Proc. Estonian Acad. Sci. Chem., 1999, **48**, 2, 51–79
https://doi.org/10.3176/chem.1999.2.01

TWO DECADES OF THE CHEMISTRY OF PROSTANOID AND RELATED COMPOUNDS IN ESTONIA

Ülo LILLE

Department of Bioorganic Chemistry, Institute of Chemistry, Tallinn Technical University, Akadeemia tee 15, 12618 Tallinn, Estonia; lille@boc.ic.ee

Received 25 January 1999

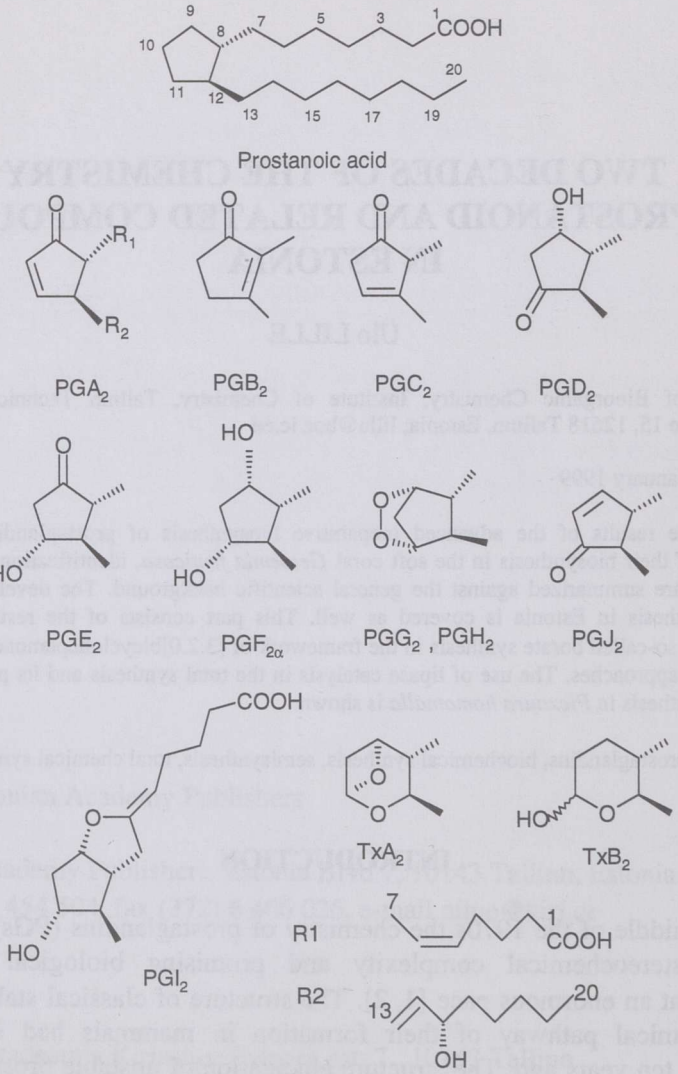
Abstract. The results of the advanced preparative biosynthesis of prostaglandins (PGs), the mechanism of their biosynthesis in the soft coral *Gersemia fruticosa*, identification of minor PGs and steroids are summarized against the general scientific background. The development of the total PG synthesis in Estonia is covered as well. This part consists of the results of cuprate synthesis, the so-called borate synthesis in the framework of [3.2.0]bicycloheptanone, and epoxyde displacement approaches. The use of lipase catalysis in the total synthesis and its possible role in the PG biosynthesis in *Plexaura homomalla* is shown.

Key words: prostaglandins, biochemical synthesis, semisynthesis, total chemical synthesis, sterols.

INTRODUCTION

In the middle of the 1970s the chemistry of prostaglandins (PGs), motivated by their stereochemical complexity and promising biological properties, developed at an enormous pace [1, 2]. The structure of classical stable PGs and the biochemical pathway of their formation in mammals had been firmly established ten years ago. The structure elucidation of unstable prostacyclin and thromboxane (Tx), the latter trapped as TxB_2, had just been completed [3]. The synthetic methods of stable PGs have passed through biochemical oxidative cyclization of proper eicosatri- and eicosatetraenic acids in the presence of enzyme preparations from ram seminal vesicles in the middle of the 1960s [4] via semisynthesis based on 15-epi-PGA_2 from the Caribbean coral *Plexaura*

homomalla in the early 1970s [5] to the pilot plant total multistep chemical synthesis [6, 7]. The use of PG drugs in human and veterinary reproduction has started and guidelines for creating metabolically stabilized PG analogues designated all together as prostanoids (Scheme 1) with prolonged action have been clarified.



Scheme 1. Legend to the prostaglandin (PG) nomenclature. PGs of the second series are shown. In the first series the C5–C6 double bond is changed to single bond, in the third series the *cis* double bond C17–C18 is present. In PGG the 15-OH group is changed to 15-OOH group. Greek letters α and β denote the location of the substituent below and above the plane of paper respectively ("upper" and "lower" side chains are designated analogously). Numbered *-epi* and *-iso* prefixes in the text denote an inversion of the normal configuration of a particular substituent.

At the time when the number of free PG samples delivered by Upjohn for biological studies reached five thousand per year the leadership of the Estonian Academy of Sciences supported the author's idea to launch a project on the PG chemistry, although it seemed scientifically suicidal at first glance. The project was aimed at preparing these valuable compounds to fill the niche in the USSR, in a country with well-known closed totalitarian system inlcuding also incorporated Estonia. Up to the 1970s in this enormous country little attention had been paid to PG chemistry and our project was readily included into the corresponding central program being just formed [8]. At that time much attention was given to the development of biomedicinal sciences on the initiative of Yurij Ovchinnikov, Vice President of the USSR Academy of Sciences. So the author, an oil shale chemist with research experience of 20 years in an industrial research institute, started the project with a team consisting mainly of young enthusiastic technologists and chemists on the level of graduate students. The results of their research are shown in numerous quotations in this paper. Particularly it is proper to mention here Margus Lopp and Nigulas Samel, who have been dealing with PG chemistry from the beginning of the project.

The aim of this article is to show the development of ideas and to summarize the main innovative and scientific results of this long-lasting endeavour in order to estimate the past and and to facilitate the planning of future development. Mainly articles published in refereed journals (at least in *Chemical Abstracts*) have been quoted. From numerous dissertations, patents, and abstracts of conferences only those containing data so far unpublished or fixing certain time relevant to the project have been included.

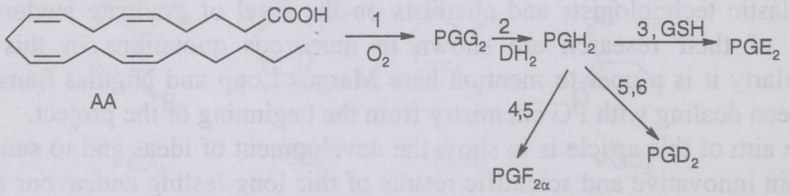
BIOCHEMICAL SYNTHESIS

It would be naive to assume that an inexperienced team can carry out multistep synthesis in a poorly equipped laboratory and prepare in a short time molecules that seem relatively simple at first sight yet consist of a number of chemically reactive functional groups and stereogenic centres. Therefore, the method of biosynthesis was chosen to accomplish the preparation of natural PGs in quantities necessary for their biological studies and possibly for the use in human medicine.

Preparative biochemical and semisynthesis

The introduction of biosynthesis (Scheme 2) was supported by (1) the easily available biological material as the source of PG synthetase complex (ca 25 thousand rams were slaugthered per year in Estonia) and arachidonic acid (AA); (2) relatively good knowledge of the methods of separation and structure elucidation; (3) the designing and manufacture of the corresponding apparatus in

Estonia; and (4) by a simple-minded hope of elaborating a modern technology of biosynthesis with the use of immobilized enzymes. In the light of the statement of E. Corey (Nobel prize winner in 1990): "PG-synthetase of this easily available sea whip *Plexaura homomalla* ... might be solubilized, purified and affixed to a column so as to allow an in vitro enzymatic synthesis of PG-s in a continuous flow system" [9] the last idea was not a new one (we shall return to this coral later). It was obvious that membrane bound PG synthetase complex from ram seminal vesicles, consisting of cyclooxygenase/hydroperoxydase and PGE isomerase activities, did not necessarily require expensive and limiting redox cofactors. Why not bind this complex to an artificial membrane? By the way, at that time the immobilization of penicillin amidase was intensively studied in Tallinn Technical University.



Scheme 2. Oxidative cyclization of arachidonic acid (AA), using enzyme preparation from ram seminal vesicles. 1, cyclooxygenase activity; 2, peroxidase activity; DH_2, electron donor; 3, PGE isomerase activity; GSH, glutathione; 4, chemical reduction; 5, non-enzymatic decomposition; 6, selective inhibition of 3. Under rigorous stirring the PGE synthesis proceeds in 10 min.

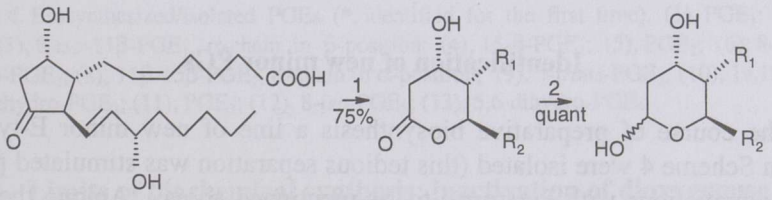
On this and following schemes no by-products are shown.

The first batch of PGE_2 was obtained in 1976 [10] with microsomal enzyme as acetone–pentane powder [11] and AA separated from adrenal glands of cattle and purified finally on an $AgNO_3$ impregnated silica column [12]. So the story that had occurred ca 15 years ago on the western coast of the Baltic Sea was repeated on the eastern coast. The PGE_2 standard was obtained later, after the author's fleeting contact with coworkers of the Upjohn company in Moscow in 1978. Our microsomal enzyme version of biosynthesis [13, 14] was later used in the framework of the general programme for the preparation of labeled PGs [15]. Further the synthesis was indeed carried out on a semipermeable membrane with continuous separation of products [16]. However, this technique did not give any advantages expected and later an essentially simplified technology including batch reactor and enzyme preparation as tissue homogenate was exploited for the synthesis of stable natural PGs [17–19]. A fatty acid substrate was used as concentrate of polyenic acids. This concentrate consisted of the first series PG precursor 8,11,14-eicosatrienoic acid as well. Along with adrenal glands, a rich source of steroids, the liver of cattle and pigs was used for the preparation of the

fatty acid substrate mentioned above. Later we developed a method for the preparation of 8,11,14(all *cis*)-eicosatrienoic acid from AA [20].

This "first generation" technology of biochemical synthesis is physically a very complicated multiphase process which has been considerably intensified using AA concentrations up to 10 mM and highly dispersed reaction media. The high dispersity of the media, also revealed by microscopic studies with 378-fold magnification, was achieved by using a special device – the disintegrator. Such machines had been developed and built at that time in Tallinn for the production of building materials. (The leader of the innovative research into disintegration processes, talented scientist Johannes Hint, died in prison in 1985 being in deep conflict with the totalitarian regime.) The productivity of the modified technology had been increased up to 1 g of PGE_2 per 1 L of reactor volume.

During the following years, until 1995, the biosynthetic unit of the pilot plant of the Estonian Academy of Sciences manufactured a number of natural PGs, mainly of second series, including the highly unstable endoperoxide PGH_2. The kinetics of the degradation of PGH_2 was studied in a collaborating laboratory [21]. PGE_1 was produced as well. The total capacity of the pilot plant was nearly one order of magnitude higher than that of Upjohn Ltd. in the 1960s. PGB_2, $PGF_{2\alpha}$, PGI_2 sodium salt (all based on E_2), 11-didehydro-TxB_2, and TxB_2 were produced semisynthetically [22, 23] (TxB_2 was synthesized starting with PGD_2, Scheme 3). Recently in a small enterprise Kevelt Ltd. (Tallinn) an efficient chemo-enzymatic method for the preparation of PGD_2, a powerful physiological sleep inducing substance, from $PGF_{2\alpha}$ was developed [24]. Much attention was paid to the analytical and structural problems [25–29] and to the preparative separation using HPLC apparatus, constructed for this purpose in the Estonian Academy of Sciences [30, 31].



Scheme 3. Semisynthesis of TxB_2. 1, MCPBA, H_2O, $NaHCO_3$, CH_2Cl_2, –78 °C (the yield is expressed on transformed PGD_2, 60% of the latter was recovered); 2, DIBAH, THF, –78 °C.

In the early 1980s intensive negotiations were conducted for the transfer of our biochemical technology to Perstorp Ltd. (Sweden). These negotiations failed mainly due to the centralized foreign trade bureaucracy of the closed totalitarian country.

