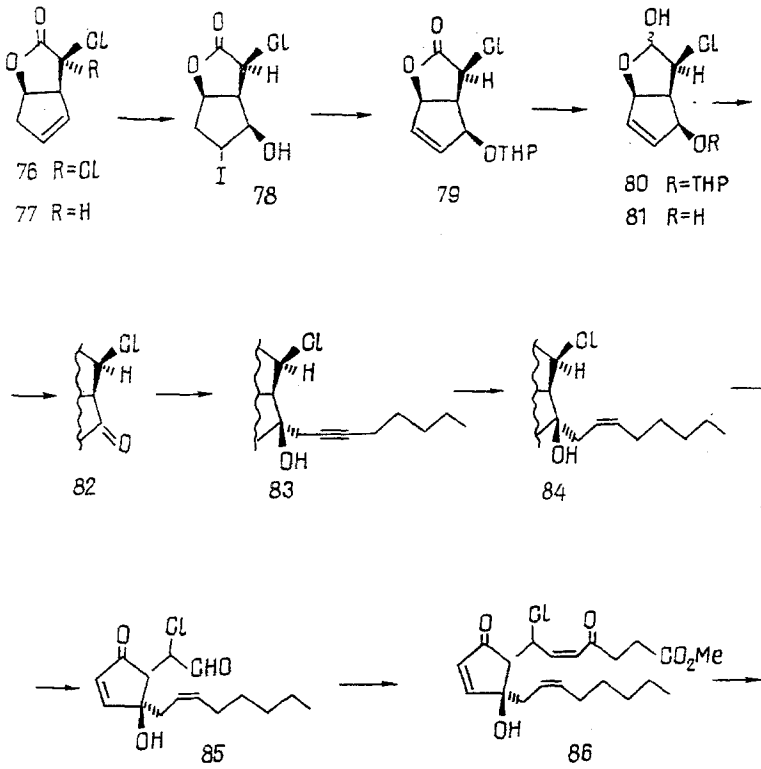


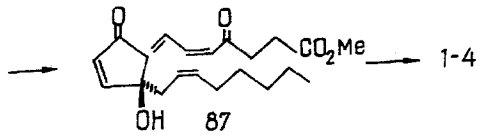



The synthesis of the natural clavulones II (4) and III (3) was proposed by Japanese authors on the basis of Corey's lactone (54) [28]. Corey's lactone (54) was converted into the phenylselenyllactone (55), which, on oxidation, gave the $\alpha,\beta$-unsaturated lactone (56). Compound (56) was transformed into the allyl alcohol (57) by the action of DIBAH. The unsaturated bond of (57) was oxidized stereoselectively by tert-butyl hydroperoxide in the presence of a vanadium catalyst, giving the epoxide (58). The reductive cleavage of the epoxide took place with high regioselectivity, giving the required triol (59) as the sole product.

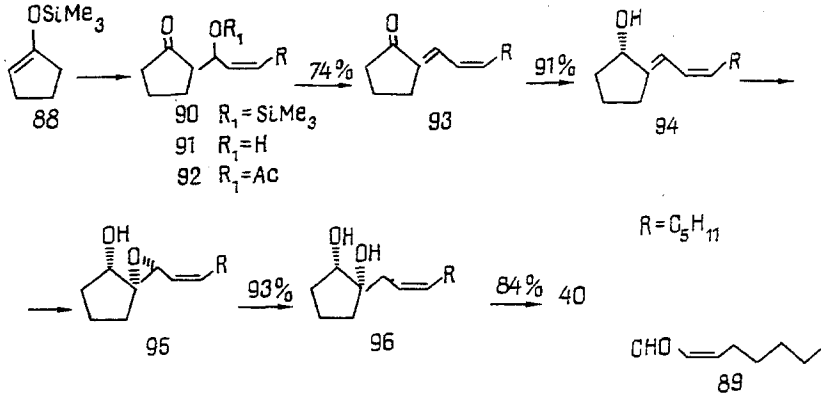
The subsequent introduction and elimination of benzoyl and silyl protective groups and the Collins oxidation of the primary alcohol led in four stages ((59) → (63)) to the aldehyde (63) with a yield of 36%. The Wittig addition of *n*-hexylidenetriphenylphosphorane to the aldehyde (63) gave the olefin (64) and its isomer in a ratio of 2:1. The manipulation of acetyl and silyl protective groups ((64) → (67)) with subsequent Collins oxidation of the primary alcohol group led in four stages with a yield of 48% to the aldehyde (68).

The optically active vinylstannane reagent (69) containing the $C_1$—$C_6$ fragment of the carbon skeleton of the clavulone was obtained from *D*-glutamic acid in 10 stages. The aldehyde (68) reacted with the vinyl anion (70) obtained from the vinylstannone (69) giving the allyl alcohol (71). The successive introduction and elimination of acetyl and tetrahydropyranyl protective groups ((71) → (73)) led to compound (73), containing three free hydroxy groups and three acetoxy functions (29%), which was isolated in the form of a mixture of diastereomers at C-7. Subsequent Jones oxidation and treatment with diazomethane gave the keto ester (74) which, in chromatography on silica gel, underwent deacylation, leading to a mixture of the two olefins (75) isomeric at the $\Delta^7$ bond. Completing acetylation of the alcohol group at C-12 and separation of the epimers with the aid of HPLC gave clavulones (3) and (4) in a ratio of 2:1 with a total yield of 77%.






