Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw

XVII CONFERENCE ON ISOPRENOIDS

ABSTRACTS OF PAPERS

Kraków, Poland, 21–26 September, 1997

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Donation from Schering AG, Berlin, Merck Poland Sp z o.o., Linegal Chemicals, are gratefully acknowledged.

LIST OF PLENARY LECTURES

ONE HOUR

G. Cimino
Institute per la Chimica di Molecole Interesse Biologico, C. N. R., Italy
Are Terpenoids a Driving Force in the Evolution of Opisthobranch Molluscs?

P. J. Kocieński
University of Glasgow, UK
Synthetic Approaches to Biologically Active Natural Products Containing the 2-Oxetanone Ring System

K. Mikami
Tokyo Institute of Technology, Japan
Carbonyl-Ene Approach to Isoprenoids

K. Mori
Science University of Tokyo, Japan
Recent Results in the Synthesis of Bioactive Natural Products

K. Nakanishi
Columbia University, USA
Recent Studies on Retinal Pigments

K. C. Nicolaou
The Scripps Research Institute, USA
Total Synthesis, New Synthetic Technology and Chemical Biology of Natural and Designed Molecules

C. D. Poulter
University of Utah, USA
How Nature Synthesizes Non-Head-to-Tail Isoprenoids?

K. Slàma
Entymological Institute; Laboratory of Ecological Chemistry, Czech Republic
Polyhydroxylated Sterols in Biology and Medicine

W. Steglich
Universität München, Germany
Novel Terpenoids from Mushrooms

H. Waldmann
Universität Karlsruhe, Germany
Lipidated Peptides — Tools for the Study of Signal Transduction Processes via Lipidated Proteins

P. A. Wender
Stanford University, USA
The Chemistry-Medicine Continuum: Synthetic, Computer, Spectroscopic and Biological Studies on New Medicinal Leads

D. R. Williams
Indiana University, USA
Studies for the Synthesis of Marine Natural Products. New Developments for the Stereocontrolled Synthesis of Complex Macrocycles

HALF HOUR

T. G. Back
The University of Calgary, Canada
New Developments in the Chemistry of Brassinosteroids

J. R. Bull
University of Cape Town, Republic of South Africa
Synthesis of Sterically Congested Estradiol Analogues as Receptor Binding Probes

M. J. Calverley
Leo Pharmaceutical Products, Denmark
The Evolution of the Side Chain in Vitamin D Analogues

D. Craig
Imperial College of Science, England
Cyclisation- and Cycloaddition-based Approches to Taxol Synthesis

A. de Groot
Wageningen Agricultural University, The Netherlands
S-(+) — and R(-) — Carvone as Starting Material in the Enantioselective Synthesis of Natural Products

M. M. Kabat
Hoffmann-La Roche Inc., USA
Application of the Ene Reaction to the Synthesis of Trans 1,3-Cyclohexadiols

T. Katsuki
Kyushu University, Japan
Catalytic Asymmetric Oxidation Reactions

W. Kreiser
Universität Dortmund, Germany
Homochiral Building Blocks with High Symmetry for Terpene Synthesis

PLENARY LECTURES ABSTACTS

RECENT STUDIES ON RETINAL PIGMENTS.

Koji Nakanishi, Department of Chemistry, Columbia University, New York, NY 10027

A_2E, the fluorescent eye pigment involved in macular degeneration.

The structure of the fluorophore A_2E which accumulates in old age eyes and is associated with macular degeneration, an incurable eye disease that may lead to blindness, has been determined.[1] The structure consists of two retinal moieties condensed with an ethanolamine group. A convergent synthesis has been completed.[2] Its properties in relation to age-related blindness and other aspects will be presented.

Absolute conformation of the rhodopsin chromophore in its binding site.

Photoaffinity studies indicate that the C-3/C-4 of the retinal ionone moiety is located close to the mid-section of helix F of rhodopsin.[3] The absolute sense of twist around C-12/C-13 of the 11-cis-retinal chromophore in the rhodopsin binding site, as determined by exciton coupled CD,[4] and studies aimed to determine the twist around the 6-s-cis bond will be presented.

Changes in chromophore/opsin interactions accompanying visual transduction.

We plan to perform photoaffinity cross-linking of the retinal chromophore to the first sequestable intermediate in the transduction process, i.e., bathorhodopsin at -140° C; this will be followed by a similar sequencing at a higher temperature corresponding to the next intermediate, and so on. This should clarify the changes in chromophore /receptor interactions accompanying visual transduction. This study requires 11-cis-3-diazo-4-oxo-retinal; this has been prepared chemoenzymatically using the squid isomerase retinochrome,[5] and also by chemical synthesis.[6]

The CD of bacteriorhodopsin, is it an exciton couplet or not ?