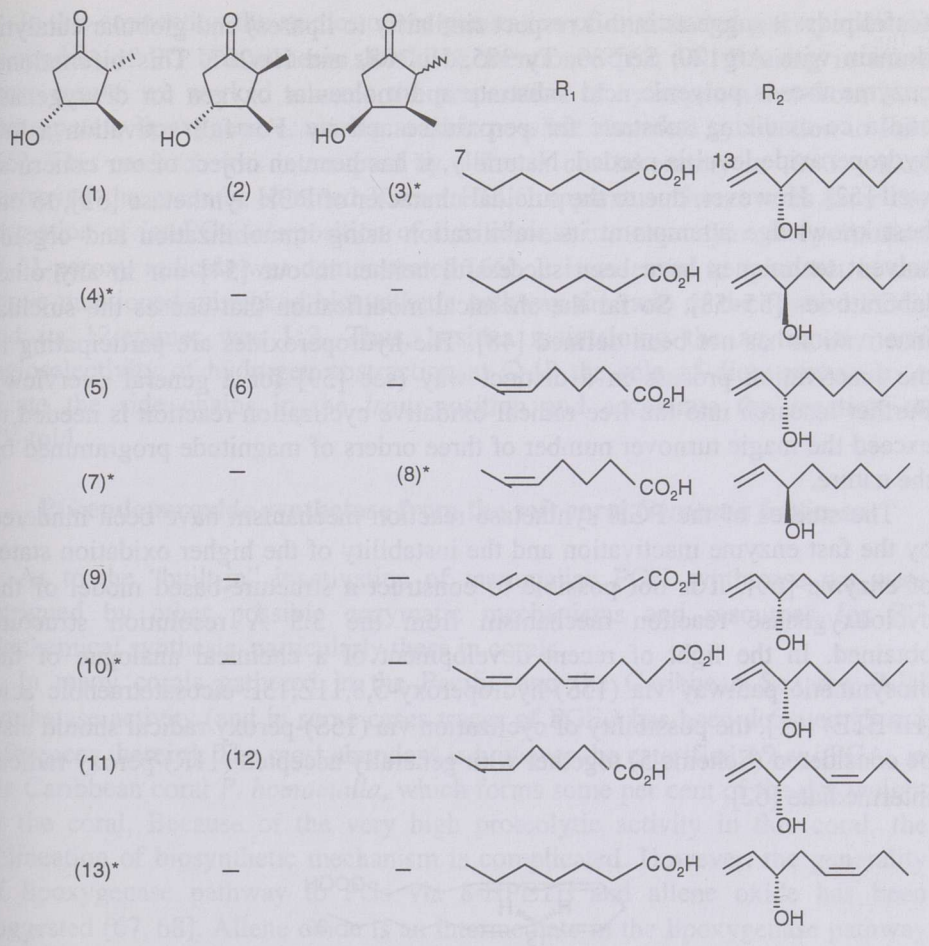
It must be noted that biochemical synthesis of PGs gives in one stage absolute sterocontrol over five carbon atoms and e.p. products are obtained. Under certain circumstances interest in this process seems to be continuing [32].

Application of natural PGs

The biological activities of manufactured natural PGs have been widely studied, especially at the beginning of the 1980s, as partially reviewed in [33]. The samples of natural PGs were delivered over a large area, from Lvov to Vladivostok. On the basis of PGE_2 a child birth stimulating drug "Prostenon" (an analogue to "Prostin E" of Upjohn, whereas "Prostenon" is used additionally for the treatment of acute kidney insufficiency) was developed and its manufacture started in the Tallinn Pharmaceutical Works in 1986 [34]. At present it is registered in the Baltic countries and produced as a stable gel in Kevelt Ltd. (Tallinn). It should be noted that in the USSR a full cycle of research including pharmacological/toxicological studies and two-stage clinical trials was required even for generic drugs at that time. PGE_1 was used in clinical studies for the treatment of peripheral blood circulation disorders (analogue of "Prostavasin", Schwartz Gmbh, Germany). The semisynthetic $PGF_{2\alpha}$ THAM salt was used for synchronization of oestrus in cattle [35]. Much attention was paid to this problem as the country could not afford to buy enough of the corresponding ICI drug "Estrumate" (produced on the basis of cloprostenol, see below). In 1990 experimental studies of vasocyclin (PGI_2 sodium salt, analogue of epoprostenol, Wellcome Ltd., UK) for the treatment of ischemia were finished. Projects for the preparation of antibodies of natural PGs, derivatives with prolonged action [36], and studies of the interaction of PGs with components of biological membranes [37] were launched in collaborating laboratories.

Identification of new minor PGs

In the course of preparative biosynthesis a line of new minor E-type PGs listed in Scheme 4 were isolated (this tedious separation was stimulated partially by our negotiations with Perstorp Ltd. as mentioned above). Among them were 5,6-dihydro-PGE_3, a candidate for selective antithrombotic agent, synthesized biochemically from 8,11,14,17-tetraenoic acid as well [38, 39], 1a,1b-dihomo-2,3-didehydro-PGE_2 [40], 11-*iso* and 15-*iso*-PGE_1 and 15-*iso*-PGE_2 [41]. The *iso* compounds could probably be formed by different mechanisms: autoxidation [42] and isomerization (8-*iso*, 15-*iso*), "mistakes" of enzymatic synthesis (?,11-*iso*). In the light of special attention to *iso*-PGs of F type [43] the effects of isolated compounds on platelates and smooth muscles were studied [44, 45].



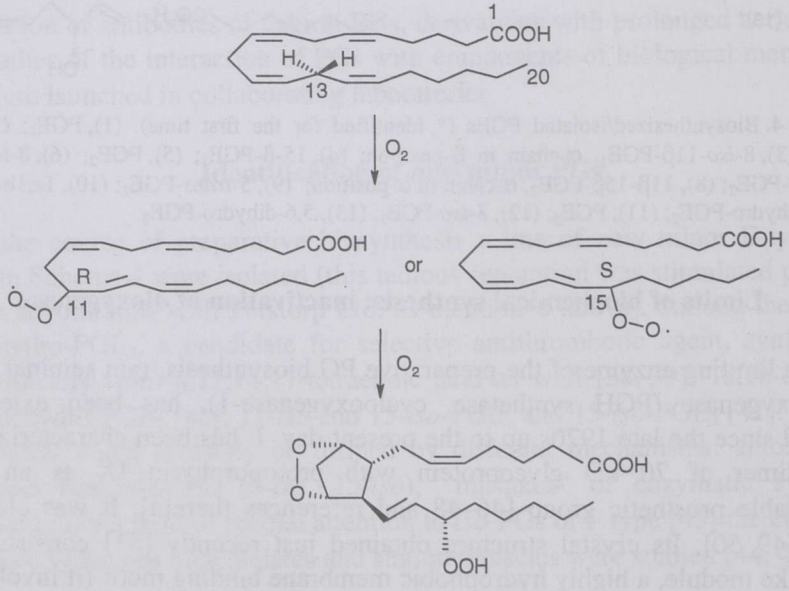
Scheme 4. Biosynthesized/isolated PGEs (*, identified for the first time). (1), PGE_1; (2), 8-*iso*-PGE_1; (3), 8-*iso*-11β-PGE_1, α-chain in β-position; (4), 15-β-PGE_1; (5), PGE_2; (6), 8-*iso*-PGE_2; (7), 15β-PGE_2; (8), 11β-15β-PGE_2, α-chain in α-position; (9), 5-*trans*-PGE_2; (10), 1a,1b-dihomo-2,3-didehydro-PGE_2; (11), PGE_3; (12), 8-*iso*-PGE_3; (13), 5,6-dihydro-PGE_3.

Limits of biochemical synthesis: inactivation of dioxygenase

The limiting enzyme of the preparative PG biosynthesis, ram seminal vesicle cyclooxygenase (PGH synthetase, cyclooxygenase-1), has been extensively studied since the late 1970s up to the present day. It has been characterized as a homodimer of 70 kD glycoprotein with protoporphyrin IX as an easily dissociable prosthetic group [46–48 and references therein]. It was cloned in 1988 [49, 50]. Its crystal structure obtained just recently [51] consists of an EGF-like module, a highly hydrophobic membrane binding motif (it involves the channel for the access of endogenous substrate released in membrane from

fosfolipids: it suggests in this respect similarity to lipases) and globular catalytic domain with Arg120, Ser530, Tyr385, His388, and His207. This bifunctional enzyme uses a polyenic acid substrate and molecular oxygen for dioxygenase and a co-oxidizing substrate for peroxidase activity. For full activation a low hydroperoxide level is needed. Naturally, it has been an object of our conern as well [52]. However, due to the suicidal character of PGH synthetase [53], to our best knowledge attempts at its stabilization using immobilization and organic solvent techniques have been successful neither in our [54] nor in any other laboratories [55–58]. So far the chemical modification that causes the suicidal inactivation has not been defined [48]. The hydroperoxides are participating in the inactivation process in a distinct way (see [59] for a general overview). Further research into the free radical oxidative cyclization reaction is needed to exceed the magic turnover number of three orders of magnitude programmed by the nature.

The studies of the PGH synthetase reaction mechanism have been hindered by the fast enzyme inactivation and the instability of the higher oxidation states of enzyme [60]. It is not possible to construct a structure-based model of the cyclooxygenase reaction mechanism from the 3.5 Å resolution structure obtained. In the light of recent development of a chemical analogue of the biosynthetic pathway via (15S)-hydroperoxy-5,8,11Z,13E-eicosatetraenoic acid (HPETE) [61], the possibility of cyclization via (15S)-peroxy radical should also be considered (Scheme 5) together with generally accepted (11R)-peroxy radical intermediate [62].



Scheme 5. Dilemma of two routes leading to PGG_2.

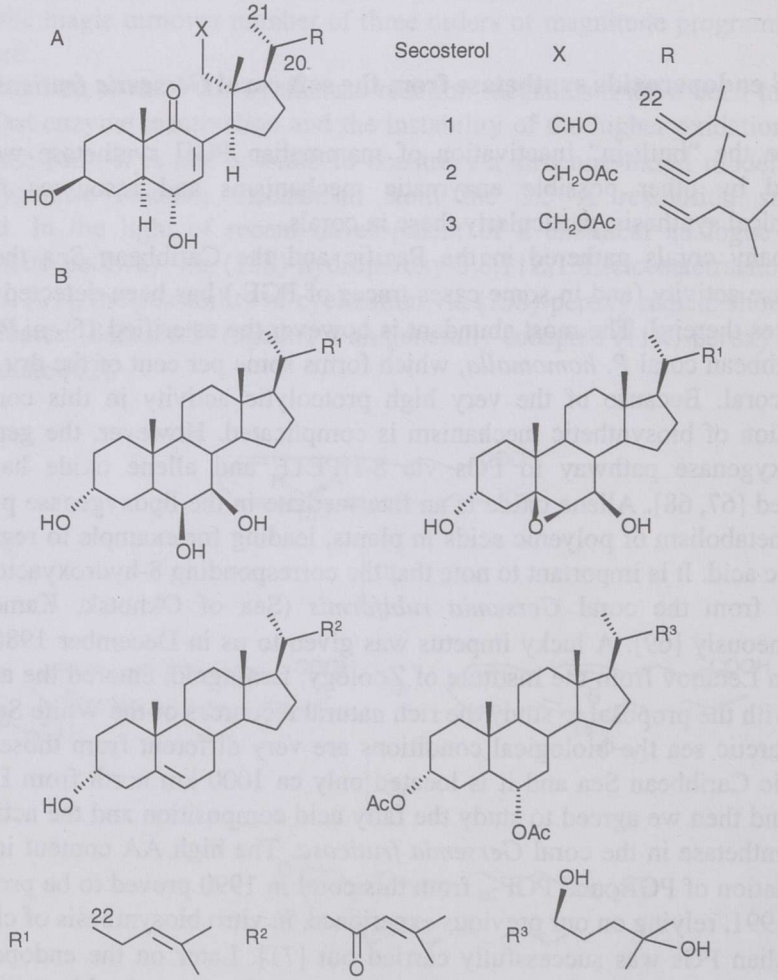
In this connection the studies of the generation of unsaturated peroxy radicals as models of PG biosynthesis should be mentioned [63, 64]. Bearing in mind these results we worked towards the preparation of hydroperoxides from AA, using potato lipoxygenase, aiming at their possible chemical cyclization to PGs [65]. This research was interrupted by a fire in our laboratory in 1980, which destroyed the recently obtained Varian HPLC apparatus. Some years later the formation of *iso*-PGs (*cis*-position of side chains) in non-enzymatic cyclization of 11-peroxy radicals was demonstrated [66]. It is essential to note that in the above-mentioned mimicked biosynthetic pathway the ratio of the formed PGG_2 and its 12-epimer was 1:3. Thus, besides maintaining the asymmetry and regioselectivity of hydrogen abstraction at C-13 the role of dioxygenase is to locate the side chains in the *trans*-position and accelerate the reaction ca 10^5-fold.

PG endoperoxide synthetase from the soft coral *Gersemia fruticosa*

As to the "built-in" inactivation of mammalian PGH synthetase we were intrigued by other possible enzymatic mechanisms and resources for PG biochemical synthesis, particularly these in corals.