Takemoto et al. [29] have given a brief description of the synthesis of clavulones from Corey's dichlorolactone, which was converted in three stages into the iodide (78). Successive protection of the hydroxy group, dehydroiodination, reduction of the lactone, and elimination of the tetrahydropyranyl group led to the allyl alcohol (81), the Jones oxidation of which gave the $\alpha,\beta$-unsaturated ketone (82). The $\omega$-chain was introduced by the reaction of ketone (82) with the lithium derivative of octyne and subsequent reduction of the ethylenic bond over Lindlar catalyst. Jones oxidation of lactone (84) led to the ketoaldehyde (85), the interaction of which with the appropriate ylide in a Wittig reaction completed the construction of the carbon skeleton of clavulone. The dehydrochlorination of compound (86) with a base led to the $\Delta^7$-olefin (87). The subsequent stages of the reduction of the carbonyl group in the $\alpha$-chain and acetylation at C-7 gave clavulones (1)-(4) with unspecified stereochemistry.



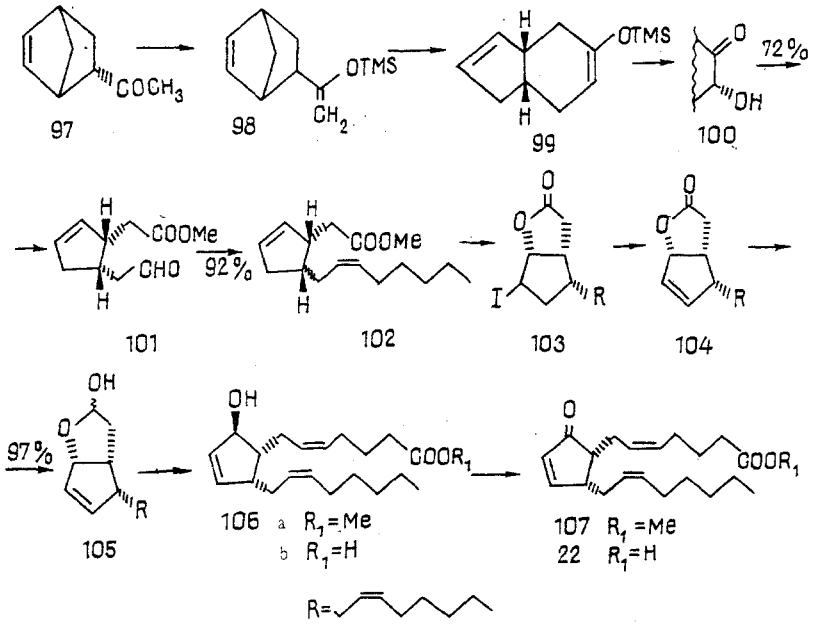

An approach to the asymmetric synthesis of the clavulones has been proposed by Japanese authors on the basis of the silyl enol ether of cyclopentanone (88) [30]. The interaction of the enol ether (88) with the $\alpha,\beta$-unsaturated aldehyde (89) gave the $\alpha$-substituted cyclopentanone (90) which, after elimination of the protective group, formed the $\beta$-hydroxyketone (91) (69%). Conversion of the latter into the acetate (92) and treatment with potassium tert-butanolate gave the dienone (93), which was subjected to asymmetric reduction with lithium tetrahydroaluminate in the presence of (—)-N-methylephedrine and 2-ethylaminopyridine, with the production of the optically active allyl alcohol (94), having the R- configuration, in 96% optical purity. Epoxidation of the alcohol (94) with tert-butyl hydroperoxide in the presence of vanadyl acetylacetonate gave the unstable epoxide (95) which was immediately reduced with lithium tetrahydroaluminate to the diol (96) (93%). Oxidation of the diol by the $SO_3$—pyridine complex led to (2R)-2-hydroxy-2-[oct-2(Z)-en-1-yl]cyclopentenone (40) with an optical purity greater than 95%. The use of this intermediate in the synthesis of the clavulones had been described by the authors previously [26], however, to obtain clavulones with the natural 12S-configuration the authors proposed to use (+)-N-methylephedrine in the (93) → (94) stage.

## CHEMICAL SYNTHESIS OF CLAVULONE ANALOGUES

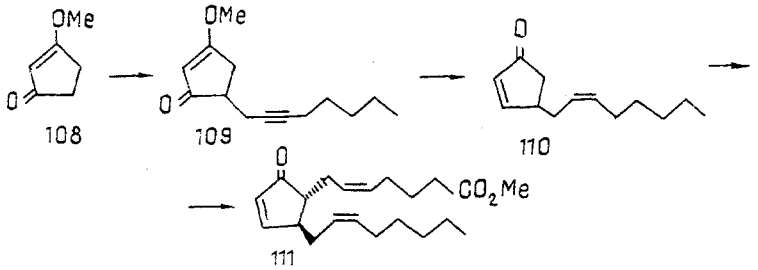
Preclavulone A (22) is formed from arachidonic acid in the course of the biosynthesis of the prostanoids in marine organisms and is presumably the biosynthetic precursor of all marine prostanoids [14, 15]. The importance of this compound for studying the biosynthesis of marine prostanoids has predetermined the necessity for developing a method for its chemical synthesis, since the biosynthetic preparation and isolation of this compound in appreciable amounts is an extremely complex task technically.

