

PREFACE

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.

Jerzy Wicha
Jacek W. Morzycki

***Ent*-Steroids Chemistry and Biology**

by Douglas F. Covey

*Department of Molecular Biology and Pharmacology, 660 S. Euclid Ave, Campus Box 8103,
Washington University School of Medicine, St. Louis, Missouri, 63110, USA*

(Received October 14th, 2005; accepted December 12th, 2005)

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

by Marcin Górecki, Anna Kamińska, Patrycja Ruškowska, Agata Suszczyńska
and Jadwiga Frelek

Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw, Poland

(Received November 14th, 2005; accepted December 12th, 2005)

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 [Mo₂(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

by Florence C.E. Saraber¹, Svetlana V. Drach^{1,2}, Alexander Baranovsky^{1,2},
Tanya Charnikhova^{1,2}, Serghei Pogrebnoi^{1,3}, Ben J.M. Jansen¹
and Aede de Groot¹

¹Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8,
6703 HB Wageningen, The Netherlands

²Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus,
Kuprevich str. 5/2, 220141, Minsk, Belarus

³Institute of Chemistry, Academy str. 3, MD-2028 Kishinev, Republic of Moldova

(Received October 20th, 2005; accepted December 12th, 2005)

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**

**by Andrei V. Bekish, Konstantin N. Prokhorevich, Tamara S. Pritytskaya and
Oleg G. Kulinkovich**

Department of Chemistry, Belarusian State University, Nezavisimosty Av. 4, Minsk, 220050, Belarus

(Received November 30th, 2005; accepted December 12th, 2005)

Syntheses of methyl and methylene branched natural compounds based on the ring-forming 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

The Department of Chemistry, Moscow State Lomonosov University, 119992, Moscow, Russia

(Received September 28th, 2005; accepted December 12th, 2005)

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 $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, the coupling with 6-chloro steroid (chlormadinone acetate) requires the use of $\text{Pd}(\text{dppb})\text{Cl}_2$ or $\text{Pd}(\text{dppf})\text{Cl}_2$. The palladium-catalyzed amination of bis(3-bromophenyl) ether of (5 β)-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, lithocholic acid, polyamines, macrocycles, amination, catalysis

2-Alkylidene Analogs of 19-nor-1 α ,25-(OH) $_2$ D $_3$: Synthesis and Biological Activity

by Rafał R. Siciński

Department of Chemistry, University of Warsaw, ul. Pasteura 1, 02-093 Warsaw, Poland

(Received December 7th, 2005; accepted December 12th, 2005)

A growing body of biological data indicate that the function of 1 α ,25-dihydroxyvitamin D $_3$, [1 α ,25-(OH) $_2$ D $_3$], 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-1 α ,25-dihydroxyvitamin D $_3$, 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-1 α ,25-dihydroxyvitamin D $_2$ (Zemlar®), successfully marketed by Abbott for renal osteodystrophy. As a continuation of these studies we synthesized analogs of the natural vitamin D hormone, 1 α ,25-(OH) $_2$ D $_3$, characterized by transposition of its A-ring exocyclic methylene group from carbon 10 to carbon 2. Among such vitamins, 2-methylene-19-nor-1 α ,25-(OH) $_2$ D $_3$, 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-1 α ,25-(OH) $_2$ D $_3$ 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-1 α ,25-(OH) $_2$ D $_3$ analogs. Biological tests revealed that calcemic activity of *E*-geometrical isomers considerably exceeds that of the native hormone, 1 α ,25-(OH) $_2$ D $_3$.