In many corals gathered in the Pacific and the Caribbean Sea the PGH synthetase activity (and in some cases traces of PGE_2) has been detected [5 and references therein]. The most abundant is however the esterified 15-*epi* PGA_2 in the Caribbean coral *P. homomalla*, which forms some per cent of the dry weight of the coral. Because of the very high proteolytic activity in this coral, the delineation of biosynthetic mechanism is complicated. However, the generality of lipoxygenase pathway to PGs via 8-HPETE and allene oxide has been suggested [67, 68]. Allene oxide is an intermediate in the lipoxygenase pathway of the metabolism of polyenic acids in plants, leading for example to regulatory jasmonic acid. It is important to note that the corresponding 8-hydroxyacids were isolated from the coral *Gersemia rubiformis* (Sea of Okhotsk, Kamchatka) simultaneously [69]. A lucky impetus was given to us in December 1988 when Valentin Letunov from the Institute of Zoology, Leningrad, entered the author's office with the proposal to study the rich natural recources of the White Sea [70]. In this arctic sea the biological conditions are very different from those of the subtropic Caribbean Sea and it is located only ca 1000 km north from Estonia. There and then we agreed to study the fatty acid composition and the activity of PGH synthetase in the coral *Gersemia fruticosa.* The high AA content in lipids and isolation of PGE_2 and $PGF_{2\alpha}$ from this coral in 1990 proved to be promising and in 1991, relying on our previous experience, in vitro biosynthesis of classical mammalian PGs was successfully carried out [71]. Later on the endoperoxide pathway, characteristic of mammals, has been clearly shown in this arctic coral (however, with an exceptionally low peroxidase activity) [72–74]. Two distinct routes for initial oxidation of polyenic acids exist in this coral: the

cyclooxygenase route leading to chiral PGs and the lipoxygenase-allene oxide one leading to 8-H(P)ETE and other lipoxygenase and allene oxide products [75]. It turned out that *G. fruticosa* was a good choice for research as demonstration of the dioxygenase pathway in this coral was successful (in vitro biosynthesis of e.p. PGs in the presence of the enzymatic preparations from *P. homomalla* had so far failed [68]). Unlike in case of mammals, the mechanism of the synthesis of PGs in this and related corals has remained so far unclear and is an object of intensive research [76]. Recent work in our laboratory has revealed that lipases promote selective dehydration of 11,15-diacetoxy-PGE_2 to the corresponding PGA_2 derivative [77], it follows that the formation of the latter via PGE_2 is possible. Note that traces of 11R-HETE had been found in polar



Scheme 6. New sterols isolated from the soft coral *Gersemia fruticosa.* A, secosterols; B, other oxygenated sterols.

lipids and acetone powder of *P. homomalla,* interpretated as the result of corresponding low lipoxygenase activity [78].

In this place it is proper to mention the identification of a peroxidase-lipoxygenase fusion protein in *P. homomalla* with the participation of our laboratory [79].

Our research department isolated and characterized the cDNA encoding dioxygenase from *G. fruticosa* in 1998 [80]. The protein predicted from nucleic acid sequence contains a 68 kD polypeptide and consists of the same three domains with crucial Tyr385, His388, His207, and Ser530 as have been shown for PGH synthetase from sheep seminal vesicles. May be one day the time will be ripe for genetically engineered synthesis [81] of PGs and in this way a new curve on the everlasting spiral will be reached.

New sterols from *Gersemia fruticosa*

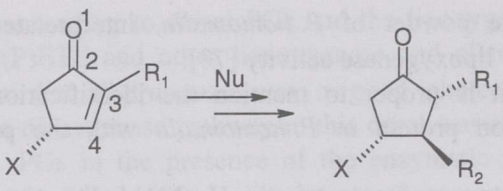
Along with the studies of PGs biosynthetic pathway other lipidic compounds – seven new sterols – have been isolated from *G. fruticosa* [82, 83] (Scheme 6). Semisynthetic routes to isolated secosterols are under study [84–87].

TOTAL CHEMICAL SYNTHESIS

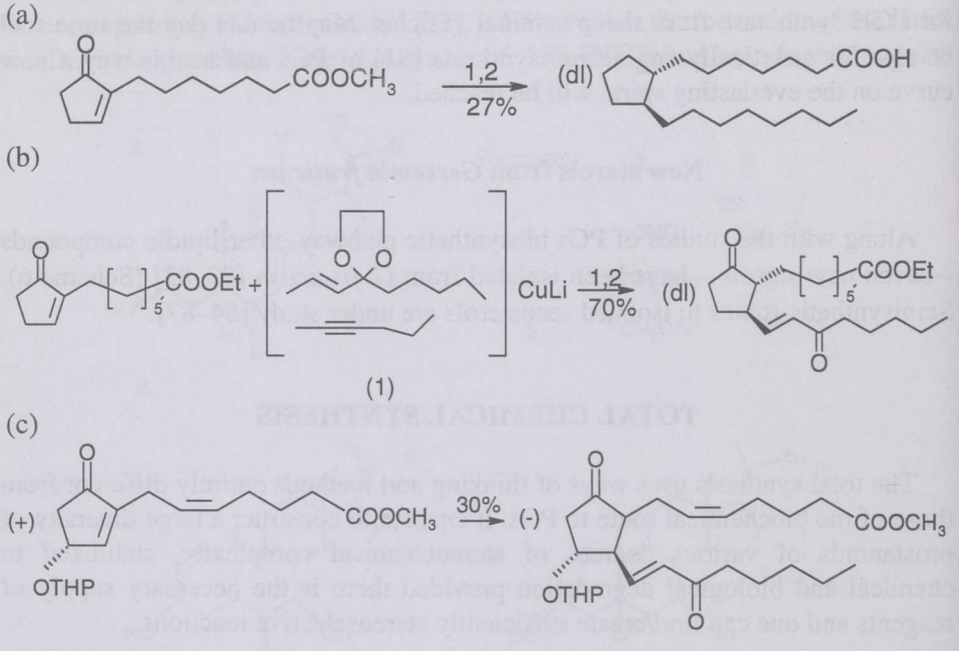
The total synthesis uses ways of thinking and methods entirely different from those of the biochemical route to PGs. It enables to construct a large diversity of prostanoids of various degrees of stereochemical complexity, stabilized to chemical and biological degradation provided there is the necessary supply of reagents and one can find/create sufficiently stereoselective reactions.

Conjugate addition approach: synthesis of 11-deoxy- and E-type PGs

The 11-deoxy-PGs possess many of the biological properties of natural PGs and because of their structural simplicity and stability they have frequently served as models for the synthesis of more complex PGs [6, 7]. At the first stage of our synthetic work we used the 1,4-conjugate addition (Scheme 7) of an unfunctionalized or properly functionalized β-chain (in general as a mixed cuprate) to methyl 3-oxocyclopentene-2-heptanoate (alfa-alkylated cyclopentenones), which is easily obtainable starting from diethyladipinate. The crucial choice of the cuprate method could have been the result of our previous interest in metalloorganics used for the synthesis of standard alkylresorcinols for shale oil phenols research via directed benzylic and aromatic metalation [88, 89] and seemingly readily comprehensible chemistry of the conjugate addition/cuprate approach. In this way the parent prostanoid, rac-prostanoic acid, and a



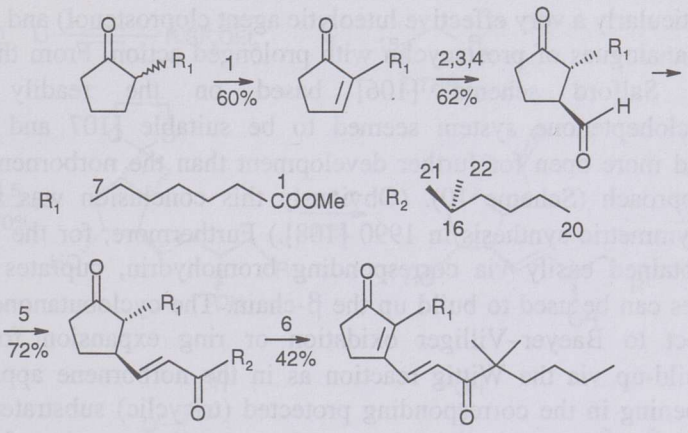
Scheme 7. 1,4-Conjugate addition approach to the total synthesis of PGs. X:H or OH; Nu, nucleophile, precursor of R_2.



Scheme 8. Cuprate synthesis. a, Prostanoic acid. 1, $(C_8H_{17})_2$. CuLi, pentane/ethyl ether, –78 °C; 2, NH_2–NH_2, KOH, diethylene glycol, 190 °C, H^+ (probably the severest conditions ever used in the PG chemistry). b, 11-deoxy-15-keto-PGE_1 ethyl ester. 1, DEE, hexane, –78/–20 °C; 2, H^+. c, 15-keto-PGE_2. Conditions as in b.

line of rac-11-deoxy-PGs (belonging mostly to the first series) were obtained, among them 15-alkylsubstituted and 15-dehydro analogues [90–92] (Scheme 8a, b). At that time in our laboratory much attention was paid to β-chain precursors [93–95]. Our cuprate method experience was later transferred to a cooperating laboratory in Riga (Latvia) for scale-up [96]. However, the metalloorganics and low temperatures needed appeared to be too cumbersome for industrial synthesis at that time and other methods have been elaborated in the above-mentioned laboratory for the preparative synthesis of 11-deoxy-PGs. Later our experience was used for laboratory synthesis of 16-arylsubstituted-17,18,19,20-tetranor-11-deoxy-PGE_1s in a collaborating laboratory in Ufa (Bashkirya) [97]. The

conjugate addition approach to the above-mentioned cyclopentenone synthon was exploited once more using the Nef reaction in the synthesis of 15-keto-PGB_1 and its 16,16-dimethyl analogues [98] (Scheme 9) for the preparation of corresponding polymeric PGB_x oligomers via base-catalyzed oligomerization [99], protecting rat liver mitochondria from the effects of aging [100 and references therein]. As a result of these studies the beneficial anti-ischemic effect of trimer on myocard was shown [101 and references therein].



Scheme 9. Synthesis of 15-keto-16,16-dimethyl-PGB_1 using the Nef reaction. 1, $CuBr_2$, ethyl acetate, reflux; 2, CH_3NO_2/CH_3ONa, CH_3OH, reflux; 3, CH_3ONa; 4, H^+; 5, NaH, $(CH_3O)_2POCH_2COR_2$; 6, as in 1.

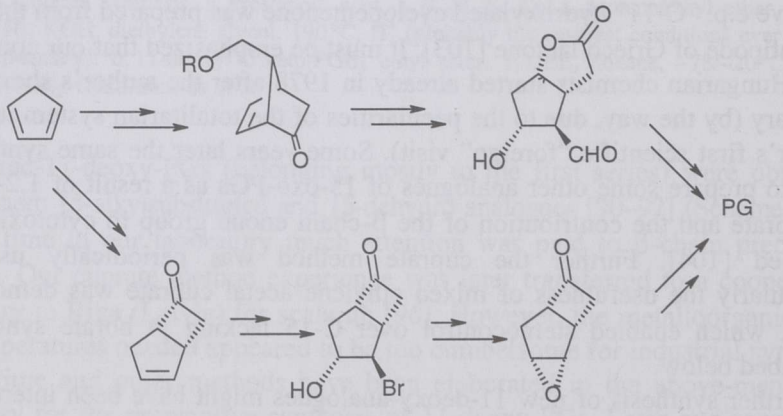
The cuprate method was used in cooperation with Hungarian chemists to get e.p. Me-esters of PGE_2 and 15-keto-PGE_2 [102] (Scheme 8c). These were the first e.p. PGs prepared in our laboratory by total synthesis. The corresponding decisive e.p. "C-11" hydroxylated cyclopentenone was prepared from the unused (+)-antipode of Grieco lactone [103]. It must be emphasized that our cooperation with Hungarian chemists started already in 1978 after the author's short visit to Hungary (by the way, due to the pecularities of the totalitarian system it was the author's first scientific "foreign" visit). Some years later the same synthon was used to prepare some other analogues of 15-oxo-PGs as a result of 1,2-addition of cuprate and the contribution of the β-chain enone group to cytotoxicity was clarified [104]. Further the cuprate method was periodically used, and particularly the usefulness of mixed ethylene acetal cuprate was demonstrated [105], which enabled stereocontrol over C-15 lacking in borate synthesis as described below.