This controversial issue is being checked by incorporating two retinal analogs with different absorption maxima into bacteriorhodopsin and measuring the CD of the formed bacteriorhodopsin.[7]

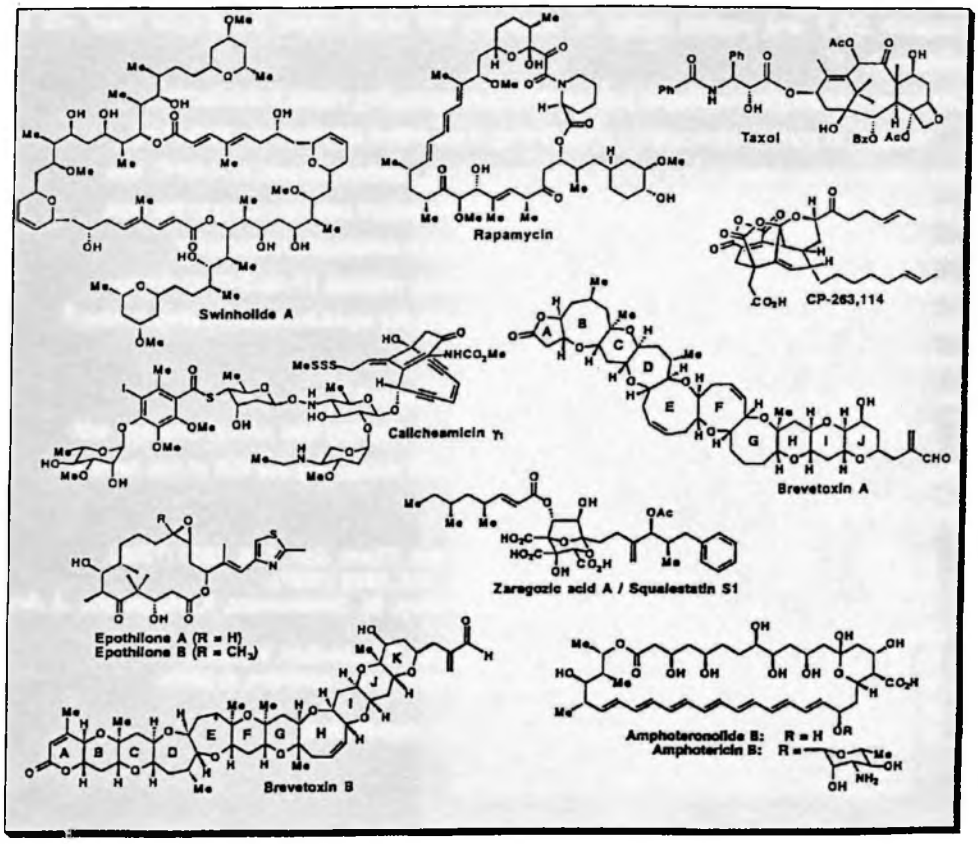
1. N. Sakai, J. Decatur, K. Nakanishi, G. E. Eldred, *J. Am. Chem. Soc.*, **118**, 1559 (1996).
2. R. Ren, N. Sakai, K. Nakanishi, *J. Am. Chem. Soc.*, **119**, 3619 (1997).
3. H. Zhang, K. Lerro, T. Yamamoto, T. Lien, L. Sastry, M. Gawinowicz, K. Nakanishi, *J. Am. Chem. Soc.*, **116**, 10165 (1994).
4. Q. Tan, J. Lou, B. Borhan, E. Karnaukhova, N. Berova, K. Nakanishi, in press.
5. B. Borhan, R. Kunz, A.Y. Wang, K. Nakanishi, N. Bojkova, K. Yoshihara, in press.
6. B. Borhan, K. Nakanishi, in preparation.
7. E. Karnaukhova, B. Borhan, N. Berova, K. Nakanishi, unpublished.

TOTAL SYNTHESIS, NEW SYNTHETIC TECHNOLOGY, AND CHEMICAL BIOLOGY OF NATURAL AND DESIGNED MOLECULES

K.C. Nicolaou

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093

Natural products provide unique opportunities for the discovery and invention of new synthetic methods and strategies and for chemical biology investigations. In this lecture, a number of such molecules will be discussed as targets for total synthesis and as opportunities to make contributions in chemistry, biology and medicine.