In 1984, Corey proposed an enantioselective method for the synthesis of (—)-preclavulone A, starting from cyclopentadiene [14]. The use of Diels—Alder reaction of the latter with (R)-pantolactone acrylate gave (—)-(1S,2S)-5-norbornene-2-carboxylic acid, which, after reaction with methyllithium led to the 2-endo methyl ketone (97) with an overall yield of 89%. The ketone was converted into the enolic silyl ether 98 and this was subjected to a Cope rearrangement with the

isolation of the tetrahydroindene (99) (80%). Without purification, the latter was oxidized with *m*-chloroperbenzoic acid and was then treated with 48% HF and triethylamine to give the hydroxyketone (100) together with the epimeric alcohol in a ratio of 6:1 [total yield 61%, calculated on the (97)],



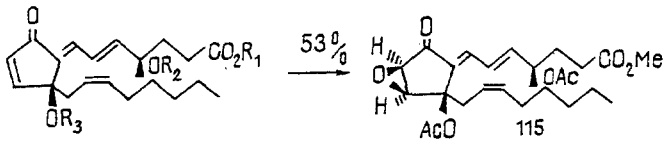

The oxidative cleavage of the hydroxyketone (100) together with the epimeric alcohol under the action of lead tetraacetate gave the aldehydoester (101), the Wittig reaction of which with *n*-hexyltriphenylphosphine led to the dienic ester (102). The latter was hydrolyzed under alkaline conditions and treated with iodine, and then the iodolactone (103), after treatment with diazabicycloundecene, was smoothly converted into the dienic lactone (104) with a yield of 89% [calculated on the (102)]. The reduction of (104) with diisobutylaluminum hydride led to the lactone (105), which, after interaction with the appropriate Wittig reagent, gave the hydroxy acid (106b), isolated in the form of its methyl ester (106a) with a yield of 84% [calculated on the (104)]. Oxidation of the latter led to the enone (107), while oxidation of the acetate (106b) gave preclavulone A (22) with a yield of 89%. The angle of rotation for the methyl ester (107) was given.

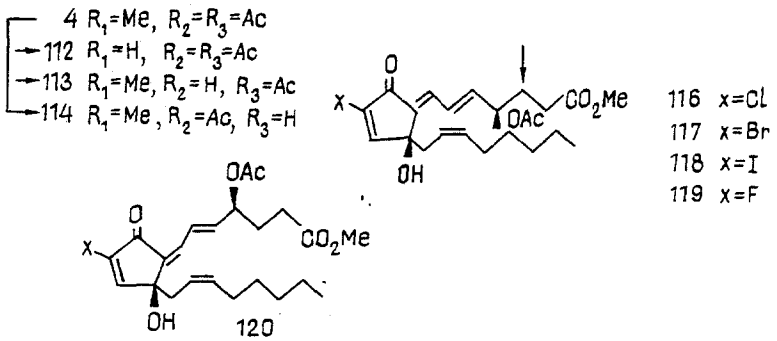



In a study of the structure of preclavulone A, its 8(12)-*trans* isomer (111) was synthesized, starting from the enolic methyl ether of cyclopentane-1,3-dione (108) by the scheme shown [16].

To study biological activity and to establish structure-activity relationships in the clavulone series, derivatives of these compounds have been obtained from clavulin II (4) [31, 33].

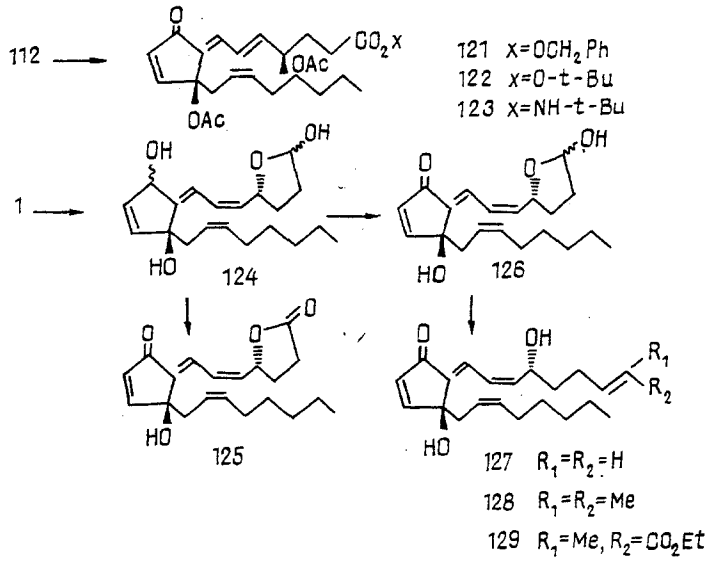
By a combination of chemical and enzymatic methods it was possible to perform the selective hydrolysis of the ester groups and to obtain compounds (112)-(114). The epoxide (115) was obtained from clavulone II (4) by the action of tert-butyl hydroperoxide.






The same authors have developed a method of synthesizing 10-halogenated clavulones from natural clavulone II (4) [32]. Epoxide (115), obtained by the method described above [31], was treated with anhydrous lithium halides in dimethylformamide, giving the Cl, Br, and I derivatives (116)-(118) with yields of 47-60%. At the same time, the 7Z- isomers (120) were formed in small amount (up to 5%). The 10-fluoro derivative (119) was obtained by the interaction of epoxide (115) with $KHF_2$ in a yield of 51%.

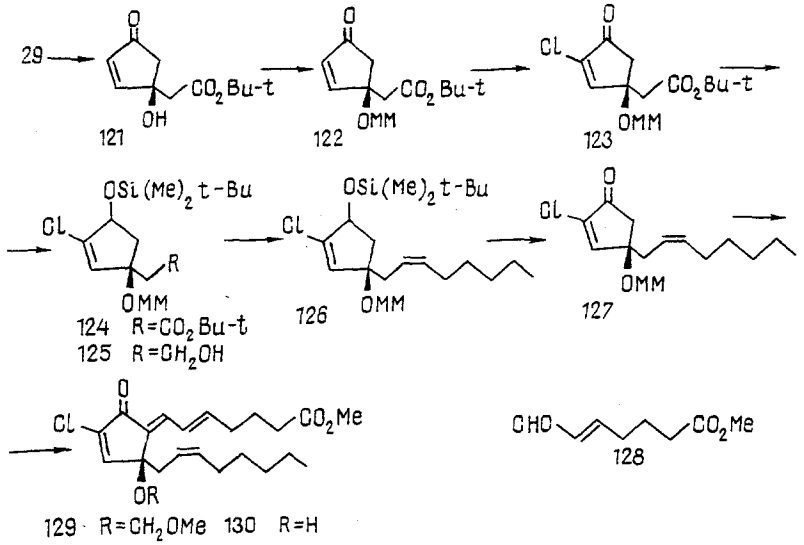
The esters (121) and (122) and the amide (123) were synthesized in a development of this work [33].