Further synthesis of new 11-deoxy-analogues might have been interesting in some aspects. However, we estimated that the costs of comprehensive biological studies of new analogues and uncertainty in results would be too high. On the

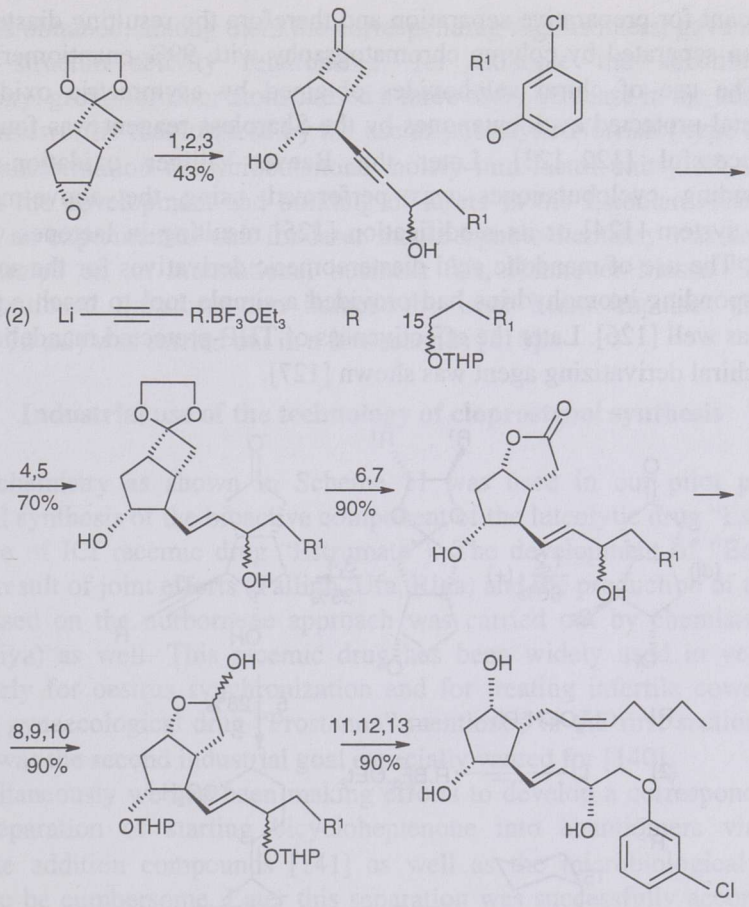
other hand, our biochemical production was unable to satisfy all the demand for the luteolytic agent for veterinary use and stabilized preparation of prostacyclin-like activity for medical research aimed at elaboration of a vasoactive drug.

[3.2.0]Bicycloheptenone approach: synthesis of $PGF_{2\alpha}$ and prostacyclin analogues

We looked for a scheme of total synthesis which could give both analogues of $PGF_{2\alpha}$ (particularly a very effective luteolytic agent cloprostenol) and in a simple way carba-analogues of prostacyclin with prolonged action. From this point of view the Salford scheme [106] based on the readily available [3.2.0]bicycloheptenone system seemed to be suitable [107 and references therein] and more open for further development than the norbornene (Corey's lactone) approach (Scheme 10). (Obviously this conclusion was wrong, see Corey's asymmetric synthesis in 1990 [108].) Furthermore, for the opening of epoxide obtained easily via corresponding bromohydrin, cuprates and other nucleophiles can be used to build up the β-chain. The cyclobutanone moiety is then subject to Baeyer–Villiger oxidation or ring expansion followed by α-chain build-up via the Wittig reaction as in the norbornene approach. The epoxide opening in the corresponding protected (tricyclic) substrates, obtained after the optimization of their routes of preparation starting from cyclopentadiene [109–113 and references in 113], with cuprates has demonstrated both relatively good regioselectivity of cuprates (4 to 1) and certain disadvantages of these reagents, partially low reactivity towards synthons with [3.3.0]bicyclooctenone skeleton. The simpler and recoverable lithium alkynide/BF_3 complex proposed in 1983 [114, 115] appeared to be far more suitable in the preparative work despite of the loss of regioselectivity in bicyclic systems under



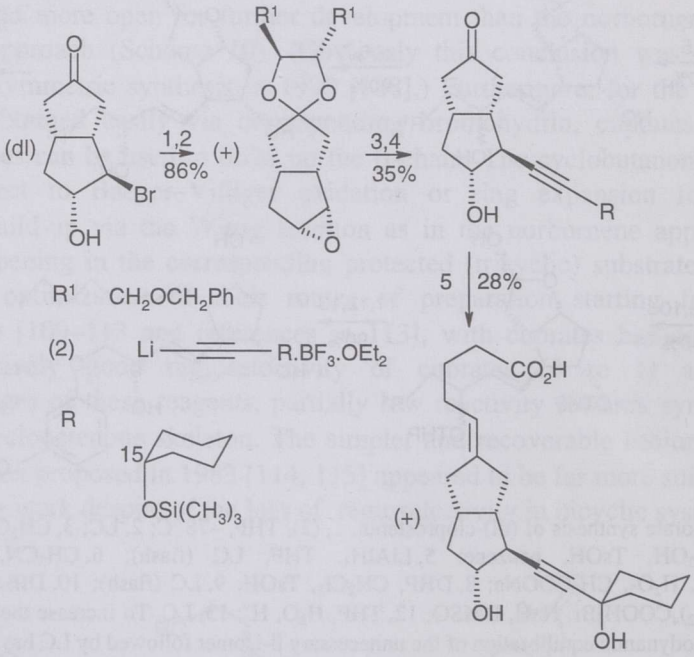
Scheme 10. Norbornene (upper) and bicycloheptenone (lower) approaches to the total synthesis of PGs.



Scheme 11. Borate synthesis of (dl)-cloprostenol. 1, (2), THF, –78 °C; 2, LC; 3, CH_3CN, H_2O, H^+; 4, $HOCH_2CH_2OH$, TsOH, benzene; 5, $LiAlH_4$, THF, LC (flash); 6, CH_3CN, H_2O, H^+; 7, CH_3COOH, H_2O_2, CH_3COONa; 8, DHP, CH_2Cl_2, TsOH; 9, LC (flash); 10, DIBAH, CH_2Cl_2; 11, $[Ph_3P(CH_2)_4COOH]Br$, NaH, DMSO; 12, THF, H_2O, H^+; 13, LC. To increase the yield of end product thermodynamic equilibration of the unnecessary β-isomer followed by LC has been used.

discussion [116]. As regards the oxirane ring opening in a molecule based on the [4.2.0]bicyclooctenone system it is highly regioselective (8:1) as was shown later [117]. Stoicheiometric amounts of lithium alkynide and BF_3 were necessary to suppress the possible side reactions caused by the catalytic properties of this reagent [118] and the best results of oxirane opening reaction were obtained at –70 °C in THF [119]. Further we studied the effects of various protecting groups of the ketone moiety in tricyclic substrates as bulky substituents and chiral auxiliaries. As a result, using acetalization with tartaric acid derivatives, the regioselectivity was increased to 2:1 [120] and the kinetic differentiation of the corresponding diastereomers was observed (3:2). However, this effect was too

insignificant for preparative separation and therefore the resulting diastereomers have been separated by column chromatography with 99% enantiomeric purity [121]. The use of chiral sulphoxides obtained by asymmetric oxidation of dithioacetal-protected cyclobutanones by the Sharpless reagent was found to be less successful [122, 123]. Later the Baeyer–Villiger oxidation of the corresponding cyclobutanones was performed using the above-mentioned catalytic system [124] or its modification [125] resulting in lactones with e.p. 30–75%. The use of mandelic acid diastereomeric derivatives for the separation of corresponding bromohydrins had provided a simple tool to reach e.p. cyclic synthon as well [126]. Later the effectiveness of THP-protected mandelic acid as a novel chiral derivatizing agent was shown [127].



Scheme 12. Borate synthesis of 15-nonstereogenic carbaprostacyclin. 1, (S,S)-(-)-1,4-bis(benzyloxy)-2,3-butanediol, TsOH/benzene, reflux, HPLC; 2, K_2CO_3, acetone, water, r.t.; 3, (2), THF, −78 °C; 4, H_2SO_4/MeCN, water, 60 °C, LC; 5, NaH/DMSO, (4-carboxybutyl)triphenylphosphonium bromide, HPLC.

Using the borate method of PG total synthesis elaborated in this way, a number of analogues of $PGF_{2\alpha}$ and prostacyclin were synthesized, among them (rac)-carbacyclin [128], (rac)-cloprostenol [129] (Scheme 11), and optically pure 15-nonstereogenic carbaprostacyclin [130] (Scheme 12), a novel analogue with separated platelate antiaggregatory and smooth muscle activity [131–136] and 15-fluorosubstituted carbacyclin [137]. The antiaggregatory activity studies of

analogues obtained, among them the corresponding regioisomers, gave new data on the structure–activity relationship, for example the substitution of 15-hydroxyl group for fluor atom caused a three order decrease in the activity.

It is noteworthy that inspired by the use of photolytic Norrish I type cleavage in the transformation of cyclobutanone moiety into lactol unit [138, 139] and based on the development and building of lasers in the Estonian Academy of Sciences an experimental unit for laser induced photochemistry was developed (demonstrated on an international business fair, Hannover Messe '96). The above-mentioned transformation induced by laser beam impulses (308 nm, intensity 70 mJ) was carried out in a few seconds [110].

Industrial use of the technology of cloprostenol synthesis

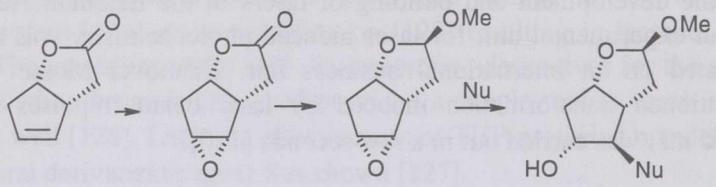
The chemistry as shown in Scheme 11 was used in our pilot plant for industrial synthesis of the bioactive component of the luteolytic drug "Estufalan" (analogue of ICI racemic drug "Estrumate"). The development of "Estufalan" was the result of joint efforts (Tallinn, Ufa, Riga) and the production of the same agent based on the norbornene approach was carried out by chemists in Ufa (Bashkiriya) as well. This racemic drug has been widely used in veterinary, particularly for oestrus synchronization and for treating infertile cows. Along with the gynaecological drug "Prostenon" mentioned in the first section of this paper it was the second industrial goal especially waited for [140].

Simultaneously we had been making efforts to develop a corresponding e.p. drug. Separation of starting bicycloheptenone into enantiomers via amine bisulphite addition compounds [141] as well as the microbiological method proved to be cumbersome. Later this separation was successfully accomplished through lipase-catalyzed enantioselective hydrolysis. The cyclic and β-chain synthons are produced in e.p. state and so is the final product. Cloprostenol can be produced in enantiomerically highly pure form to be used as a component of the veterinary drug "Esteksaan" registered recently in Estonia. Lipase-catalyzed hydrolysis appeared to be a powerful tool to achieve this goal [142–145].

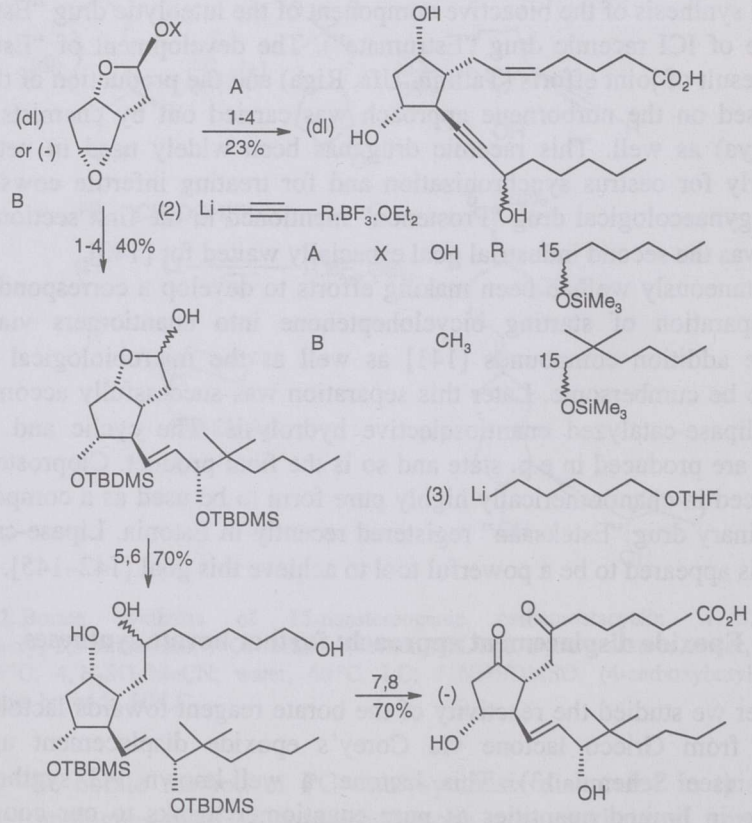
Epoxide displacement approach: further borate syntheses

Further we studied the reactivity of the borate reagent towards lactolepoxide obtained from Grieco lactone via Corey's epoxide displacement approach [6, p. 73] (see Scheme 13). This lactone, a well-known PG synthon, was accessible in limited quantities as pure enantiomer thanks to our cooperation with Hungarian chemists. These studies demonstrated high chemoselectivity of the borate reagent, which resulted in "one-pot" synthesis of 13,14-dehydro-$PGF_{2\alpha}$ [146] and in a novel short synthesis of (-)-16,16-dimethyl-6-oxo-PGE_1 [147] (Scheme 14, a and b respectively). The latter is a prolonged-action analogue of prostacyclin metabolite,6-keto-PGE_1, the most vaso-active

compound in the AA cascade. A number of $PGF_{2\alpha}$ analogues were prepared as well [148], the reactivity of oxyaminoacetic acid towards lactol moiety gave access to carboxymetoxyimino-analogues [149]. Our borate method of PG synthesis and most of the analogues prepared are reviewed in [150].