HOW NATURE SYNTHESIZES NON-HEAD-TO-TAIL ISOPRENOIDS

C. Dale Poulter, Department of Chemistry, University of Utah,
Salt Lake City, Utah 84112, USA

Irregular isoprenoids contain one or more non-head-to-tail linkages between isoprene units. Although not as common as their regular counterparts, irregular isoprenoids are widely distributed in nature and comprise several important families of isoprenoids. The two most prominent groups are sterols, formed from the 1'-1 isoprenoid squalene, and carotenoids, formed from the 1'-1 isoprenoid phytoene. The cyclopropylcarbinyl derivatives, presqualene diphosphate and prephytoene diphosphate, are direct precursors of squalene and phytoene, respectively. Presqualene diphosphate is also the immediate precursor of the 1'-3 isoprenoid botryococcene. The gene for yeast squalene synthase was cloned into an *E. coli* expression vector, and the recombinant enzyme catalyzes the two step sequence farnesyl diphosphate → presqualene diphosphate → squalene upon incubation with NADPH. When NADPH is replaced with a non-reactive analog or is omitted from the reaction, squalene synthase catalyzes formation of both 1'-1 and 1'-3 products. The implications of these observations on how isoprenoid enzymes control the formation of 1'-1 and 1'-3 products will be discussed.

R-(-)- AND S-(+)-CARVONE AS STARTING MATERIAL IN THE ENANTIOSELECTIVE SYNTHESIS OF NATURAL PRODUCTS

Æde de Groot, A.A. Verstegen-Haaksma, H.J. Swarts, B.J.M. Jansen, T.M. Meulemans, L.H.W. Jenniskens, S.V. Dratch and A. Baranovsky.

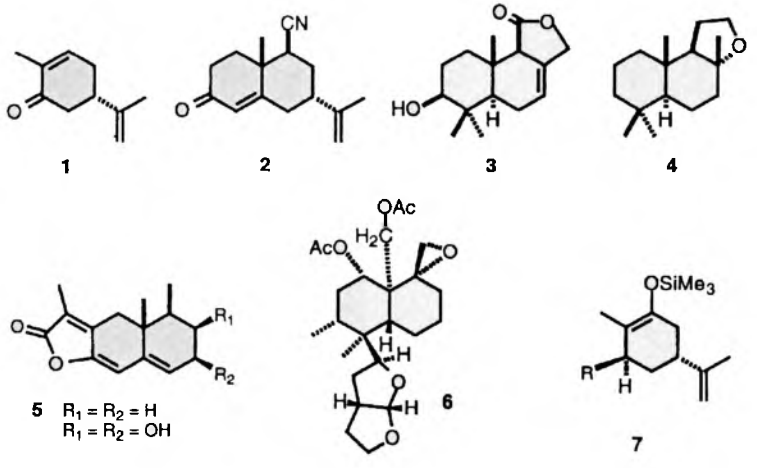
Laboratory of Organic Chemistry, Wageningen Agricultural University, Dreijenplein 8, 6708 HB Wageningen, The Netherlands

The conjugate addition of nucleophiles followed by annulation is investigated for R-(-) and S-(+)-carvone to obtain highly functionalized chiral decalins. The isopropenyl group in carvone first serves as a chiral handle. After the addition and annulation, it can be transformed into an alcohol or a carbonyl group and in this way it can be considered as a protecting group for these functionalities.

One new approach in this field starts with the conjugate addition of cyanide to the enone in S-(+)-carvone (**1**), followed by an annulation reaction. Thus a functionalized chiral decalone **2** with a nitrile group at C9 and a potential functional group at C7 is obtained in an easy way and in high yield. This decalone will be applied in the synthesis of drimanes **3**, Ambrox® (**4**), and other flavour compounds.

Conjugate addition to S-(+)-carvone followed by annulation also provides easy access to again ambrox and ermophilane sesquiterpenes **5**.

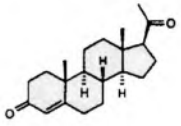
A second subject is the transformation of R-(+)-carvone into insect antifeedant clerodanes like dihydroclerodin (**6**) and into homo steroids.



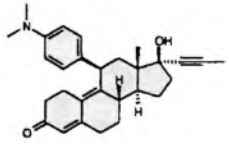
CHALLENGES FOR STEROID CHEMISTRY IN THE SERIES OF 11β-ARYLSUBSTITUTED ANTIPROGESTINS

Günter Neef
Research Laboratories of Schering AG, D-13342 Berlin, Germany

Although the discovery of RU 486 (mifepristone) as the first competitive progesterone antagonist dates back to the early nineteen eighties, uncertainty persists about the specific type of interaction that must be postulated for the binding of 11β-arylsubstituted steroids to the progesterone receptor protein. A large number of structurally modified analogues has made clear that a substituted 11β-phenyl residue is an essential prerequisite for antiprogestational activity. So far however, the existing data fail to provide a conclusive picture of steric versus electronic contributions.

