The XXI Conference on Isoprenoids was held in Białowieża, Poland, September 23–29, 2005. A series of conferences began in 1966 as national meetings on steroid chemistry organized by the late Professor Marian Kocór of the Institute of Organic Chemistry, Polish Academy of Sciences. Soon the meetings gained international character and since 70-ties they were organized biannually alternately by Polish or Czech (Drs. Vaclav Cerny and Vlastimil Herout) chemists. Outstanding scientists participated in the conferences including D. H. R. Barton and R. Noyori (Nobel prize winners, each attended the conference twice), A. Birch, H. DeLuca, M. Julia, P. Kocienski, S. V. Ley, K. Mori, W. Okamura, C. D. Poulter, A. B. Smith III, G. J. Stork, M. Shibasaki, L. Tietze, I. V. Torgov, B. M. Trost, J. Tsuji and many others. The Conferences on Isoprenoids integrated chemists working in the field of natural products from different countries, which was particularly important at that time when the world was divided by the Iron Curtain. Today, the principal aim of the conference is to promote research at chemistry – biology – medicine inter-phase, international scientific cooperation and exchange of information. The conference in Białowieża was organized jointly by the Polish Academy of Sciences and the University of Białystok. During the Conference 30 plenary lectures, 12 young scientist oral communications and many posters were presented. Topics covered by lectures ranged from “pure” organic synthesis through biochemistry and medicinal chemistry to practical applications of isoprenoids.

The meeting showed that natural product chemistry remains one of the most important areas of research and emphasized the continual need for Conferences on Isoprenoids.

This special issue of the Polish Journal of Chemistry presents only a part of the Conference program (a contribution to this Journal was facultative). We hope that the papers will be of interest for the chemical community.

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Ent-Steroids Chemistry and Biology

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Ent-steroids, the enantiomers of naturally-occurring steroids, are useful tools for distinguishing between receptor and non-receptor mediated actions of steroids. In particular, ent-steroids are useful for evaluating the relative importance of the direct (receptor binding) and indirect (membrane perturbation) effects of steroids on the function of membrane-bound proteins. A distinction between these two processes can be made on the basis of the different degrees of enantioselectivity expected for the two types of steroid actions. Receptor binding of steroids is expected to be enantioselective, whereas steroid effects on membrane properties are not. The synthesis of ent-steroids and examples of their use in biological studies are presented.

Key words: steroids, ent-steroids, enantiome
Dimolybdenum Method for Determination of the Absolute Configuration of vic-Diols – Foundations and Developments

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A straightforward and versatile method for the determination of the absolute configuration of vic-diols is presented. The proposed method involves the in situ formation of chiral complexes of optically active vic-diols with the achiral dimolybdenum tetraacetate \([\text{Mo}_2(\text{OAc})_4]\) acting as an auxiliary chromophore. The resulting CD spectra are suitable for the assignment of absolute configuration, since the observed sign of Cotton effects arising within the \(d-d\) absorption bands of the metal cluster depends solely upon the chirality of the 1,2-diol ligands. An empirically based rule correlating a positive/negative helicity expressed by the O–C–C–O torsional angle with the sign of Cotton effects occurring in the 400–280 nm spectral range has been presented. The applicability of the rule is extended to sterically hindered sec/tert vic-diols.

Key words: absolute configuration, circular dichroism, transition metal complexes, chiral Mo complexes
Mukaiyama and Torgov Chemistry in the Synthesis of (D-homo) Steroid Skeletons