In order to study the influence of the length of the α-chain on the antileukemic activity of the clavulones, analogues of clavulone I (1) with modified α-chains have been synthesized [33]. The reduction of the clavulone (1) with diisobutylaluminum hydride gave the triol (124) in the form of an unstable diastereomeric mixture, which, under the conditions of Jones oxidation, was converted into lactone (125) with a yield of 62% [calculated on the (1)]. Oxidation of the triol (124) under the action of active manganese dioxide gave the enone (126) with retention of the lactol grouping [32%, calculated on the (1)]. On the Wittig olefination of the semiacetal (126) with various alkylidenetriphenylphosphoranes the clavulone analogues (127)-(129) with α-chains of different lengths were formed (24-79%). An investigation of the antileukemic activities of the compounds obtained showed that compounds (114) and (125)-(128) exhibited a considerably greater activity than the initial clavulone I (1) [34].

## CHEMICAL SYNTHESIS OF HALOGEN-CONTAINING PROSTANOIDS — HALOGENOVULONES, PUNAGLANDINS, AND THEIR ANALOGUES

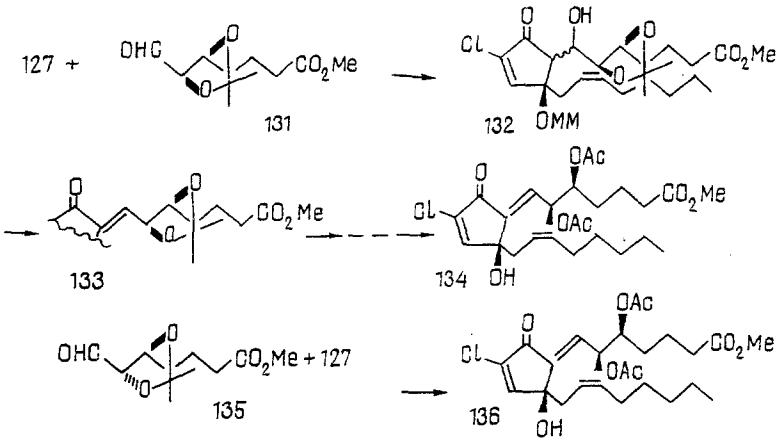
In order to establish the accurate configuration of the chlorovulones, Japanese researchers carried out the total synthesis of (—)-chlorovulone II, starting from (4S)-4-hydroxycyclopent-2-enone (28) [9].

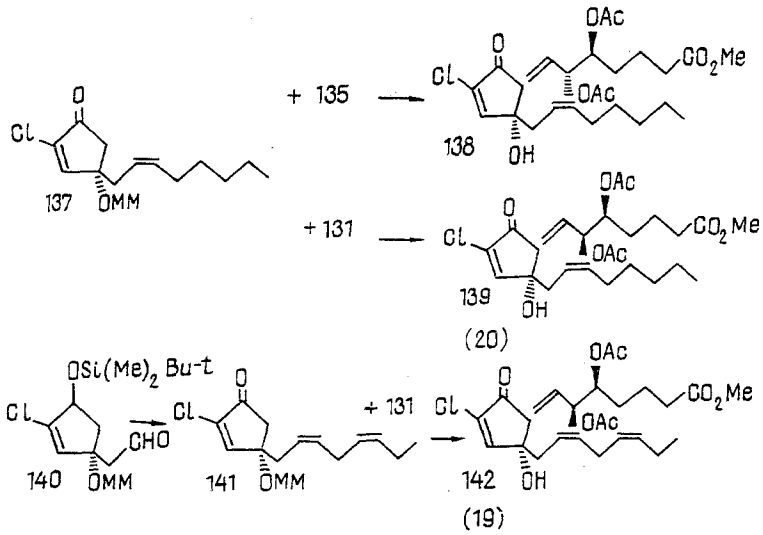



The *cis*-diol (29) obtained from the optically active hydroxyketone (28) [25] was oxidized by the Jones method to the $\alpha,\beta$-unsaturated ketone (121). Protection of the tertiary alcohol group in the form of the methoxymethyl ether led to the cyclopentenone (122) which, after treatment with gaseous chlorine, gave the chloro derivative (123) with an overall yield of 75% [calculated on the (29)].

The Swern oxidation of the alcohol group to an aldehyde group followed by the Wittig reaction with hexylidenetriphenylphosphorane gave the Z-olefin (126). Elimination of the silyl group and Jones oxidation led to the enone (127) with a yield of 68%. The interaction of the lithium enolate of compound (127) with aldehyde (128), obtained in three stages from $\delta$-valerolactone, led to compound (129) (68%), which, after elimination of the methoxymethyl group under acid conditions, gave (—)-clavulone II (130), differing from the natural compound by the sign of the angle of optical rotation.

The synthesis of punaglandins 3 (19) and 4 (20) and also their stereoisomers, was achieved by Japanese authors in 1986 [13]. Here they used an approach that they had used previously for the synthesis of (—)-chlorovulone [9]. Initially, basing themselves on the structure of punaglandin 4 ascribed to it on its isolation [10], they synthesized the (5S,6S,12S)- isomer (134) by the scheme given below. The lithium enolate of the chlorocyclopentenone (127) obtained previously [9] was condensed with the aldehyde (131) synthesized from 2-deoxy-*D*-ribose, yielding a diastereomeric mixture of aldols (132) (79% on the enone that had reacted), which, after treatment with acetic anhydride and N-dimethylaminopyridine, gave compound (133) and its 7Z- isomer in a ratio of 2:3 with a total yield of 92%.