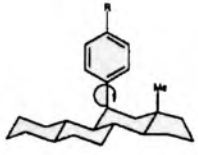


Progesterone

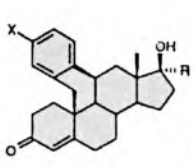


RU 486 (Mifepristone)

Besides the more conventional approaches to structure variation, 11β-arylsteroids of the RU 486 type offer the possibility of manipulating rotational isomerism. The respective influences on biological activity of hindered or restricted rotation around the single bond link between phenyl ring and steroid skeleton could be expected to lead to a deeper insight into structure activity relations.



Synthetic strategies will be disclosed aimed at derivatives **1** - **5** which are either frozen into distinct rotational situations (**1**, **2**) or forced into rotameric preferences by steric hindrance (**3**) and steroid skeleton rigidity (**4**, **5**).



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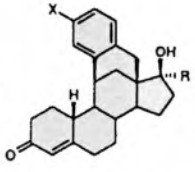

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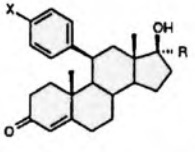

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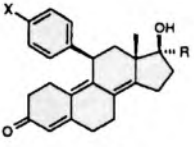

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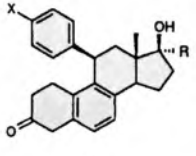


5

Polyhydroxylated sterols in biology and medicine

K. Sláma, Institute of Entomology, Czech Academy of Sciences, Prague.

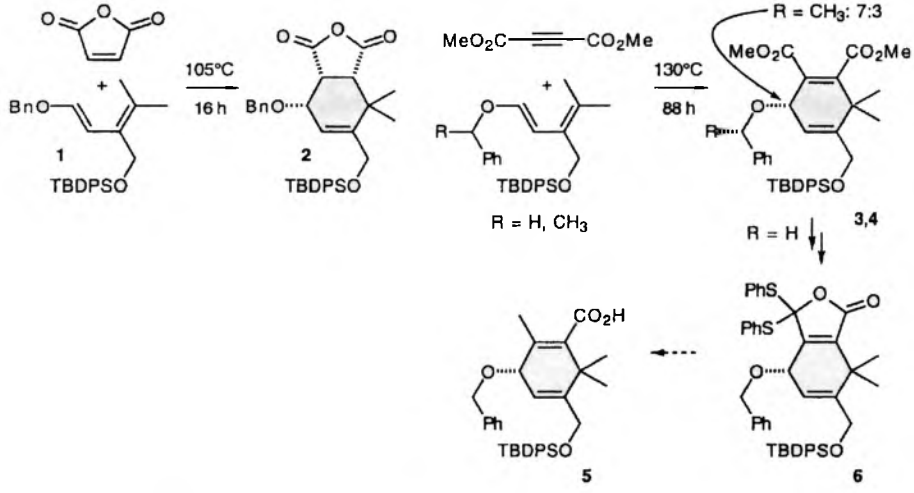
Existence of some slightly polar, partly water soluble, polyhydroxylated sterols was first recognized in 1965 when Karlson and his co-workers elucidated the structure of insect moulting hormone, ecdysone (2β, 3β,14α,22α,25-pentahydroxy-5β-cholest-7-en-6-on). Extensive screenings for biological activity of ecdysone soon revealed a wide distribution of these polyhydroxylated sterols, generally known as ecdysteroids, in Arthropods other than insects (Crustacea) and in a number of taxonomically unrelated families of lower and higher plants. Chemical structure of these compounds of animal, as well as of plant origin, is mostly derived from cholestane, although there are numerous ecdysteroid derivatives of ergostane or stigmastane type. Physiological role of polyhydroxylated sterols in plants is still merely unknown. There are some indications suggesting their defensive role against insect herbivores. It appears that ecdysteroids have no direct phytohormonal activity in plants, in contrast to another class of polyhydroxylated sterols, the brassinosterols, which do show true phytohormonal growth effects in certain models of plants. The occasional, enormous accumulation of polyhydroxylated sterol in plants suggests that plants may use these partly water soluble compounds as a depot for transport of sterol, which is absolutely essential for cell proliferation. Recent studies have shown metabolism stimulating, anabolic, antidepressive, adaptogenic and other beneficial pharmacological effects of the polyhydroxylated sterols in human medicine. These effects in the vertebrates are certainly not hormonal; they have a character of some essential sterolic vitamin, whose existence has been hitherto seriously ignored.