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Three new, short, and efficient procedures have been developed for syntheses of steroid and D-homo steroid skeletons by application of Mukaiyama and Torgov chemistry. An important element in the first and in the second route is a Mukaiyama-Michael reaction with transfer of the silyl group from the starting silyl enol ether to the carbonyl group of the receiving enone. In this way a new silyl enol ether is obtained which enables either a selective reaction with the silyl enol ether in ring D as in route 1, or a selective reaction with the unprotected carbonyl group in ring B as in route 2. In all three approaches the C12–C13 bond is constructed using a Mukaiyama reaction of a Torgov type carbocation precursor with a silyl enol ether as the key transformation. In route 1, Zieglers triketone, which has been used before in the synthesis of 9,11-dehydroestrone methyl ether, has been prepared in four easy steps and in 70% overall yield, using the reactions mentioned above. In the second route a selective Grignard reaction of vinyl magnesium bromide with the unprotected carbonyl group of methoxy tetralone leads to a Torgov type intermediate. This can be converted easily into a carbocation, which then reacts intramolecularly with the silyl enol ether in ring D, under formation of the C12–C13 bond to complete the synthesis of cis (D-homo) steroid skeletons. In the third route, C17 substituted C,D trans coupled (D-homo) steroid skeletons have been prepared via an intermolecular addition of a carbocation, generated with ZnBr₂ from a Torgov reagent, to a silyl enol ether containing ring D precursor. The adducts have been cyclized under formation of the C8–C14 bond by treatment with acid and the double bonds in the cyclized products have been reduced to all trans steroid skeletons. A chiral five membered silyl enol ether containing ring D precursor has been synthesized from carvone, and used as starting compound in the synthesis of a chiral C17 functionalized steroid.

Key words: Torgov reagent, Mukaiyama-Michael addition, silyl enol ethers, (D-homo) steroid synthesis, carvone
Recent Development of the Cyclopropanol Methodology
for the Preparation of Methyl or Methylene
Branched Natural Compounds

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Syntheses of methyl and methylene branched natural compounds based on the ring-form-
ing and subsequent ring-opening reactions of strained three-membered ring of
cyclopropanol intermediates are reviewed.

Key words: carbonyl compounds, alkylation, cyclopropanol derivatives, ring-opening,
natural compounds
Cross-coupling Reactions for Steroid Modification: from Arylation to Macrocycle Syntheses

by Nikolay V. Lukashev, Alexei D. Averin, Gennadij V. Latyshev, Pavel A. Donez, Elena R. Ranyuk and Irina P. Beletskaya

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The Suzuki-Miyaura coupling of 4- and 6-halosteroids affords good to excellent yields of potential aromatase inhibitors. While the reaction with 4- and 6-bromo derivatives is catalyzed by Pd(PPh₃)₂Cl₂, the coupling with 6-chloro steroid (chlormadinone acetate) requires the use of Pd(dppb)Cl₂ or Pd(dppf)Cl₂. The palladium-catalyzed amination of bis(3-bromophenyl) ether of (5β)-cholane-3,24-diol with different polyamines leads to new macrocycles comprising one steroid and one polyamine fragments. Possibility of synthesis of macrocyclodimers containing two steroid and two polyamine fragments have been investigated.

Key words: cross-coupling, palladium, nickel, steroids, chlormadinone acetate, Suzuki reaction, litocholic acid, polyamines, macrocycles, amination, catalysis
2-Alkylidene Analogs of 19-nor-1α,25-(OH)2D3: Synthesis and Biological Activity

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A growing body of biological data indicate that the function of 1α,25-dihydroxyvitamin D3, [1α,25-(OH)2D3], extends beyond calcium and phosphorus homeostasis. The vitamin was also found to regulate cellular differentiation and to play a role in immunoregulatory activity. In 1990 we reported a synthesis of the first member of the so-called 19-norvitamins D. This analog, 19-nor-1α,25-dihydroxyvitamin D3, was characterized by the replacement of the A-ring exocyclic methylene substituent at C-10 by two hydrogen atoms. Biological testing of this compound revealed its selective activity profile with high potency in inducing cellular differentiation and very low calcium mobilizing response. Several similar 19-norvitamins were prepared to date and the most notable among them is 19-nor-1α,25-dihydroxyvitamin D2 (Zemplar®), successfully marketed by Abbott for renal osteodystrophy. As a continuation of these studies we synthesized analogs of the natural vitamin D hormone, 1α,25-(OH)2D3, characterized by transposition of its A-ring exocyclic methylene group from carbon 10 to carbon 2. Among such vitamins, 2-methylene-19-nor-1α,25-(OH)2D3, possessing an unnatural configuration at C-20 (2MD), is most remarkable due to its unique ability to induce bone formation. 2-Methylene-substituted 19-norvitamin D compounds with truncated side chains were also prepared and two of them (2MP and 2MbisP) show great promise in the treatment of secondary hyperparathyroidism, cancer and psoriasis. In an effort to further explore the 19-nor class for pharmacologically important vitamin D compounds, the isomeric 2-ethylidene-19-nor-1α,25-(OH)2D3 compounds were successfully prepared. Promising biological potencies of such analogs, especially those with E-geometry of the ethylidene group, encouraged us to further explore this A-ring modification by the synthesis of 2-(3′-hydroxypropylidene)-19-nor-1α,25-(OH)2D3 analogs. Biological tests revealed that calcemic activity of E-geometrical isomers considerably exceeds that of the native hormone, 1α,25-(OH)2D3.