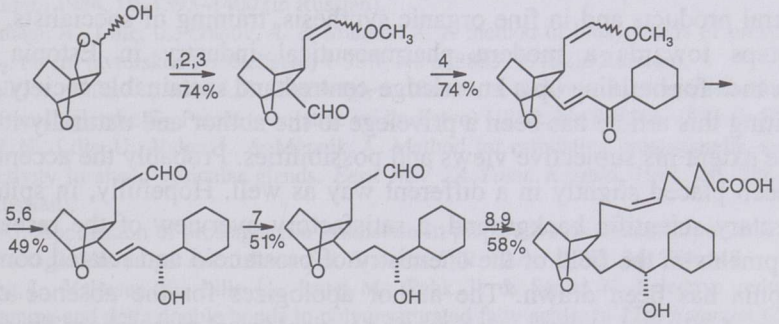
Scheme 13. Epoxide displacement approach.



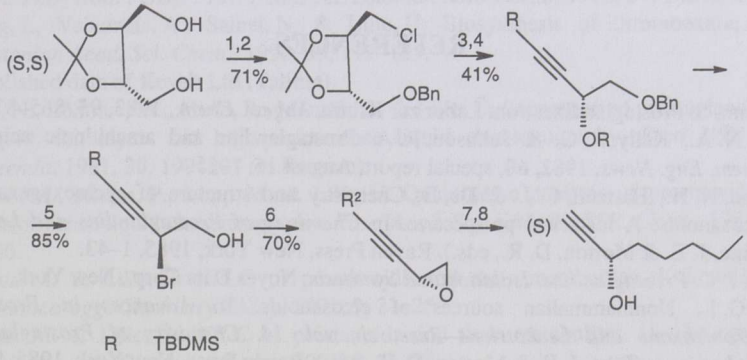
Scheme 14. Borate synthesis based on lactolepoxide. A, "One pot" synthesis of 13,14-dehydro-$PGF_{2\alpha}$. (dl)-epoxide. 1, (2) in THF, –78 °C; 2, $[Ph_3P(CH_2)_4CO_2H]Br$, *n*-BuLi, toluene; 3, H^+; 4, LC. B, Synthesis of 16,16-dimethyl-6-oxo-PGE_1, (-)-epoxide. 1, as in A, then LC; 2, $LiAlH_4$ in THF; 3, *tert.*-$BuMe_2SiCl$,DMF; 4, H^+; 5, (3) in ether/THF, –10 to 0 °C; 6, Et_2O/conc. HCl (0.02 M); 7, Jones reagent, Et_2O/acetone, 0 °C; 8, 40% HF, H_2O-CH_3CN, r.t.

2.5. Some other syntheses

The versatility of lactol moiety in the synthesis of PGs was demonstrated in the synthesis of analogues of potent vasoconstrictor and platelate aggregator TxA_2 [151, 152] (Scheme 15). In this case the lactol unit was used as a precursor of both side chains and the consecutive order of addition of side chains determined the absolute configuration of the target molecule [152]. In some cases alkynyllithium was used for alkynylation of other substrates having significance in leukotriene and pheromone synthesis [153–155]. Along with the use of tartaric acid derivatives as useful auxiliaries, inspired by Polish chemists [121] during the author's visit to Warszaw in 1978, they have been used as chiral starting material for the synthesis of enantiomerically pure PG β-chains [156, 157] and chiral building blocks of more general use [158, 159] (Scheme 16). See [160] as well.



Scheme 15. Synthesis of 7-oxabicyclo[2.2.1]heptane analogue of TxA_2. 1, $(CH_3OCH_2Ph_3)Cl$, *t*-BuOK, THF; 2, CrO_3, Py; 3, NaOMe, MeOH; 4, $(MeO)_2P(O)CH_2–CO–C_6H_{11}$, NaH, DME; 5, a. $NaBH_4$, $CeCl_3$, MeOH, b. LC; 6, 2N HCl, THF; 7, H_2, Pd/C; 8, $Br[PPh_3(CH_2)_4COOH]$; 9, NaOH, DMSO.



Scheme 16. Synthesis of (S)-oct-1-yn-3-ol from tartaric acid derivative. 1, NaH, BnCl, DMFA, –20 to 0 °C; 2, Ph_3P, CCl_4, 70 °C; 3, $LiNH_2$, liq. NH_3, –33 °C; 4, BuLi, THF, –78 °C followed by *tert*.$BuMe_2SiCl$, –20 °C to r.t.; 5, BBr_3, CH_2Cl_2, –70 °C; 6, K_2CO_3, acetone/H_2O; 7, Bu_2LiCu, Et_2O, –60 °C; 8, Bu_4NF, THF.

The synthetic methods used have not been selective enough in every step of synthesis. For this reason liquid chromatography was widely used throughout the research and preparative synthesis (accompanied by corresponding structural studies [161]), partially for the separation of regioisomers of oxirane ring opening, *E*/*Z* isomers of carbacyclins, and α/β isomers of cloprostenol [162–166].

FINAL REMARKS

Relatively good preconditions and creative work compensated for the late start of the project and restricted possibilities of scientific contacts. Thus, the project resulted in a certain contribution to scientific knowledge in this field. Not less important has been the spread of possibilities to use these promising expensive local hormones over a large area. Finally, innovation in the chemistry of natural products and in fine organic synthesis, training of specialists, and the first steps towards a modern pharmaceutical industry in Estonia are of significance for building up a knowledge-centred and sustainable society.

Writing this article has been a privelege to the author and naturally it reflects to some extent his subjective views and possibilities. Probably the accents might have been placed slightly in a different way as well. Hopefully, in spite of the fragmentary scientific background, a satisfactory overview of the research and developments in the field of the chemistry of prostanoid and related compounds in Estonia has been drawn. The author apologizes for the absence of many citations of relevant pharmacological and toxicological researches. These would have been outside the limits of this article. Finally, my thanks are due to all coworkers and partners from other laboratories and countries. The names of our distinguished partners have been shown in the references to our joint articles.

REFERENCES

1. Bergström, S. Prostaglandine: vom Labor zur Klinik. *Angew. Chem.*, 1983, **95**, 865–873.
2. Nelson, N. A., Kelly, R. C. & Johnson, R. A. Prostaglandins and arachidonic acid cascade. *Chem. Eng. News*, 1982, **60**, special report, August 16, 1–15.
3. Andersen, N. H., Hartzell, C. J. & De, B. Chemistry and structure of cyclooxygenase-derived eicosanoids: A historical perspective. In *Chemistry of Prostaglandins and Leukotrienes* (Pike, J. E. & Morton, D. R., eds.). Raven Press, New York, 1985, 1–43.
4. Colbert, J. C. *Prostaglandins. Isolation and Synthesis*. Noyes Data Corp., New York, 1973.
5. Bundy, G. L. Nonmammalian sources of eicosanoids. In *Advances in Prostaglandin, Thromboxane and Leukotriene Research, vol. 14. Chemistry of Prostaglandins and Leukotrienes* (Pike, J. E. & Morton, D. R., eds.). Raven Press, New York, 1985, 229–262.
6. Bindra, J. S. & Bindra, R. *Prostaglandin Synthesis*. Academic Press, New York, 1977.
7. Szantay, C. & Novak, L. *Synthesis of Prostaglandins*. Akademiai Kiado, Publishing House of the Hungarian Acad. Sci., Budapest, 1978.
8. Bergelson, L. D. Project "Prostaglandins". *Khim. i Zhizn'*, 1977, **2**, 18–23 (in Russian).

9. Corey, E. J., Washburn, W. N. & Chen, J. C. Studies on the prostaglandin A_2 synthetase complex from *Plexaura homomalla*. *J. Am. Chem. Soc.*, 1973, **95**, 6, 2054.
10. Jagomägi, A., Ivanov, A. & Lille, Ü. Elaboration of biosynthetic technology of 11-(S),15-(15S)-dihydroxy-9-oxo-5-*cis*-13-*trans*-prostadienoic acid (PG E_2). In *V Biokhimicheskaya konferentsiya Pribaltijskikh respublik i Belorusskoj SSR*. Vol. 1. Tallinn, 1976, 97 (in Russian).
11. Wallach, D. P. & Daniels, E. G. Properties of a novel preparation of prostaglandin synthetase from sheep seminal vesicles. *Biochem. Biophys. Acta*, 1971, **231**, 445–457.
12. Jagomägi, A., Lille, Ü. & Saks, T. Preparative separation of methylarachidonate by liquid column chromatography. *Eesti NSV TA Toim. Keemia*, 1979, **28**, 151–154 (in Russian).
13. Lille, Ü., Smorodin, Y. & Marvet, R. On kinetic properties of prostaglandin-endoperoxide synthetase. *Eesti NSV TA Toim. Keemia*, 1979, **28**, 108–112 (in Russian).
14. Lille, Ü., Männik, A., Jagomägi, A., Samel, N. & Saks, T. On preparative scale biosynthesis of prostaglandins E and F groups using acetone-pentane powder synthetase. *Eesti NSV TA Toim. Keemia*, 1979, **28**, 145–150 (in Russian).
15. Dukat, L. P., Vrzheshch, P. V., Shevchenko, V. P., Lys, Y. I., Myagkova, G. I., Yakushewa, L. A., Mevkh, A. T., Varfolomeev, S. D., Fedoseev, V. M. & Myasoedov, N. F. Enzymatic synthesis of tritium-labeled prostaglandins from (^{3}H)eicosatrienoic acid. *Bioorg. Khim.*, 1984, **10**, 1395–1400 (in Russian).
16. Jagomägi, A., Lille, Ü., Ivanov, A. & Männik, A. A method of biosynthesis of prostaglandin E_2. Patent (avtorskoe svidetel'stvo) USSR, No 658883, 1978 (in Russian).
17. Männik, A., Lille, Ü., Ivanov, A., Jagomägi, A., Samel, N. & Kraav, L. A method of synthesis of prostaglandin E_2. Patent (avtorskoe svidetel'stvo) USSR, No 835106, 1981 (in Russian).
18. Samel, N., Lille, Ü., Valge, L. & Männik, A. Method for estimating prostaglandin–synthetase activity in sheep vesicular glands. *Eesti NSV TA Toim. Keemia*, 1981, **30**, 288–291 (in Russian).
19. Lille, Ü. Application of prostaglandin synthetase in preparative oxidation of polyenic acids to prostaglandin drugs. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1985, **34**, 134–142.
20. Järving, I., Valmsen, K., Lille, Ü., Lopp, M., Pehk, T. & Samel, N. Selective reduction of gamma and delta double bonds in polyunsaturated fatty acids. In *17th Estonian Chemistry Days. Abstracts of Scientific Conference*. Tartu, 1996, 62.
21. Basevich, V. V., Mevkh, A. T., Järving, I. & Varfolomeev, S. D. Kinetics of the prostaglandin H_2 degradation. A method for determination of the activity of prostaglandin H-convertases. *Bioorg. Khim.*, 1983, **9**, 658–665 (in Russian).
22. Järving, I., Varvas, K., Vahemets, A., Samel, N. & Lille, Ü. A short way to 11-dehydro-TxB_2 and TxB_2 from PGD_2. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1988, **37**, 148–149.
23. Järving, I., Vahemets, A., Samel, N. & Lille, Ü. Biosynthesis of thromboxane B_2. *Proc. Estonian Acad. Sci. Chem.*, 1990, **39**, 119–125.
24. Unpublished data of Kevelt Ltd (Tallinn).
25. Samel, N., Lõhmus, M., Aliste, R., Männik, A. & Lille, Ü. Separation of prostaglandins by gas-liquid, thin-layer- and high-performance liquid chromatography. *Eesti NSV TA Toim. Keemia*, 1981, **30**, 199–207 (in Russian).
26. Lõhmus, M., Niidas, P., Lopp, M. & Lille, Ü. Quantitative analysis of prostacyclin by high performance liquid chromatography. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1984, **33**, 181–186.
27. Lõhmus, M. & Lille, Ü. HPLC of prostanoids and their metabolites. I. Stability aspects. *Chimica-oggi/Chemistry Today*, 1991, **9**, 21–25.
28. Lõhmus, M. & Lille, Ü. HPLC of prostanoids and their metabolites. II. Detection aspects. *Chimica-oggi/Chemistry Today*, 1991, **9**, 21–25.
29. Pehk, T., Välimäe, T., Samel, N., Lopp, M., Lille, Ü. & Lippmaa, E. ^{13}C NMR spectroscopy of prostaglandins. *Eesti NSV TA Toim. Keemia*, 1982, **31**, 85–90 (in Russian).
30. Veisserik, J., Sõmer, T., Lõhmus, M. & Lille, Ü. Automated preparative chromatography of prostanoids. *Chromatographia*, 1987, **24**, 593–596.