Dr Donald Craig
Imperial College of Science, Technology and Medicine

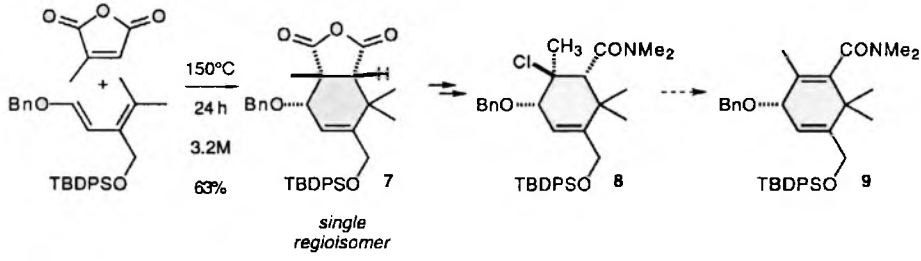
Cyclisation- and Cycloaddition-based Approaches to Taxol Synthesis

Abstract:

Results of investigations of in*ter*molecular Diels–Alder reactions of highly substituted, electron-rich alkoxydienes with electron-deficient dienophiles will be presented. Diene **1** reacts efficiently with maleic anhydride to give **2** and dimethyl acetylenedicarboxylate (DMAD) to give **3**. In the latter case, substitution of a benzylic hydrogen in the diene with a methyl group gives a chiral Diels–Alder substrate, which reacts diastereoselectively with DMAD to give **4** as a 7:3 mixture. The products of these reactions have been converted to butenolides **6**, and studies are underway to identify conditions for their reductive ring-opening–desulfurisation to give **5**.



In an alternative approach, reaction of **1** with citraconic anhydride gives a cycloadduct **7** in good yield. This has been converted into the chloroamide **8** via aminolysis followed by radical-mediated decarboxylation. Current efforts are directed towards **9**, via base-mediated elimination of the elements of hydrogen chloride.

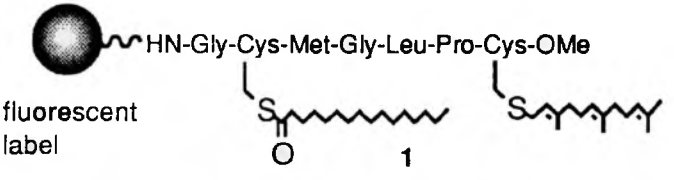


LIPIDATED PEPTIDES - TOOLS FOR THE STUDY OF SIGNAL TRANSDUCTION PROCESSES VIA LIPIDATED PROTEINS

Herbert Waldmann
Institut für Organische Chemie, Universität Karlsruhe, Willstätter-Allee 2, D-07128 Karlsruhe
Fax: Intl. (+)721-608-4825, e-Mail: waldmann@ochhades.chemie.uni-karlsruhe.de

Lipid modified peptides like the plasma membrane bound *Ras* protein and further protein conjugates which carry different modifications like phospho-, nucleo- and glycoproteins are critically involved in the transduction of signals from the extracellular space into the cell and ultimately to the cell nucleus. A recent spectacular example which highlights in particular the biological importance of lipidated proteins is provided by the elucidation of the *Ras* pathway of signal transduction which is central to growth control in numerous organisms. If the *Ras* pathway is disturbed an uncontrolled growth and proliferation of cells may be established, resulting in cell transformation. For the study of such signal transduction pathways often structurally well defined lipo-, phospho-, nucleo- and glycopeptides, carrying the characteristic structural elements of their parent proteins, are required. Their synthesis, however, is complicated by the multifunctionality and the pronounced chemical lability of these compounds. To achieve this goal, numerous orthogonally stable protecting groups have to be applied, which all must be removable under mild, preferably neutral conditions.

We have developed enzymatic protecting group techniques as efficient synthetic tools which fulfill these criteria [1]. By means of these methods we were able to construct complex and very sensitive peptide conjugates. The paper will present the development of these techniques and their application [2,3] in the synthesis of different peptide conjugates like **1**, which represents the S-palmitoylated and S-farnesylated characteristic C-terminal hexapeptide of the human N-*Ras* protein.



By means of the biocatalyzed transformations a set of tools for biological investigations was generated (see **1**) which was employed in e.g. membrane insertion and microinjection experiments and inhibition of proteins involved in signal transduction processes [4].

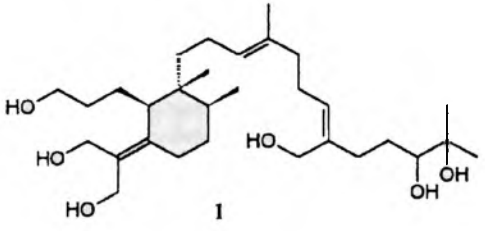
[1] Review: M. Schelhaas, H. Waldmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2056.
[2] H. Waldmann, E. Nägele, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2259.
[3] M. Schelhaas, S. Glomsda, M. Hänsler, H.-D. Jakubke, H. Waldmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 106.
[4] Review: K. Hinterding, D. Alonsó-Diaz, H. Waldmann, *Angew. Chem. Int. Ed. Engl.*, in the press.