Key words: vitamins D, 19-norvitamins D, vitamin D analogs, calcemic activity
Recent Developments in Palladium-Catalyzed Carbonylation of Steroids – An Alternative Approach to Steroidal Carbonyl Compounds and Carboxylic Acid Derivatives

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There is an increasing interest in developing new strategies to introduce functional groups into specific positions of steroidal nuclei in order to modify their biological properties. Transition metal catalyzed reactions have proved to be versatile tools both for the construction of the steroid framework from easily available building blocks and for the functionalization of the steroidal skeleton. By palladium-catalyzed carbonylation, carbon monoxide can be introduced directly into a number of different sites in an organic molecule leading to the synthesis of aldehydes, ketones, carboxylic acids and their derivatives, lactones, lactames, etc. The products can often be obtained in good yield and with high selectivity usually under very mild conditions. In addition, palladium-catalyzed carbonylation is compatible with many functional groups, and therefore, more advantageous than conventional methods. In the present paper the most important achievements in carbonylation of steroidal substrates is reviewed together with a more detailed discussion of our own results obtained in this field.

Key words: palladium catalysts, carbonylation, enol triflate, alkenyl halide, steroids
A Convenient Method for the Preparation of 
Δ⁴,⁷-Steroidal 3-Ketones and Δ⁵,⁷ Sterols

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A method is described for the preparation of Δ⁴,⁷-steroidal ketones or Δ⁵,⁷-sterols from Δ⁵-sterols via the sequence Wettstein-Oppenauer oxidation, trifluoroacetylation to give the Δ⁴,⁷-enol ester, and acid catalyzed isomerization to the Δ⁵,⁷-enol ester, followed by acid hydrolysis, or sodium borohydride reduction, respectively.

Key words: steroids, provitamin D₃, desaturation
Synthesis of 23-Oxa-22-deoxo Analogues of OSW-1 Aglycone

by Anna Kruszewska, Agnieszka Z. Wilczewska, Agnieszka Wojtkielewicz and Jacek W. Morzycki

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Four ether analogues of OSW-1 aglycone were obtained by alkylation of a steroid alcohol with alkyl bromide. During the Williamson reaction promoted by sodium hydride in addition to alkylation, an unusual dehydrogenation of secondary alcohol was observed.

Key words: OSW-1, Williamson reaction, dehydrogenation, antitumor agent
Chemical Composition and Biological Activity of Essential Oil from Flowerheads of *Centaurea polymorpha* Lag. (Asteraceae) Growing Wild in Spain

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The volatile constituents of the flowerheads of *Centaurea polymorpha* Lag. were extracted by hydrodistillation and analysed by GC and GC-MS. 63 components, amounting to 91.6% of the oil, were identified. Waxes and sesquiterpenes were the most abundant components in the oil. α-Cedrene (3.9%), β-cedrene (3.6%) and β-curcumene (3.0%) were the most representative sesquiterpene hydrocarbons while caryophyllene oxide (2.6%) was the most abundant oxygen containing sesquiterpene. The study on the biological activity of the oils showed no significant activity.

**Key words:** *Centaurea polymorpha*, Asteraceae, essential oil, waxes, α-cedrene, β-cedrene, β-curcumene, caryophyllene oxide, hexahydrofarnesyl acetone
Chemical Composition and Antimicrobial Activity of the Essential Oils from Aerial Parts of Two Marrubium sp. (Lamiaceae) Growing Wild in Lebanon

by Armando Grassia\textsuperscript{1}, Felice Senatore\textsuperscript{1}, Nelly Apostolides Arnold\textsuperscript{2}, Maurizio Bruno\textsuperscript{3}, Franco Piozzi\textsuperscript{3}, Daniela Rigano\textsuperscript{1} and Carmen Formisano\textsuperscript{1}

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The essential oils of aerial parts of Marrubium globosum Monbr. et Auch. ex Benth. ssp. libanoticum (Boiss) Davis and M. cuneatum Banks et Solander (Lamiaceae) growing wild in Lebanon were obtained by hydrodistillation and were analysed by GC and GC-MS. Altogether 64 compounds, representing 93.4\% and 91.4\% of the oils, were identified. The main components of both oils were \(\beta\)-caryophyllene (12.4\%–5.2\%), hexadecanoic acid (7.4\%–6.5\%) and spathulenol (5.2\%–6.5\%). Bicyclogermacrene (5.2\%) was present only in the oil of M. cuneatum characterized by high amount of germacrene D (15.6\%). Oils showed a moderate antimicrobial activity.