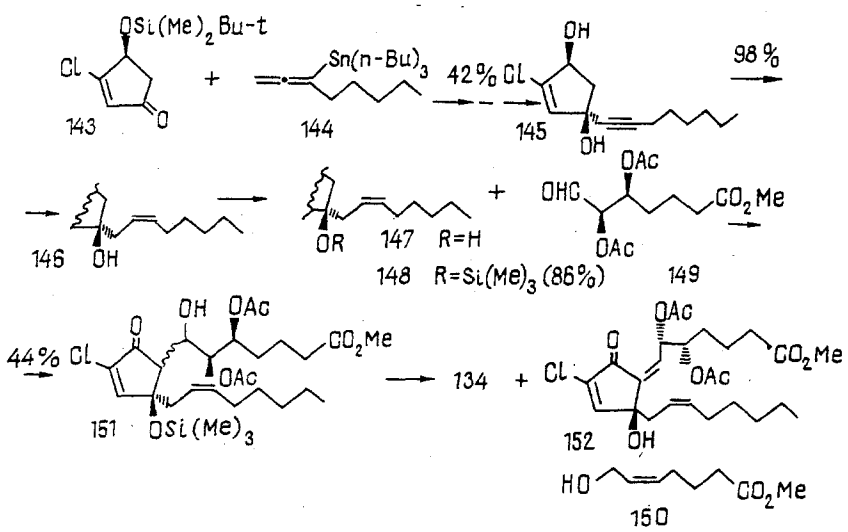


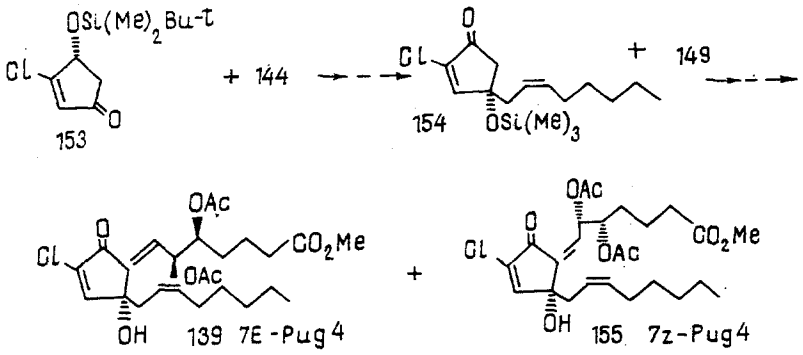


After chromatographic separation, compound (133) was converted into (134) in three stages: 1) elimination of the isopropylidene protective group; 2) acetylation; 3) demethoxymethylation; with an overall yield of 43%. However, according to its spectral characteristics, compound (134) was not identical with the natural punaglandin 4. To establish the true structure of punaglandin 4 and its 17,18-dehydro analogue — punaglandin 3, the authors undertook the synthesis of a series of isomeric compounds. Thus, by the interaction of the chlorocyclopentenone (127) with the aldehyde (135), which is an intermediate in the synthesis of the aldehyde (131), they obtained the 5S,6R,12S- isomer (136). The interaction of the chlorocyclopentenone (137), obtained from (R)-4-hydroxycyclopent-2-enone by the method described in [9], with aldehydes (135) and (131) by the same scheme gave the (5S,6R,12R)- and the (5S,6S,12R)- isomers (138) and (139), respectively. Its spectral characteristics (PMR, IR, CD), optical rotation, and chromatographic mobility (HPLC) showed that compound (139) was identical with natural punaglandin 4 (20).

Then, to establish the structure of punaglandin 3 (19), the chlorocyclopentenone (141) was synthesized from the aldehyde (140) [which had been used in the preparation of chloropentenone (137)] by the Wittig condensation of the latter with the ylide obtained from (Z)-hex-3-enyltriphenylphosphonium bromide, followed by desilylation and Jones oxidation, with 83% overall yield. Interaction of the enone (141) with the aldehyde (131) by the scheme shown above gave compound (142), identical with punaglandin 3 (19), with an overall yield of 8%.

Practically simultaneously with this work, a communication appeared on the results of another group of Japanese researchers, that were obtained in association with the authors who had isolated punaglandins from marine organisms [11]. Initially, as in the preceding investigation, compounds (134) and (152) were synthesized. For this purpose, a crystalline acetylenic diol (145) was obtained by the interaction of (143) with the allenyltin derivative (144) followed by desilylation, and this, after reduction on Lindlar catalyst, gave the Z-olefinic diol (146). Oxidation of the latter with pyridine dichromate led to the allyl alcohol (147), the silylation of which gave compound (148).