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

by Rita Skoda-Földes¹ and László Kollár²

¹*Department of Organic Chemistry and Research Group for Petrochemistry of the Hungarian Academy of Sciences, University of Veszprém, H-8201 Veszprém, P.O. Box 158, Hungary*

²*Department of Inorganic Chemistry and Research Group for Chemical Sensors of the Hungarian Academy of Sciences, University of Pécs, H-7624 Pécs, P.O. Box 266, Hungary*

(Received September 28th, 2005; accepted December 12th, 2005)

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, lactams, *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 $\Delta^{4,7}$ -Steroidal 3-Ketones and $\Delta^{5,7}$ Sterols

by José-Luis Giner and Hui Zhao

Department of Chemistry, SUNY-ESF, Syracuse NY 13210, USA

(Received November 7th, 2005; accepted December 12th, 2005)

A method is described for the preparation of $\Delta^{4,7}$ -steroidal ketones or $\Delta^{5,7}$ -sterols from Δ^5 -sterols *via* the sequence Wettstein-Oppenauer oxidation, trifluoroacetylation to give the $\Delta^{2,4,6}$ -enol ester, and acid catalyzed isomerization to the $\Delta^{3,5,7}$ -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**

Institute of Chemistry, University of Białystok, al. Piłsudskiego 11/4, 15-443 Białystok, Poland

(Received October 24th, 2005; accepted December 12th, 2005)

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

by Carmen Formisano¹, Felice Senatore¹, Gabriella Bellone², Maurizio Bruno², Armando Grassia¹, Aida Raio³ and Daniela Rigano¹

¹*Dipartimento di Chimica delle Sostanze Naturali, Università degli Studi di Napoli "Federico II",
Via D. Montesano, 49, I 80131 Napoli, Italy*

²*Dipartimento di Chimica Organica, Università degli Studi di Palermo,
Viale delle Scienze, Parco d'Orleans II, I 90128 Palermo, Italy*

³*Istituto per la Protezione delle Piante - CNR, Sezione di Portici (NA),
Via Università, 133, I 80055 Portici (NA), Italy*

(Received September 28th, 2005; accepted December 12th, 2005)

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 Grassia¹, Felice Senatore¹, Nelly Apostolides Arnold²,
Maurizio Bruno³, Franco Piozzi³, Daniela Rigano¹ and Carmen Formisano¹**

¹Dipartimento di Chimica delle Sostanze Naturali, Università degli Studi di Napoli "Federico II",
Via D. Montesano, 49, I-80131 Napoli, Italy

²Faculté de Sciences Agronomiques, Université de Saint Esprit, Kaslik, (Beyrouth), Lebanon

³Dipartimento di Chimica Organica, Università degli Studi di Palermo,
Viale delle Scienze, Parco d'Orleans II, I-90128 Palermo, Italy

(Received September 28th, 2005; accepted December 12th, 2005)

The essential oils of aerial parts of *Marrubium globosum* Montbr. 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 β -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, β -caryophyllene, germacrene D, hexadecanoic acid, spathulenol

Synthesis, Biological, Immunological and Anticancer Properties of a New Brassinosteroid Ligand

by **Jana Swaczynová¹**, **Miroslav Šiša²**, **Jaroslava Hniličková²**,
Ladislav Kohout² and **Miroslav Strnad¹**

¹*Laboratory of Growth Regulators, Palacky University and Institute of Experimental Botany ASCR, Šlechtitelů 11, 783 71 Olomouc, Czech Republic*

²*Department of Steroid Chemistry, Institute of Organic Chemistry and Biochemistry ASCR, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic*

(Received October 11th, 2005; accepted December 12th, 2005)

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 bioassay 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

by Caridad M. Robaina Rodríguez¹, Marco António Teixeira Zullo²,
Helena Müller Queiróz², Mariangela de Burgos Martins de Azevedo²,
Esther Alonso Becerra¹ and Francisco Coll Manchado¹

¹Laboratorio de Productos Naturales, Facultad de Química, Universidad de La Habana,
Calzada de Zapata y Calle G, Vedado, Habana 10400, Cuba

²Laboratório de Fitoquímica, Instituto Agrônomo, Caixa Postal 28,
13001-970, Campinas, SP, Brasil

(Received September 21th, 2005; accepted December 12th, 2005)