Key words: Marrubium globosum ssp. libanoticum, Marrubium cuneatum, Lamiaceae, essential oil, bicyclogermacrene, \(\beta\)-caryophyllene, germacrene D, hexadecanoic acid, spathulenol
Synthesis, Biological, Immunological and Anticancer Properties of a New Brassinosteroid Ligand

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We have developed polyclonal antibodies against the brassinosteroid, 24-epicastasterone. Antiserum against this substance was produced by immunizing rabbits and mice with 24-epicastasterone O-(carboxymethyl)oxime (24-epiCS-CMO) conjugated with bovine-serum albumin (BSA). The conjugates were prepared by a mixed anhydride procedure. The antibodies obtained were tested in enzyme-linked immunosorbent assay (ELISA) using 24-epiCS-CMO-peroxidase conjugate. The use of the ELISA allowed detection over the range of 0.01 to 500 pmoles. Natural brassinosteroids (BRs) like brassinolide, and 24-epibrassinolide exhibited relatively high cross-reactivities but many other natural BRs were inactive. The 24-epiCS-CMO ligand was also slightly active in second bean internode bioasay and on cancer cell lines of different histopathological origin.

**Key words**: brassinosteroids, phytohormones, antibodies, structure-activity relationship, cancer
The Preparation of the Spirostanic Analogues of Brassinolide and Castasterone

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Methods for the preparation of the spirostanic analogues of brassinosteroids (25R)-5α-spirostan-6-one-2β,3α-diol and (25R)-B-homo-5α-spirostan-6-oxo-7-oxalactone-2β,3α-diol, starting from diosgenin, were examined. The best preparative route was via diosgenin tosylation, isosteroidal rearrangement with potassium acetate in aqueous acetone, oxidation with Jones reagent, cyclopropyl ring opening with hydrobromic acid, hydrogen bromide elimination with lithium bromide and carbonate, dihydroxylation with osmium tetroxide and N-methylmorpholine N-oxide, producing (25R)-5α-spirostan-6-one-2β,3α-diol in 57.3% overall yield and lactonization with trifluoroperoxyacetic acid producing (25R)-B-homo-5α-spirostan-6-oxo-7-oxalactone-2β,3α-diol in 24.6% overall yield from diosgenin. The shortest route to (25R)-5α-spirostan-6-one-2β,3α-diol results in only 39.4% overall yield.

Key words: brassinosteroids, spirostanic analogues
An Unusual Pregnan Derivative and Dibenzybutyrolactone Lignans from *Centaurea sclerolepis*

by Zerrin Erdemgil¹, Sergio Rosselli², Antonella M. Maggio², Rosa A. Raccuglia², Sezgin Çelik³, Klaudia Michalska⁴, Wanda Kisiel⁴ and Maurizio Bruno²

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Analysis of Brassinosteroids

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Methodology for a Solid-Phase Synthesis
of “Daddy Longlegs” Spiders Defense Substance

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Studies Towards Solid-Phase Synthesis of Nordihydrodarlingine and Norchalcostrobamine

by Ryszard Lazny, Aneta Nodzewska and Michal Sienkiewicz

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Application of Allyl Derivatives of Cholic Acid for the Synthesis of Macrocyclic Structures

by Dorota Czajkowska and Jacek W. Morzycki

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Reactions of Sapogenins with \( m \)-Chloroperoxybenzoic Acid Catalyzed by Lewis Acids

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Synthesis of Mechanistic Probes and Inhibitors for Prenylating Enzymes
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A Stereoselective Synthesis of Vinyl Bromides from
α-Bromo-α,β- Unsaturated Ketones Involving
Fragmentation of β,γ-Unsaturated Sulfinic Acids.
A New Approach to the Vitamin D Rings
CD Building Blocks

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