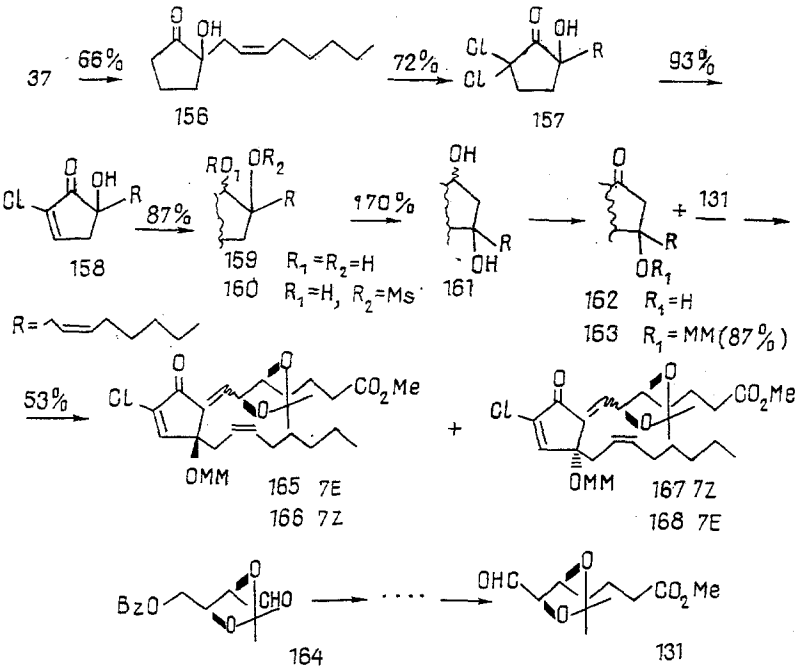


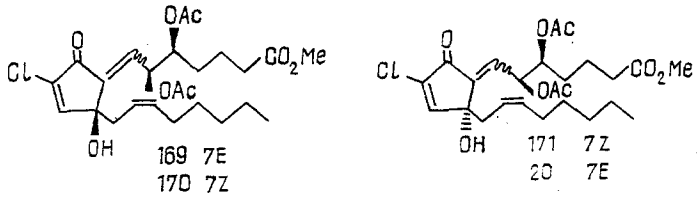


The aldol condensation of this compound with aldehyde (149), obtained from the hydroxy ester (150) with the use of *L*-(+)-diethyl tartrate led in seven stages to compound (151). Dehydration of (151) using acetic anhydride and 4-dimethylaminopyridine, followed by desilylation, gave a mixture of the required compounds (134) and (152) in a ratio of 1:4 with a total yield of 41%.

Both these compounds had the (5S,6S,12S)- configuration, but they were not identical with the natural (7E)- and (7Z)-punaglandins 4. Then, as in the preceding study, the authors synthesized all the possible diastereomers with respect to C-5, C-6, and C-12 from the appropriate chiral cyclopentenones and aldehydes. Of them, only products (139) and (155), obtained from cyclopentenone (153) [enantiomeric to compound (143)] and the aldehyde (149), were identical with the natural (7E)- and (7Z)-punaglandins 4. Here the key stage — the aldol condensation of enones (154) with aldehyde (149) — took place with 58% yield. A more detailed report of this work appeared in 1988 [12].

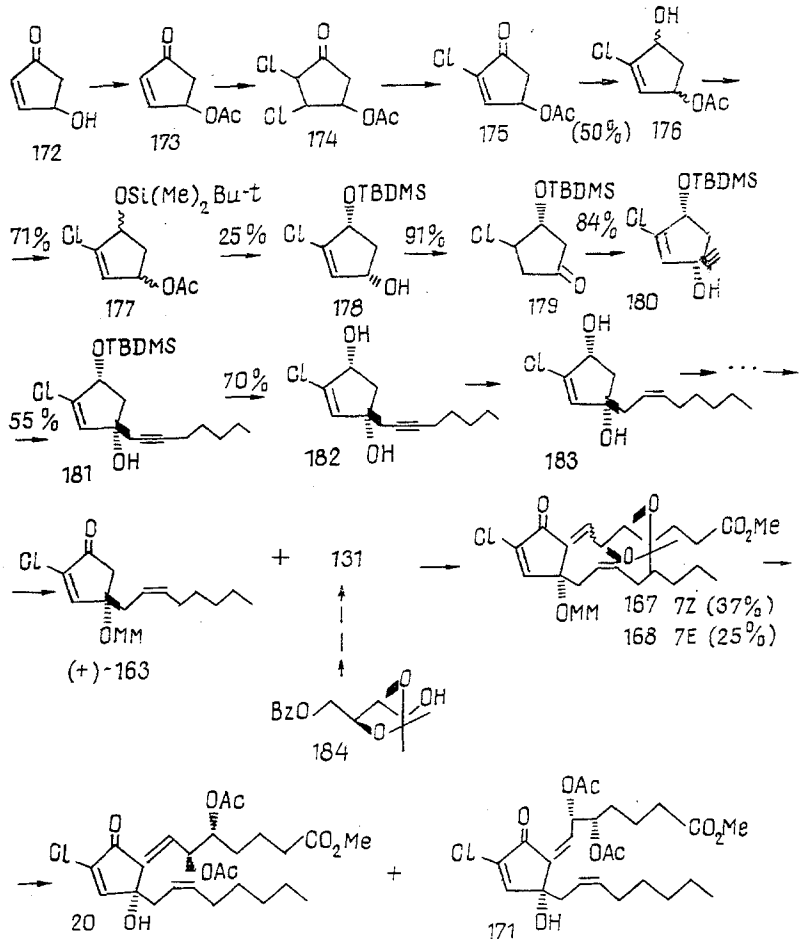
The total synthesis of punaglandin 4 (20) and three of its stereoisomers was proposed by Japanese authors in 1987, starting from 1,2-bis(trimethylsilyloxy)cyclopentene (37) [35]. Compound (37) was converted in two stages into (±)-2-hydroxy-2-[oct-2(Z)-enyl]cyclopentanone (156) the chlorination of which with N-chlorosuccinimide gave the dichlorocyclopentenone (157). The dehydrochlorination of the latter using LiCl in dimethylformamide took place at 120°C, giving the α-chloroenone (158). The reduction of this enone with sodium tetrahydroborate in the presence of $CeCl_3$ gave the diol (159) in the form of a mixture of isomers with respect to C-11. The selective mesylation of this diol was effected with methanesulfonic anhydride in the presence of dimethylaminopyridine in a mixture of pyridine and methylene chloride, giving the monomesyl derivative (160), which, under the conditions of solvolysis in 80% aqueous dimethyl sulfoxide underwent an allyl rearrangement. The diol (161) so formed was obtained in the form of a 1:1 mixture of isomers with respect to C-9.