Novel Terpenoids from Mushrooms

Wolfgang Steglich

Institut für Organische Chemie der Universität, Karlstraße 23, D-80333 München

During our studies on biologically active constituents from mushrooms several new terpenoids have been isolated. Crystallopicrin (1) is responsible for the extremly bitter taste of *Cortinarius vibratilis*. 1 contains the same skeleton as the iridals from *Iris* species.[1] Sodagnitin A (2) occurs in *C. sodagnitus* and causes the remarkable colour change to bright red when the fruit-bodies are touched with aqueous base. Interestingly, the bitter principles of *Boletus calopus*, e.g. 3, appear to be derived from a sesquiterpenoid precursor.



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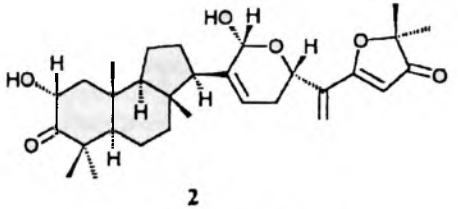

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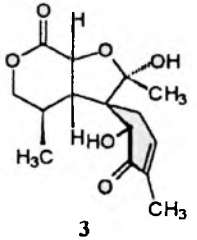

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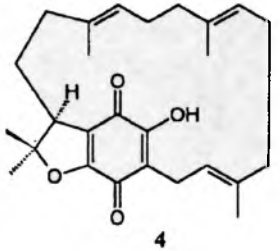

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Several mushrooms contain characteristic meroterpenoids. In the case of *Albatrellus* sp. these compounds are derived from orsellinic acid, whereas bovilactones, suillin, tridentoquinone (4), and bolegrevilol are formed from 4-hydroxybenzoic acid. The biosynthesis of the latter group of compounds was established by ^{13}C-labelling experiments which will be discussed in the lecture. Finally, joint work with Prof. T. Anke, Kaiserslautern, on the biosynthesis of cyathane derivatives from cultures of *Hericium* and *Cyathus* species will be reported.

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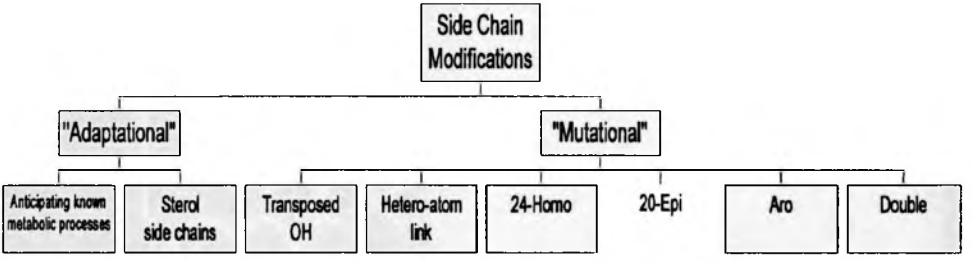
1) Jaenicke, L., Marner, F. J., *Progr. Chem. Org. Nat. Prod.* **1986**, *50*, 1 ff.

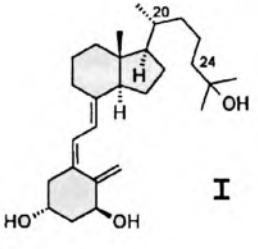
THE EVOLUTION OF THE SIDE CHAIN IN VITAMIN D ANALOGUES

Martin J. CALVERLEY
Chemical Research Department, Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark

The discovery of receptor mediated effects of the vitamin D hormone (calcitriol, I), previously associated primarily with calcium homeostasis, in controlling the growth of cancer cells heralded a renaissance of synthetic activity in the vitamin D field. It remains a goal for medicinal chemists to synthesise vitamin D analogues in which the anti-hyperproliferative effects are selected sufficiently from the classical effects for clinical use, and much progress has been achieved, primarily by altering the side chain structure. By classifying the analogues that have been tested for these effects and found to be agonists, an evolutionary process can be traced for the development of "active side chains." Thus, new modifications emerge as unpredictable structural leaps ("mutations"), including (isolated modifications in roughly chronological order):- a) transposing the side chain hydroxyl group, b) introducing a hetero-atom link or c) increasing the number of carbon links in the side chain, d) epimerising carbon-20, and e) introducing a phenylene linker group. Superimposed upon these is the more logical ("adaptational") approach to side chain modification involving:- 1) hybridisation of other sterol side chains onto vitamin D, 2) anticipation or blockade of known metabolic processes (which can be activating or deactivating) by i) incorporating an additional hydroxyl group, ii) modifying the hydroxyl by oxidation (or alkylation), iii) fluorine or alkyl substitution, iv) introducing a double or triple bond, or v) closing a ring, and, **importantly, 3) optimal combination of any or all of these isolated modifications** (including a-e !), most recently in the rational design of receptor probes by restricting the side chain conformation.