31. Lõhmus, M., Vahemets, A., Järving, I., Samel, N., Lille, Ü. & Pehk, T. Preparative separation of natural prostaglandins E. *Prep. Chromatogr.*, 1991, **1**, 279–300.
32. Kheirolomoom, A., Katoh, S. & Sada, E. Reaction mechanism of prostaglandin E_2 biosynthesis and its modeling. *J. Ferment. Bioeng.*, 1991, **71**, 12–18.
33. Mayer, M. & Lille, Ü. Biological testing of prostaglandins synthesized at the Institute of Chemistry, Academy of Sciences of the Estonian SSR. *Proc. Acad. Sci. Estonian SSR. Biol.*, 1984, **33**, 99–107 (in Russian).
34. Lille, Ü. (ed.). *Prostenon: Synthesis, Properties, Application.* Valgus, Tallinn, 1989 (in Russian).
35. Ermolov, B. N., Ponomareva, T. E., Lille, Ü. E., Männik, A. O. & Samel, N. E. Prostaglandin $F_{2\alpha}$ and reproduction of horned cattle. *Veterinariya*, 1985, 57–60 (in Russian).
36. Serkov, I., Bezuglov, V., Pachev, L., Malygin, V., Gafurov, P., Lille, Ü., Samel, N. & Bergelson, L. 1,3-Dinitroglycerol ester of prostaglandin $F_{2\alpha}$ with myotrophic smooth muscle activity. Patent (avtorskoe svidetel'stvo) USSR, № 1640963, 1990 (in Russian).
37. Sorokina, A. D., Tongur, A. M., Deborin, G. A., Lille, Ü. E. & Samel, N. E. Features of prostaglandin E_1 interaction with biological membrane components. *Biofizika*, 1986, **XXXI**, 616–620.
38. Samel, N., Järving, I., Lõhmus, M., Lopp, A., Kobzar, G., Sadovskaya, V., Välimäe, T. & Lille, Ü. 5,6-Dihydro-PGE_3 – a new natural prostaglandin. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1986, **35**, 75.
39. Samel, N., Järving, I., Lõhmus, M., Lopp, M., Kobzar, G., Sadovskaya, V., Välimäe, T. & Lille, Ü. Identification and biological activity of a novel natural prostaglandin 5,6-dihydro-prostaglandin E. *Prostaglandins*, 1987, **33**, 137–146.
40. Järving, I., Lõhmus, M., Valmsen, K., Pehk, T., Liiv, M., Lille, Ü. & Samel, N. A new series of natural prostaglandins. Identification of 1a,1b-dihomo- 2,3-didehydro-PGE_2 in ram seminal vesicles. *Nat. Prod. Lett.*, 1993, **2**, 111–114.
41. Kristjuhan, S. Formation of E-prostaglandins. Master's thesis, Tallinn Technical University, Tallinn, 1994 (in Estonian).
42. O'Connor, D. E., Mihelich, E. D. & Coleman, M. C. Stereochemical course of autoxidative cyclization of lipid hydroperoxides to prostaglandin-like bicyclo endoperoxides. *J. Am. Chem. Soc.*, 1984, **106**, 3577–3584.
43. Morrow, J. D., Harris, T. M. & Roberts, M. J. Noncyclooxygenase oxidative formation of a series of novel prostaglandins: Analytical ramifications for measurement of eicosanoids. *Anal. Biochem.*, 1990, **184**, 1–10.
44. Kobzar, G., Mardla, V., Järving, I., Lõhmus, M., Vahemets, A., Samel, N. & Lille, Ü. Comparison of the inhibitory effect of E-prostaglandins in human and rabbit platelet-rich plasma and washed platelets. *Comp. Biochem. Physiol.*, 1993, **106C**, 489–494.
45. Kobzar, G., Mardla, V., Järving, I., Samel, N. & Lõhmus, M. Effects of 8-iso-PGE_2 on platelates and smooth muscles. *Pharmacol. Toxicol.*, 1995, **76**, Suppl. III.
46. Van der Ouderaa, I., Buytenhek, M., Nugteren, T. H. & van Dorp, D. H. Purification and characterization of prostaglandin endoperoxide synthetase from sheep vesicular glands. *Biochim. Biophys. Acta*, 1977, **487**, 315–331.
47. Mevkh, A. T., Sudina, G. F., Golub, N. B. & Varfolomeev, S. D. Purification of prostaglandin H synthetase and a fluorimetric assay for its activity. *Anal. Biochem.*, 1985, **150**, 91–96.
48. Smith, W. L. & Marnett, L. J. Prostaglandin endoperoxide synthetase: Structure and catalysis. *Biochim. Biophys. Acta*, 1991, **1083**, 1–17.
49. Merlie, J. P., Fagan, D., Mudd, J. & Needleman, P. Isolation and characterization of the complementary DNA for sheep seminal vesicle prostaglandin endoperoxide synthase (cyclooxygenase). *J. Biol. Chem.*, 1988, **263**, 3550–3553.
50. Shimokawa, T. & Smith, W. L. Essential histidines of prostaglandin endoperoxide synthetase. His-309 is involved in heme binding. *J. Biol. Chem.*, 1991, **266**, 6168–6173.
51. Picot, D., Loll, P. J. & Garavito, R. M. The X-ray crystal structure of the membrane protein prostaglandin H_2 synthase-1. *Nature*, 1994, **367**, 243–249.

52. Lille, Ü., Samel, N. & Käämbre, P. Unpublished data of department.
53. Egan, R. W., Paxton, J. & Kuehl, F. Mechanism for irreversible self-deactivation of prostaglandin synthetase. *Biol. Chem.*, 1976, **251**, 7329–7335.
54. Ivanov, A., Lille, Ü. & Styopin, S. On the possibilities of stabilization of prostaglandin synthetase by entrapment in solid gels. *Eesti NSV TA Toim. Keemia*, 1980, **29**, 118–122 (in Russian).
55. Varfolomeev, S. D. Inactivation of an enzyme in the course of the reaction. Kinetic description and discrimination of mechanisms. *Biokhimiya*, 1982, **47**, 343–354 (in Russian).
56. Mevkh, A. T., Basevich, V. V., Järving, I. & Varfolomeev, S. D. Inactivation of prostaglandin endoperoxide synthetase from the microsomal fraction of human platelets during the reaction. *Biokhimiya*, 1982, **47**, 11, 1852–1858 (in Russian).
57. Ahern, T. J., Katoh, S. & Sada, E. Prostaglandin synthesis from arachidonic acid by immobilized ram seminal microsomes. *Biotechnol. Bioeng.*, 1983, **25**, 881–885.
58. Mevkh, A. T., Sudina, G. F., Lagutina, I. O. & Levashov, A. V. Catalytic properties of a prostaglandin H synthetase membrane enzyme in a system of aerosol OT reversed micelles in octane. *Biokhimiya*, 1985, **50**, 1719–1723 (in Russian).
59. Walsh, C. Suicide substrates: Mechanism-based enzyme inactivators. *Tetrahedron*, 1982, **38**, 871–909.
60. Bakovich, M. & Dunford, H. B. Reactions of prostaglandin endoperoxide synthase and its compound I with hydroperoxides. *J. Biol. Chem.*, 1996, **271**, 2048–2056.
61. Corey, E. J. & Wang, Z. Conversion of arachidonic acid to the prostaglandin endoperoxide PGG_2, a chemical analog of the biosynthetic pathway. *Tetrahedron Lett.*, 1994, **35**, 539–542.
62. Hamberg, M. & Samuelsson, B. On the mechanism of biosynthesis of prostaglandins E_1 and $F_{2\alpha}$. *J. Biol. Chem.*, 1967, **242**, 5336–5343.
63. Porter, N. A. & Funk, M. O. Peroxy radical cyclization as a model for prostaglandin biosynthesis. *J. Org. Chem.*, 1975, **40**, 3614–3615.
64. Porter, N. A. et al. The formation of cyclic peroxides from unsaturated hydroperoxides: Models for PG biosynthesis. *J. Am. Chem. Soc.*, 1976, **98**, 6000.
65. Niidas, P. Unpublished results of department.
66. Corey, E. J., Shih, C., Shih, N.-Y. & Shimoji, K. Preferential formation of 8-epi prostaglandin $F_{2\alpha}$ via the corresponding endoperoxide by a biomimetic cyclization. *Tetrahedron Lett.*, 1984, **25**, 5013–5016.
67. Corey, E. J. & Matsuda, S. P. T. Generality of marine prostanoid biosynthesis by the 2-oxidopentadienyl cation pathway. *Tetrahedron Lett.*, 1987, **28**, 4247–4250.
68. Brash, A. E., Baertschi, S. W., Ingram, C. D. & Harris, T. M. On non-cyclooxygenase prostaglandin synthesis in the sea whip coral, *Plexaura homomalla*: An 8(R)-lipoxygenase pathway leads to formation of an α-ketol and a racemic prostanoid. *J. Biol. Chem.*, 1987, **262**, 15829–15835.
69. Latyshev, N. A., Malyutin, A. N., Kogtev, L. S. & Bezuglov, V. V. Fatty acids from the soft corals *Gersemia rubiformis*. *Khim. prir. soedin.*, 1988, 447–448 (in Russian).
70. Letunov, V. N. Proposals of Kartesh White Sea Biological Station in the Gulf of Kandalaksha. 1988, personal communication.
71. Samel, N., Varvas, K., Vahemets, A., Koljak, R., Järving, I., Pehk, T., Müürisepp, A. M. & Lille, Ü. Biosynthesis of eicosanoids in the White Sea soft coral *Gersemia fruticosa*. In *2nd International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Radiation Injury. Berlin, September 17–21, 1991, Abstract Book*, 92.
72. Varvas, K., Järving, I., Koljak, R., Vahemets, A., Pehk, T., Müürisepp, A. M., Lille, Ü. & Samel, N. In vitro biosynthesis of prostaglandins in the White Sea soft coral *Gersemia fruticosa*: Formation of optically active PGD_2, PGE_2, $PGF_{2\alpha}$ and 15-keto-$PGF_{2\alpha}$ from arachidonic acid. *Tetrahedron Lett.*, 1993, **34**, 3643–3646.
73. Varvas, K., Koljak, R., Järving, I., Pehk, T. & Samel, N. Endoperoxide pathway in prostaglandin biosynthesis in the soft coral *Gersemia fruticosa*. *Tetrahedron Lett.*, 1994, **35**, 8267–8270.