Without additional purification, this mixture of isomers was oxidized with pyridine dichromate to form the enone (162) with an overall yield of 51%, calculated on the (159). Protection of the tertiary alcohol group of compound (162) in the form of the methoxymethyl ether led to the key synthon (163). This synthon was condensed with aldehyde (131), obtained from 4-O-benzyl-2,3-O-isopropylidene-*L*-threose (164) in six stages. As a result of the condensation, a mixture of four stereoisomers (165)-(168) in equal amounts was isolated. The mixture obtained was separated chromatographically, and each individual stereoisomer was subjected to successive hydrolysis of the isopropylidene protective group (80% aqueous AcOH, 80°C) acetylation ($Ac_2O$—$Py/CH_2Cl_2$) and hydrolysis of the methoxymethyl ether group (80% aqueous AcOH, 100°C). This led to 30-40% yields of the stereoisomeric compounds (169)-(171) and (20) of which compound (20) was identical with natural punaglandin 4.

The scheme for the synthesis of the punaglandins including the condensation of synthon (163) with aldehyde (131) proved to be fairly effective, and this approach was used by another group of Japanese researchers [36]. However, in contrast to the first group [35], who used an optically active aldehyde (131) in condensation with the racemic synthon (163), in [36] both reactants were chiral so that (since condensation took place nonstereoselectively), in place of the four isomers only two were obtained, which considerably facilitated the isolation of the required natural stereoisomer, punaglandin 4 (20).

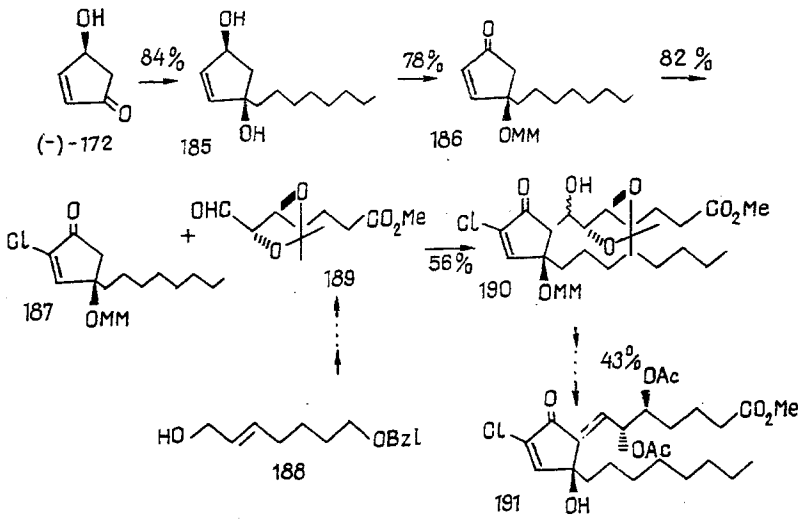



To obtain the chiral synthon (163), the authors used enzymatic cleavage in the early stages. Thus, the initial 4-hydroxycyclopent-2-enone (172) was acetylated and the acetoxy derivative obtained (173) was treated with chlorine, and the resulting dichloroketone (174) was dehydrochlorinated under the action of triethylamine, giving the enone (175) with an overall yield of 50%. Reduction of the latter with sodium tetrahydroborate in the presence of $CeCl_3$ gave a mixture of the *cis*- and

*trans*-allyl alcohols (176), which was treated with *t*-Bu(Me)$_2$SiCl in the presence of imidazole, giving a mixture of the *cis—trans* isomeric protected diols (177).

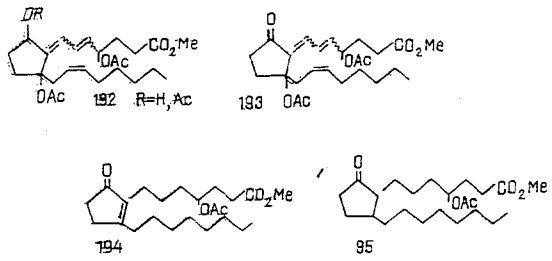
The key stage of the synthesis was the enzymatic hydrolysis of this mixture using the lipase PPC (pig pancreatic lipase). This permitted the isolation of the (1S,4R)- levorotatory alcohol (178) in 25% yield after chromatographic purification. Oxidation of the latter with pyridine dichromate gave the enone (179). The overall yield of enone (179) from compound (172) amounted to 8.2%. The interaction of the lithium anion of prop-1-yne with the enone (179) took place stereoselectively, giving the acetylene derivative (180). Reduction of the acetylenic bond over Lindlar catalyst gave the olefin (183), which was converted into the chiral synthon (+)-(163) by oxidation with pyridine dichromate and the protection of the tertiary alcohol in the form of the methoxymethyl ether with an overall yield of 23%, calculated on the (178).

Aldehyde (131) was synthesized from *L*-(+)-citric acid via the isopropylidene derivative (184) by an original scheme with an overall yield of 20%. Subsequent aldol condensation of the synthon (+)-(163) with aldehyde (131) was carried out under the action of lithium diisopropylamide, giving the isopropylidene derivatives (167) and (168). Punaglandin 4 (20) and its (7Z)- isomer (171) were isolated by the method described in [58], which gave punaglandin 4 (20) and the isomer (171) with yields of 6 and 13.7%, respectively. The overall yields of (20) and (171) were 1.4 and 3.1%, calculated on the chiral precursor (178).