Methods for the preparation of the spirostanic analogues of brassinosteroids (25*R*)-5 α -spirostan-6-one-2 α ,3 α -diol and (25*R*)-B-homo-5 α -spirostan-6-oxo-7-oxalactone-2 α ,3 α -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 (25*R*)-5 α -spirostan-6-one-2 α ,3 α -diol in 57.3% overall yield and lactonization with trifluoroperoxyacetic acid producing (25*R*)-B-homo-5 α -spirostan-6-oxo-7-oxalactone-2 α ,3 α -diol in 24.6% overall yield from diosgenin. The shortest route to (25*R*)-5 α -spirostan-6-one-2 α ,3 α -diol results in only 39.4% overall yield.

Key words: brassinosteroids, spirostanic analogues

**An Unusual Pregnane Derivative and
Dibenzylbutyrolactone Lignans
from *Centaurea sclerolepis***

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

¹*Plant & Drug & Scientific Research Center, Anadolu University, 26470 Eskisehir, Turkey*

²*Dipartimento Chimica Organica, Università di Palermo, 90 128 Palermo, Italy*

³*Çanakkale Onsekiz Mart University, Science & Literature Faculty, Biology Department,
17100 Çanakkale, Turkey*

⁴*Department of Phytochemistry, Institute of Pharmacology, Polish Academy of Sciences,
31-343 Krakow, Poland*

(Received September 28th, 2005; accepted December 12th, 2005)

Analysis of Brassinosteroids

**by Vladimir A. Khripach, Oleg V. Sviridov, Raisa P. Litvinovskaya,
Andrey G. Pryadko, Svetlana V. Drach and Vladimir N. Zhabinskii**

*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus,
Kuprevich str., 5/2, 220141 Minsk, Belarus*

(Received November 2nd, 2005; accepted December 12th, 2005)

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

by Ryszard Lazny, Aneta Nodzewska and Michal Sienkiewicz

Institute of Chemistry, University of Bialystok, al. Pilsudskiego 11/4, 15-443 Bialystok, Poland

(Received November 24th, 2005; accepted December 12th, 2005)

**Studies Towards Solid-Phase Synthesis of
Nordihydrodarlingine and Norchalcostrobamine**

by Ryszard Lazny, Aneta Nodzewska and Michal Sienkiewicz

Institute of Chemistry, University of Bialystok, al. Pilsudskiego 11/4, 15-443 Bialystok, Poland

(Received September 28th, 2005; accepted December 12th, 2005)

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

by **Dorota Czajkowska and Jacek W. Morzycki**

Institute of Chemistry, University of Białystok, Al. Piłsudskiego 11/4, 15-443 Białystok, Poland

(Received October 26th, 2005; accepted December 12th, 2005)

**Reactions of Sapogenins with *m*-Chloroperoxybenzoic
Acid Catalyzed by Lewis Acids**

by **Martin A. Iglesias-Arteaga**¹, **Izabella Jastrzębska**² and **Jacek W. Morzycki**²

¹*Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria,
04510 México D.F., México*

²*University of Białystok, Institute of Chemistry, al. J. Piłsudskiego 11/4, 15-443 Białystok, Poland*

(Received October 7th, 2005; accepted December 12th, 2005)

**Synthesis of Mechanistic Probes and Inhibitors
for Prenylating Enzymes**

by **Ludger A. Wessjohann, Michael Fulhorst and Svetlana Zakharova**

*Department of Bio-organic Chemistry, Leibniz Institute of Plant Biochemistry,
Weinberg 3, D-06120 Halle (Saale), Germany*

(Received October 28th, 2005; accepted December 12th, 2005)

**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**

by Paweł Chochrek, Alicja Kurek-Tyrlik and Jerzy Wicha

*Institute of Organic Chemistry, Polish Academy of Sciences,
ul. Kasprzaka 44/52, POB 58, 01-224 Warsaw 42, Poland*

(Received November 10th, 2005; accepted December 12th, 2005)