74. Varvas, K., Järving, I., Valmsen, K., Koljak, R. & Samel, N. Effect of selective inhibitors on arachidonic acid metabolism in the soft coral *Gersemia fruticosa*. *Prostaglandins, Leukotrienes Essent. Fatty Acids*, 1996, **55/1**, 55.
75. Varvas, K., Järving, I., Koljak, R., Valmsen, K. & Samel, N. Oxidative metabolism of arachidonic acid in coral: Definition of different cyclooxygenase and lipoxygenase pathways. In *24th Estonian Chemistry Days. Abstracts of Scientific Conference*. Estonian Chemical Society, Tartu, 1998, 79.
76. Brash, A. E., Baertschi, S. W. & Harris, T. M. Formation of prostaglandin A analogues via allene oxide. *J. Biol. Chem.*, 1990, **265**, 6705–6710.
77. Parve, O. Unpublished results of department.
78. Brash, A. R., Baertschi, S. W., Ingram, C. D. & Harris, T. M. Allene oxides as intermediates in biosynthesis of ketols and cyclopentenones. In *Advances in Prostaglandin, Thromboxane and Leukotriene Research, vol. 19* (Samuelsson, B., Wong, P. Y. K. & Sun, F. F., eds.). Raven Press, New York, 1989, 70–73.
79. Koljak, R., Boutaud, O., Shieh, B. H., Samel, N. & Brash, A. R. Identification of a naturally occurring peroxidase-lipoxygenase fusion protein. *Science*, 1997, **277**, 1994–1996.
80. Koljak, R., Varvas, K., Järving, I. & Samel, N. Isolation and characterization of the cDNA for prostaglandin endoperoxide synthase from the White Sea soft coral *Gersemia fruticosa*. In *24th Estonian Chemistry Days. Abstracts of Scientific Conference*. Estonian Chemical Society, Tartu, 1998, 29.
81. Roessner, C. A. & Scott, A. I. Genetically engineered synthesis of natural products: From alkaloids to corrins. *Annu. Rev. Microbiol.*, 1996, **50**, 467–489.
82. Koljak, R., Pehk, T., Järving, I., Liiv, M., Lopp, A., Varvas, K., Vahemets, A., Lille, Ü. & Samel, N. New antiproliferative 9,11-secosterol from soft coral *Gersemia fruticosa*. *Tetrahedron Lett.*, 1993, **34**, 1985–1986.
83. Koljak, R., Lopp, A., Pehk, T., Varvas, K., Müürisepp, M., Järving, I. & Samel, N. New cytotoxic sterols from the soft coral *Gersemia fruticosa*. *Tetrahedron*, 1997, **54**, 179–186.
84. Jäälaid, R., Järving, I., Pehk, T. & Lille, Ü. An advanced intermediate for the synthesis of 9,11-secosterols. *Proc. Estonian Acad. Sci. Chem.*, 1998, **47**, 39–43.
85. Jäälaid, R., Järving, I., Pehk, T. & Lille, Ü. First partial synthesis of 9,11-secosterols with the modified side chain. *Proc. Estonian Acad. Sci. Chem.*, 1998, **47**, 196–199.
86. Kuhl, A. & Kreiser, W. Progress in partial synthesis of a marine secosterol from *Gersemia fruticosa*: Preparation of the intermediate precursor 3b, 6a-diacetoxy-24-methyl-12-oxo-5a-chol-9,11-ene-24-oate(14). *Tetrahedron Lett.*, 1998, **39**, 1145–1148.
87. Kuhl, A. & Kreiser, W. Progress in partial synthesis of a marine secosterol from *Gersemia fruticosa*: Preparation of steroidal core unit. *Coll. Czech. Chem. Comm.*, 1999 (in press).
88. Lille, Ü., Bitter, L., Murd, A. & Vysotskaya, V. Condensation of lithium alkyles with 3,5-dimethoxybenzylchloride. *Eesti NSV TA Toim. Keemia. Geol.*, 1971, **20**, 328–335 (in Russian).
89. Lille, Ü., Bitter, L. & Peinar, U. Über die Synthese der 2-Alkylresorzine und ihre IR-Spektren. *Eesti NSV TA Toim. Keemia. Geol.*, 1969, **18**, 365–369 (in Russian).
90. Lopp, M. & Lille, Ü. Stereoselective synthesis of rac-9-oxoprostanoic acid and rac-prostanoic acid. In *V Biokhimicheskaya konferentsiya Pribaltijskikh respublik i Belorusskoj SSR*. Vol. 1. Tallinn, 1976, 98 (in Russian).
91. Lopp, M. & Lille, Ü. On synthesis of 11-deoxy PGE_1, its 15-methyl derivative and prostanoic acid by organocuprates. *Eesti NSV TA Toim. Keemia*, 1979, **28**, 155–160 (in Russian).
92. Lopp, M., Lainemäe, U., Lõhmus, M. & Lille, Ü. Synthesis of 11-deoxyprostaglandins E_1 and F_1 from 11-deoxy-15-dehydroprostaglandin E_1 and analysis of the products by high performance liquid chromatography. *Eesti NSV TA Toim. Keemia*, 1981, **30**, 23–28 (in Russian).
93. Lopp, M., Pals, A. & Lille, Ü. Alkylation of β-iodovinyl ketones by organocuprates derived from ethyllithium and ethylmagnesium bromide. *Eesti NSV TA Toim. Keemia*, 1980, **29**, 191–195 (in Russian).

94. Lopp, M., Parve, O. & Lille, Ü. Alkylation of β-iodovinyl ketones by Grignard reagents. Aspects of mechanism. *Eesti NSV TA Toim. Keemia*, 1980, **29**, 185–190 (in Russian).
95. Lopp, M., Parve, O., Lille, Ü. & Andreson, N. A method of preparation of 1-iodo-3-hydroxy-*trans*-octen-1. Patent (avtorskoe svidetel'stvo) USSR, No 1102200, 1984 (in Russian).
96. Freimanis, I., Lille, Ü., Lopp, M., Sokolov, G., Koric, V. & Loza, E. A method of preparation of α,β-isomers of (rac)-11-deoxy-PGE_1 ethyl ester. Patent (avtorskoe svidetel'stvo) USSR, No 809832, 1980 (in Russian).
97. Danilova, N., Miftahov, M., Lopp, M., Lille, Ü. & Tolstikov, G. Alternative synthesis of 16-aryloxy-17,18,19,20-tetranor-11-desoxy-prostaglandin E_1. *Dokl. Akad. Nauk SSSR*, 1984, **273**, 620–622 (in Russian).
98. Martin, I., Anvelt, J., Välimäe, T., Pehk, T. & Lille, Ü. Copper(II)bromide utilization in the synthesis of 15-keto-PGB_1 and its 16,16-dimethyl analog. *Synth. Commun.*, 1990, **20**, 2597–2605.
99. Martin, I., Anvelt, J., Pehk, T. & Lille, Ü. The synthesis of 16-dimethyl-15-ketoprostaglandin B_1 oligomers. The chemical structure of dimers. *Tetrahedron*, 1991, **47**, 3999–4006.
100. Kreutter, D. K. & Devlin, T. M. Inhibition of oxydative phosphorylation by an oligomer of prostaglandin B_1, PGB_x. *Arc. Biochem. Biophys.*, 1983, **221**, 216–226.
101. Martin, I., Männik, E., Lille, Ü., Lakomkin, V., Steinschneider, A., Kuznetsov, A., Lyapina, S. & Saks, V. The effect of the trimer of 16,16-dimethyl-15-keto-PGB_1 on metabolic and functional post-ischemic recovery of the heart. *Proc. Estonian Acad. Sci. Biol.*, 1996, **45**, 93–101.
102. Paju, A., Välimäe, T., Gulácsi, E., Gruber, L., Lopp, M. & Lille, Ü. Synthesis of (-)PGE_2 methyl ester and (-)15-keto PGE_2 methyl ester. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1986, **35**, 138–141.
103. Gruber, L., Tomösközi, I., Gulácsi, E., Lopp, M. & Lille, Ü. A synthetic way to R(+)methyl-7-(3-hydroxy-5-oxo-1-cyclopentenyl)-5(Z)-heptenoate PGE_2 synthon. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1986, **35**, 134–137.
104. Lopp, M., Lopp, A., Paju, A., Lille, Ü. & Pehk, T. Synthesis and antiproliferative activity of 15-oxoprostaglandins: Contribution of the β-chain enone group to cytotoxicity. *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1739–1744.
105. Parve, O., Pals, A., Lahe, L., Lopp, M. & Lille, Ü. Synthesis of prostaglandins F and I series. 3. Synthesis of 3-endo-hydroxy-2-exo-[(*E*)-3-oxooct-1-enyl]-6-oxabicyclo[3.3.0]octan-7-one over ethylene ketal of 2,3-endo-epoxybicyclo[3.2.0]heptan-6-one. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1988, **37**, 264–268 (in Russian).
106. Newton, R. F. & Roberts, S. M. Steric control in prostaglandin synthesis involving bicyclic and tricyclic intermediates. *Tetrahedron*, 1980, **36**, 2163–2196.
107. Lille, Ü. Prostaglandins today: Synthesis and application. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1987, **36**, 157–164 (in Russian).
108. Corey, E. J. New enantioselective routes to biologically interesting compounds. *Pure Appl. Chem.*, 1990, **62**, 1209.
109. Parve, O., Pals, A., Välimäe, T., Lopp, M. & Lille, Ü. The synthesis of some bicyclic synthons and transformation of them into analogs of prostaglandins. In *Tezisy dokl. I vsesoyuznogo soveshchaniya "Sintez i issledovanie prostaglandinov"*. Institut organicheskogo sinteza AN Latvijskoj SSR, Riga, 1982, 61 (in Russian).
110. Parve, O., Pals, A., Lõhmus, M., Välimäe, T., Lopp, M. & Lille, Ü. Synthesis of prostaglandins of F and I series. 1. Synthesis of (±)prostaglandin $F_{2\alpha}$ and (±)9-deoxy-Δ^5-6,9α-cycloprostaglandin F_1. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1985, **34**, 276–284 (in Russian).
111. Parve, O., Pals, A., Lõhmus, M., Välimäe, T., Lahe, L., Lopp, M. & Lille, Ü. Synthesis of prostaglandins of F and I series. 2. Synthesis of (±)13,14-didehydro-6,9α-methano-prostaglandin I_2 over ethylene ketal of 2,3-endo-epoxybicyclo[3.3.0]octan-7-one. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1985, **34**, 285–291 (in Russian).

112. Lopp, M., Mäeorg, U., Lille, Ü., Paju, A., Parve, O. & Andreson, N. A method of preparation of bicyclo(3.2.0)hept-2-en-6-one. Patent (avtorskoe svidetel'stvo) USSR, No 1300870, 1986 (in Russian).
113. Lopp, M. Some possibilities of prostanoid synthesis from bicyclic epoxide synthons using cuprate and lithium alkynide. BF_3 reagents. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1987, **36**, 165–171.
114. Yamaguchi, M. & Hirao, I. An efficient method for the alkynylation of oxiranes using alkynyl boranes. *Tetrahedron Lett.*, 1983, **24**, 391–394.
115. Brown, H. C., Racherla, U. S. & Singh, S. M. Improved highly efficient synthesis of α,β-acetylenic ketones. Nature of the intermediate from the reaction of lithium acetylide with boron trifluoride etherate. *Tetrahedron Lett.*, 1984, **25**, 2411–2414.
116. Lopp, M., Parve, O., Lõhmus, M., Müraus, A., Pals, A., Välimäe, T. & Lille, Ü. Synthesis of prostanoids via alkynyl borate oxirane opening. In *Abstracts of Papers. Fourth European Symposium on Organic Chemistry*. Aix-en-Provence (France), 1985, OC-29.
117. Kluge, A. F., Kertesz, D. J., O-Yang, C. & Wu, H. Y. Potent prostacyclin analogues based on the bicyclo(4.4.0)octane ring system. *J. Org. Chem.*, 1987, **52**, 2860–2868.
118. Kanger, T., Lopp, M. & Lille, Ü. Reactions of the oxiranes. I. The role of boron trifluoride in alkynylation of bicyclic oxiranes. *Zh. Org. Khim.*, 1988, **24**, 2543–2546 (in Russian).
119. Kanger, T., Lopp, M. & Lille, Ü. Thermal stability of the lithium alkynide/BF_3 reagent and its reaction with oxirane in different solvents. *Proc. Estoninan Acad. Sci. Chem.*, 1989, **38**, 287–288.
120. Kanger, T., Lopp, M. & Lille, Ü. Reactions of oxiranes. II. Effect of protecting groups on the regioselectivity of the opening of oxirane in 2,3-epoxybicyclo[3.2.0]heptan-6-ones by lithium alkynyde in the presence of boron trifluoride. *J. Org. Chem. USSR*, 1991, **27**, 1487–1493.
121. Kanger, T., Kabat, M., Wicha, J., Lopp, M. & Lille, Ü. The optically active intermediates for synthesis of prostanoids. I. Separation of enantiomeric 2-*exo*-bromo-3-endo-hydroxybicyclo[3.2.0]heptan-6-ones. *Zh. Org. Khim.*, 1990, **26**, 1711–1714 (in Russian).
122. Jäälaid, R., Pehk, T., Kanger, T., Lopp, M. & Lille, Ü. Chiral sulfoxides from dithioketales of bicyclo[3.2.0]hept-2-en-6-one and its epoxide. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1989, **38**, 133–134.
123. Jäälaid, R., Lopp, M., Pehk, T. & Lille, Ü. The optically active intermediates for synthesis of prostanoids. II. Separation of enantiomeric bicyclo[3.2.0]hept-2-en-6-ones via chiral sulfoxides. *Zh. Org. Khim.*, 1990, **26**, 2355–2360.
124. Lopp, M., Paju, A., Kanger, T. & Pehk, T. Asymmetric Baeyer–Villiger oxidation of cyclobutanones. *Tetrahedron Lett.*, 1996, **37**, 7583–7586.
125. Kanger, T., Kriis, K., Paju, A., Pehk, T. & Lopp, M. Asymmetric oxidation of cyclobutanones: Modification of the Sharpless catalyst. *Tetrahedron: Asymmetry*, 1998, **9**, 4475–4482.
126. Parve, O., Pals, A., Lahe, L., Välimäe, T., Lopp, M. & Lille, Ü. Synthesis of prostaglandins of the F and I series. 5. Mandelic acid diastereomeric derivatives of 2-exo-bromo-3-endo-hydroxybicyclo[3.2.0]heptan-6-one. A new simple way to optically active prostanoid synthons. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1989, **38**, 139–140.
127. Parve, O., Aidnik, M., Lille, Ü., Martin, I., Vallikivi, I., Vares, L. & Pehk, T. Preparation and use of (2R)-phenyl-2-(2S)-tetrahydro-2(2H)-pyranyloxy-acetic acid, a versatile chiral derivatizing agent. *Tetrahedron: Asymmetry*, 1998, **9**, 885–896.
128. Parve, O., Pals, A., Lõhmus, M., Välimäe, T., Lahe, L., Lopp, M. & Lille, Ü. Synthesis of prostaglandins of F and I series. 4. Synthesis of 6,9α-methanoprostaglandin I_2. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1989, **38**, 112–118 (in Russian).
129. Lõhmus, M., Paju, A., Lopp, M., Lille, Ü. & Andreson, N. A method of preparation of phenoxy-substituted prostaglandin $F_{2\alpha}$ analog. Patent (avtorskoe svidetel'stvo) USSR, No 1415695, 1988 (in Russian).