The synthesis of a punaglandin analogue containing an unsaturated ω-chain was undertaken in 1985 [37]. Chiral (4S)-hydroxycyclopent-2-enone (—)-(172) was obtained from *L*-(+)-diethyl tartrate. Its interaction with octyllithium gave the syn-diol (185) with high stereoselectivity. Jones oxidation and protection of the tertiary alcohol function in the form of the methoxymethyl ether led to the enone (186). Chlorination of the latter with gaseous chlorine and dehydrochlorination under the action of triethylamine formed the chlorocyclopentenone (187).

Aldehyde (189) was obtained from allyl alcohol (188) in ten stages using *L*-(+)-diethyl tartrate as the chiral reagent. The aldol condensation of the chiral enone (187) with the chiral aldehyde (189) took place stereoselectively, giving the aldol (190). This aldol was converted into the punaglandin analogue (191) in six stages — (1) dehydration; 2) hydrolysis of the acetonide, accompanied by partial hydrolysis of the methoxycarbonyl group; 3) methylation; 4) acetylation; 5) elimination of the protective MOM group, accompanied by partial hydrolysis of the methoxycarbonyl group; and 6) methylation).



The synthesis of seven clavulone analogues, including (192)-(195) has been described in a patent [38]; they were obtained from natural compounds by a combination of reduction, oxidation, and acylation reactions.

## BIOLOGICAL ACTIVITIES OF THE "NEW MARINE PROSTANOIDS"

The considerable efforts devoted to the synthesis and to the study of structure and biosynthesis of the "new marine prostanoids" is largely due to the detection among these compounds of the property of suppressing the growth of tumor cells without affecting the development of healthy cells. Thus, in one of the first publications on the isolation of the clavulones from marine organisms [1] it was shown that these compounds exhibited a considerable antiinflammatory activity in a dose of 30 $\mu$g/ml. It has been shown in a patent [38] that the natural clavulones (18) and (3)-(7) and their analogues exhibit a high antiinflammatory and antitumoral activity at optimum doses between 1 and 100 $\mu$g/kg.

Honda et al. [39] have reported investigations of the antitumoral activities of the clavulones and have shown that they possess a selective antiproliferative and cytotoxic action on HL-60 tumor cells with a $ED_{50}$ value of the order of 0.2 $\mu$g/ml. A study of the synthesis of DNA permits the hypothesis that the clavulones retard the growth of the cells in the $G_1$-phase and inhibit the growth of HL-60 cells by inhibiting the S-phase of DNA synthesis.

Other authors [4, 40] have reported that the clavulones exhibit an inhibiting action against leukemia L1210 at a $ED_{50}$ dose of 0.2-0.4 $\mu$g/ml. In investigations of the antitumoral activity of demethylated and deacylated clavulone analogues the 12-deacetyl derivative of clavulone (II) proved to be more active than the initial natural clavulone (II) against leukemia HL-60 cells [31].

A comparative investigation of the antitumoral activity of $\Delta^7$-$PGA_1$, $\Delta^{12}$-$PGJ_2$, and clavulones and punaglandins has been carried out by Fukushima et al. [41]. It was shown that the clavulones exhibit cytotoxicity in relation to leukemia L1210 cells in a $ED_{50}$ dose of 0.3 $\mu$g/ml, at the level of $\Delta^7$-$PGA_1$, while the punaglandins were considerably more active and exhibited the same effect in a dose of 0.02 $\mu$g/ml. Thus, it has been shown that punaglandin 3 is 15 times more active in the inhibition of leukemia L1210 cells than the clavulones. Suzuki et al. [11] showed that of the four punaglandins isolated the greatest antiproliferative activity was exhibited by punaglandins 3 and 4. It has also been shown [10] that the antiproliferative activity of punaglandin 4 in relation to leukemia L1210 cells depends little on stereochemistry. Thus, a comparative study of the antiproliferative activities of punaglandin 4 and of five of its stereomers showed that the activities of all these compounds were exhibited in $ED_{50}$ doses of 0.02-0.1 $\mu$g/ml and had little connection with the particular stereochemistry. Interesting information on the antiproliferative activity of the marine epoxy prostanoid (115) has been given by Iguchi et al. [8]. They found that this compound exhibits a higher activity against leukemia HL-60 cells than the clavulone ($ED_{50}$ 0.04 $\mu$g/ml) which refuted Fukushima's hypothesis that the antitumoral activity of the prostanoids is due to the presence of a cross-conjugated cyclopentenoid system [42]. It is true that it may be assumed that the antitumoral activity of the epoxy prostanoid (115) may be due to some cross-conjugated metabolites or other of the initial epoxide.

Information on the biological activity of 10-halogenated analogues of the clavulones has been given in the literature [11, 37, 43]. Thus, the 10-chlorinated clavulone analogue (191) inhibited the growth of melanoma B16 cells 10 times more actively than clavulone II, exhibiting an effect in an $ED_{50}$ dose of 0.03 $\mu$g/ml [37]. Investigations on the antiproliferative and antitoxic activities of the 10-halogenated clavulone analogues (116)-(119) showed that the 10-fluoro- and 10-chloro-derivatives (116) and (119) were more active than the clavulones and their 10-bromo- and 10-iodo- derivatives (117) and (118) [32, 43].

Information on the antiproliferative and cytotoxic activities of chlorovulone I in relation to leukemia HL-60 cells has been given by Iguchi et al. [6]. They showed that this compound is effective in a dose of 0.01 $\mu$g/ml, i.e., it is 13 times more active than clavulone I ($ED_{50}$ 0.4 $\mu$g/ml). A study of the activities of bromo- and iodovulones has shown that, in relation to leukemia HL-60 cells, these compounds exhibit antiproliferative activity in $ED_{50}$ doses of 0.025 and 0.030 $\mu$g/ml, respectively, and the cytotoxic activities in a $ED_{50}$ dose of 0.4 $\mu$g/ml for both compounds, which are considerably lower than the activities of chlorovulone I [7, 44].

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