The development of some clinical candidates for cancer or other non-classical vitamin D related diseases will be described against this backdrop. In addition, the synthesis of the first members of a new active series ["f)"] of "double side chain" analogues based on II (in collaboration with J. Wicha's group) as receptor probes will be presented.



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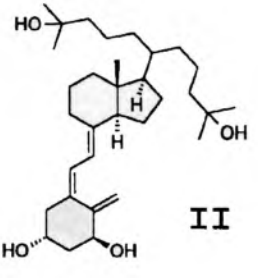


II

NITROSOCHLORIDES OF TERPENIC COMPOUNDS: SYNTHESIS AND APPLICATIONS

Aexey V. Tkachev

Novosibirsk Institute of Organic Chemistry, Novosibirsk 630090, Russia

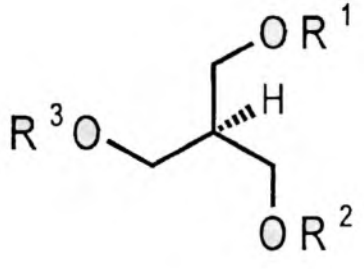
Nitrogen-containing derivatives of terpenes are of special interest from the view point of studying of their biological activity as well as of their use as intermediates in organic synthesis. Terpenoids represent one of the primary sources of chirality, so many nitrogen-containing terpenic compounds seem to be perspective precursors for available chiral reagents. Among the methods of preparation of different nitrogen-containing derivatives, addition of N-electrophilic reagents such as NOCl, N_2O_3, N_2O_4, etc., to olefins is one of the most important group of transformations. Reactions of these agents with terpenes usually result in crystalline adducts and so for a long time - for more than 100 years - these reactions have been used mostly for preparation of crystalline derivatives suitable for identification. Results of our recent research show that some of the well-known derivatives, especially nitrosochlorides and products of their further transformations, are promising group of nitrogen-containing terpenic derivatives and may be used in the syntheses of many interesting terpenoid-based molecules.

Stereochemistry of addition of NOCl to the most available terpenes (3-carene, α-pinene, limonene, α-terpineol, caryophyllene, humulene, α-muurolene, cembrene) and properties of the nitrosochlorides have been studied. Stability of the terpene nitroso-chlorides varies significantly and was found to depend on the stereochemistry of the addition. Low stability of some adducts coursed poor yields of the desired compounds prepared by traditional techniques, therefore methods of nitosochlorination of the terpenes have been improved so that to achieve the best yields of the adducts (80-95%). Reactions of nitrosochlorides with N-nucleophiles have been examined, a number of stable 1,2-bifunctional derivatives were synthesized in good yields (80-90%) and studied as intermediates in organic synthesis. The most important reaction of α-amino substituted oximes was found to be Bekman's type fragmentation that may be carried out in the case of many terpenoids under surprisingly mild conditions, yielding *seco*-derivatives such as ω-keto nitriles, ω-keto amidoximes and ω-aminonitriles in excellent yields. Based on nitrosochlorination of (+)-3-carene followed by the fragmentation, new syntheses of 1R-*cis*- and 1R-*trans*- chrysanthemium acids, 1R- and 1S- dihydrochrysanthemolactones, 1R-cis-chrysanthmylamine and its analogs have been developed. The *seco*-derivatives was used for the syntheses of a variety of new chiral fused heterocyclic systems of pyrazole, pyrazolinol, pyrimidine, isoquinuclidine and quinoxaline types.

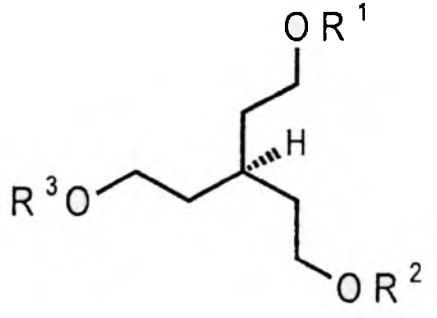
"Homochiral Building Blocks with High Symmetry for Terpene Synthesis."

Wolfgang Kreiser, Naturstoffchemie, Universität Dortmund, 44221 Dortmund, Germany.
E-mail: kreiser@citrin.chemie.uni-dortmund.de.