130. Kanger, T., Lopp, M., Müraus, A., Lõhmus, M., Kobzar, G., Pehk, T. & Lille, Ü. Synthesis of a novel optically active 15-nonstereogenic carbaprostacyclin. *Synthesis*, **1992**, 925–927.
131. Lopp, M., Kobzar, G., Bergmann, M., Pehk, T., Lopp, A., Välimäe, T., Viigimaa, M. & Lille, Ü. Synthesis and antiaggregative activity of novel w-achiral carbaanalogues of prostacyclin. *Eur. J. Med. Chem.*, 1992, **27**, 155–159.
132. Kobzar, G., Shelkovnikov, S., Mardla, V., Savitski, G., Lopp, M., Kanger, T. & Lille, Ü. A 15-nonstereogenic carbocyclic analogue of prostacyclin: Effect on human platelets and artery. *J. Lipid Mediators*, 1994, **10**, 243–249.
133. Kobzar, G., Mardla, V., Kanger, T., Lopp, M. & Lille, Ü. Comparison of the antiaggregatory activity of enantiomers of a 15-non-stereogenic carbacyclin analogue MM-706. *Pharmacol. Toxicol.*, 1995, **76**, 297–298.
134. Ragazzi, E., Chinellato, A., Lille, Ü., Lopp, M., Doni, M. G. & Fassina, G. Pharmacological properties of MM-706, a new prostacyclin derivative. *Gen. Pharmac.*, 1995, **26**, 703–709.
135. Petrukhina, G. N., Makarov, V. N., Lille, Ü. E. & Lopp, M. J. The influence of new synthetic analogue of prostacycline on some parameters of blood coagulation *in-vitro* and *ex-vivo*. *Prostaglandins, Leukotrienes Essent. Fatty Acids*, 1996, **55/1**, 71.
136. Lopp, M., Müraus, A., Parve, O., Välimäe, T., Lopp, A. & Lille, Ü. Synthesis and the antiaggregatory activity of prostacyclin analogs. I. Analogs of bicyclo[3.2.0]heptane. *Bioorg. Khim.*, 1988, **14**, 222–231 (in Russian).
137. Lopp, M., Bergmann, M., Bezuglov, V., Välimäe, T. & Lille, Ü. Synthesis and the antiaggregatory activity of prostacyclin analogs. II. Direct synthesis of 15-fluoro-13,14-didehydro-carbacyclin. *Bioorg. Khim.*, 1988, **14**, 834–836 (in Russian).
138. Newton, R. F. & Roberts, S. M. Synthesis of prostaglandins from polycyclic molecules. In *Prostaglandins and Thromboxanes* (Newton, R. F. & Roberts, S. M., eds.). Butterworth Scientific, London, 1982, 37–61.
139. Demuth, M. & Schaffner, K. Tricyclo(3.3.0.0.^{2,8})octan-3-one: Photochemisch hergestellte Bausteine zur enantiospezifischen Totalsynthese cyclopentanoider Naturstoffe. *Angew. Chem.*, 1982, **94**, 809–825.
140. Lille, Ü. Estonian prostaglandins. *Khim. i Zhizn'*, 1987, 20–23 (in Russian).
141. Wallis, C. J. Resolution of racemic bicycloheptenones. European Patent Office Patent No. 0 074 856, 1983.
142. Parve, O., Pals, A., Kadarpik, V., Lahe, L., Lille, Ü., Sikk, P., Lõokene, A. & Välimäe, T. High-purity porcine pancreatic lipase: Novel effects in catalyzing hydrolysis of esters derived from bicyclo[3.2.0]hept-2-en-ols. *Bioorg. Med. Chem. Lett.*, 1993, **3**, 357–358.
143. Parve, O., Pals, A., Kadarpik, V., Lahe, L., Lille, Ü., Sikk, P., Lõokene, A. & Välimäe, T. Enantioselective preparation of novel bicyclo[3.2.0]heptane derivatives using ester hydrolysis catalyzed by Novo Lipolase TM. *Bioorg. Med. Chem. Lett.*, 1993, **3**, 359–362.
144. Parve, O., Vallikivi, I., Lahe, L., Metsala, A., Lille, Ü., Tõugu, V., Vija, H. & Pehk, T. Lipase-catalysed enantioselective hydrolysis of bicyclo(3.2.0.)heptanol esters in super-critical carbon dioxide. *Bioorg. Med. Chem. Lett.*, 1997, **7**, 811–816.
145. Parve, O., Vallikivi, I., Metsala, A., Lille, Ü., Tõugu, V., Sikk, P., Käämbre, T., Vija, H. & Pehk, T. Lipase-catalysed enantioselective hydrolysis: Interpretation of kinetic results in terms of frontier orbital localizaton. *Tetrahedron*, 1997, **53**, 4889–4900.
146. Lopp, M., Paju, A., Pehk, T. & Lille, Ü. The chemoselective addition of alkynyllithium/BF_3 OEt_2 reagents to 2,3-endo-epoxy-6-oxabicyclo[3.3.0]octane-7-ol: An extremely short route to PGF_2 derivatives. *J. Chem. Res. (S)*, **1989**, 210–211.
147. Paju, A., Pehk, T., Lille, Ü. & Lopp, M. A novel and short synthesis of (-)-16,16-dimethyl-6-oxoprostaglandin E_1. *J. Chem. Res. (S)*, **1994**, 132–133.
148. Lopp, M., Paju, A., Niidas, P., Välimäe, T., Pehk, T. & Lille, Ü. The interaction of alkynyllithium boron trifluoride reagents with 2,3-epoxy-6-oxabicyclo[3.3.0]octan-7-ol. Synthesis of 13,14-didehydro analogues of prostaglandin $F_{2\alpha}$. *Zh. Org. Khim.*, 1989, **25**, 2312–2321 (in Russian).

149. Lopp, M., Niidas, P., Paju, A., Välimäe, T. & Lille, Ü. Synthesis of 1,2,3,4,5-pentanor-6-carboxymetoxyimino analogues of prostaglandin $F_{2\alpha}$. *Zh. Org. Khim.*, 1988, **24**, 2007–2008 (in Russian).
150. Lopp, M. & Lille, Ü. Synthesis of prostanoids using alkynyllithium/boron trifluoride reagents. *Zh. Vsesoyuz. Khim. Obshch. D. I. Mendeleeva*, 1991, **XXXV**, 423–427 (in Russian).
151. Sprague, P. W., Heikes, J., Harris, D. N. & Greenberg, R. 7-Oxabicyclo(2.2.1)heptane analogs as modulators of the thromboxane A_2 prostacyclin receptors. In *Advances in Prostaglandin, Thromboxane and Leukotriene Research. Vol. 11* (Samuellson, B., Paoletti, R. & Ramwell, P., eds.). Raven Press, New York, 1983, 337–343.
152. Paju, A., Soone, A., Pehk, T. & Lopp, M. Synthesis of omega-saturated 7-oxabicyclo(3.2.1)heptane analogues of thromboxane A_2. *Tetrahedron*, 1995, **51**, 10561–10570.
153. Paju, A., Lopp, M. & Lille, Ü. Alkylation of 1-chloro-3,4-epoxy-1*E*-butene by alkynyllithium. *Proc. Estonian Acad. Sci. Chem.*, 1989, **38**, 284–285.
154. Lopp, M., Paju, A., Kanger, T., Välimäe, T. & Lille, Ü. Alkynylation of ethylene ketale of 1-chloro-4-bromo-1*E*-buten-3-one. Synthesis of fragments for leukotriene and feromone synthesis. *Zh. Org. Khim.*, 1989, **25**, 869–870 (in Russian).
155. Lopp, M., Paju, A., Välimäe, T. & Lille, Ü. The reactions of oxiranes. III. Alkynylation of 1-chloro-3,4-epoxy-1*E*-butene with lithium acetylenide. *Zh. Org. Khim.*, 1992, **28**, 243–248.
156. Niidas, P., Kanger, T., Lopp, M. & Lille, Ü. Synthesis of (R)-(-)-4-phenoxy-3-hydroxy-1-butyne from tartaric acid derivatives. *Proc. Estonian Acad. Sci. Chem.*, 1989, **38**, 285–286.
157. Lopp, M., Kanger, T., Müraus, A., Pehk, T. & Lille, Ü. Synthesis of novel four-carbon chiron-(r)-1-*t*-butyldimethylsilyl-3,4-epoxy-but-1-yne. *Tetrahedron: Asymmetry*, 1991, **2**, 943–944.
158. Kanger, T., Liiv, M., Pehk, T. & Lopp, M. A highly stereoselective synthesis of a new propargylic epoxide: (3R,4S)-1-*tert*-butyldimethylsilyl-3,4-epoxy-1-pentyne. *Synthesis*, **1993**, 91–93.
159. Kanger, T., Niidas, P., Müürisepp, A. M., Pehk, T. & Lopp, M. Synthesis of chiral epoxyalkynes. *Tetrahedron: Asymmetry*, 1998, **9**, 2499–2508.
160. Seebach, D. & Hungerbühler, E. Synthesis of enantiomerically pure compounds (EPC-syntheses).Tartaric acid, an ideal source of chiral building blocks for synthesis. In *Modern Synthetic Methods* (Scheffold, R., eds.). Otto Salle Verlag, Frankfurt am Main, 1980, 91–171.
161. Välimäe, T., Pehk, T., Lippmaa, E., Lopp, M. & Lille, Ü. ^{13}C NMR spectroscopy of prostaglandins. 2. Prostanoids with oxygen at C9 and their intermediates. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1986, **35**, 165–192.
162. Lõhmus, M., Parve, O., Müraus, A., Lopp, M. & Lille, Ü. Resolution of *E*- and *Z*-isomers of prostacyclin carba-analogs by high performance liquid chromatography. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1985, **34**, 221–230.
163. Lõhmus, M., Parve, O., Müraus, A., Lopp, M. & Lille, Ü. Possibilities of separating 5*E*/*Z* and 15α/β isomers of prostacyclin carba-analogs by high performance liquid chromatography. *Proc. Acad. Sci. Estonian SSR. Chem.* 1986, **35**, 55–62.
164. Lõhmus, M., Paju, A., Samel, N., Lopp, M. & Lille, Ü. Adsorption high-performance liquid chromatography of prostanoids, use of water-containing mobile phases for separation of 15*R*/*S*-isomers of cloprostenol, and prostaglandins E_1 and E_2. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1986, **35**, 142–148.
165. Lõhmus, M., Lopp, M. & Lille, Ü. Preparative liquid chromatographic separation of isomers of prostaglandin carbaanalogues and their intermediates. *J. Chromatogr.*, 1988, **450**, 105–109.
166. Lõhmus, M., Kirjanen, I., Lopp, M. & Lille, Ü. Solvent selectivity in resolution of some regioisomeric prostaglandin intermediates. *J. Chromatogr.*, 1988, **449**, 77–94.

KAKS AASTAKÜMMET PROSTANOIDIDE JA NENDE SUGULASÜHENDITE KEEMIAT EESTIS

Ülo LILLE

On käsitletud prostanoidide keemia ja tehnoloogia arengut Eestis aastail 1975–1998.

Biosünteetilise meetodi alusel Eestis rajatud looduslike prostaglandiinide tootmine võimaldab nende hinnaliste lokaalsete hormoonide laialdast tutvustamist ja bioloogilis-meditsiinilisi uuringuid. Kasutusele on võetud günekoloogiline preparaat prostenoon. On määratud mitmeid uusi looduslikke prostaglandiine ja steroole. Uudseid seisukohti on esitatud prostaglandiinide tekkemehhanismi kohta korallides ja tõestatud nende tekkimine arktilises korallis *Gersemia fruticosa* imetajatele omase mehhanismi kaudu. Geenianalüüsi abil on kindlaks tehtud vastava dioksügenaasi aminohappeline järjestus.

On arendatud prostaglandiinide keemilise täissünteesi meetodeid ja loodud uusi, sealhulgas lipaaskatalüütilisi meetodeid enantiomeerselt puhaste ühendite saamiseks. Tootma on hakatud veterinaarset preparaati estufalaan ja loodud vastav enantiomeerselt puhas preparaat esteksaan. Hulgaliselt on sünteesitud looduslike prostaglandiinide analooge ja uuritud nende bioloogilisi omadusi selgitamaks viimaste seost aine struktuuriga. On leitud sobivaid vasoaktiivseid ja teisi struktuure vastavate preparaatide loomiseks.

Tehtud tööde tsükkel esitas uudseid seisukohti prostaglandiinide keemia ja tehnoloogia alal, arendas looduslike ühendite keemiat ja süvendas eeldusi moodsa teadusmahuka farmaatsiatööstuse loomiseks Eestis.