Compounds of type **I** and **II** are chiral, as long as their protective groups R differ. The former class has been adressed in the literature since 1990 for various reasons[1,2,3]. Apart from symmetrical beauty these molecules form ideal building blocks for synthesis, because by an identical sequence of reactions both enantiomers are accessable simply by reversing the mode of unprotection. Given one versatile stock compound of known absolute configuration, any required abs. configuration in a target may be achieved.



I



II

As a first step we report herein on the conventional preparation of one member of the **II** family in enantiomerically pure form (100 % e.e.) and a chemical correlation of ist absolute configuration.

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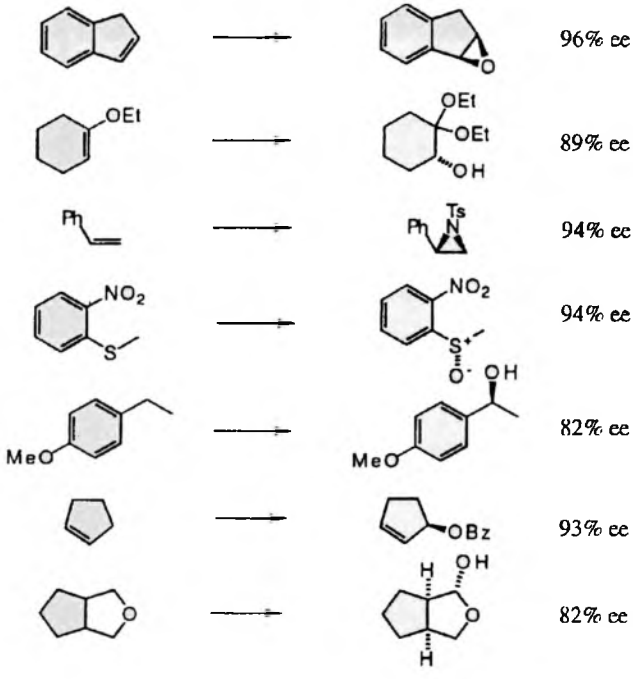
1) J. Ehrler, D. Seebach, Liebigs Ann. Chem. **1990**, 379.
2) G. Guanti, L. Banfi, E. Narisano, *J. Org. Chem.* 57, 1540 (1992).
3) H. Heidel, G. Huttner, R. Vogel, G. Helmchen, Chem. Ber. **1994**, 271.

Catalytic Asymmetric Oxidation Reactions

Tsutomu Katsuki
Department of Chemistry, Faculty of Science, Kyushu University, Fukuoka 812-81, Japan

Oxidation is a fundamental organic reaction and of high use in organic synthesis. Therefore, much attention has been devoted toward the stereocontrol of oxidation reactions but there is still a room for improvement. On the other hand, there exist various types of biological oxidation reactions which proceed with high stereospecificity. Most of these biological oxidations are catalyzed by oxidizing enzymes which carry a metallocomplex as an active site. This suggests that highly enantioface and enantiotopic-place selective oxidations can be realized in a chemical way by introduction of an appropriate metallocomplex as a catalyst. Along this line, we designed new metallocomplexes which were structurally related to the active sites of enzymes and examined asymmetric oxidation of various substrates with these complexes as catalysts. High enantioselectivity has so far been achieved in oxidation of double bond, hetero atom, and C-H bond and also in aziridination, as shown below. We will discuss in more detail about metal-catalyzed asymmetric oxidation in our paper.

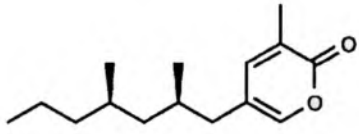


RECENT RESULTS IN THE SYNTHESIS OF BIOACTIVE NATURAL PRODUCTS

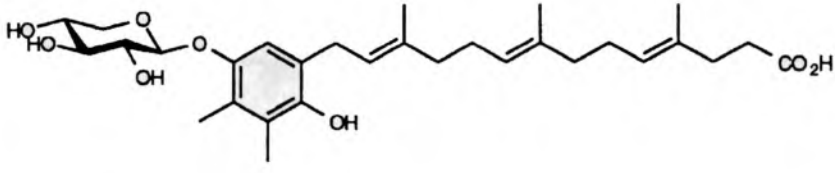
Kenji Mori

Department of Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka 1-3,
Shinjuku-ku, Tokyo 162, Japan
FAX +81-3-3235-2214

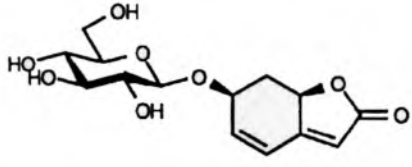
Synthesis and bioactivity of the following three compounds will be presented to illustrate the role of synthesis in natural products chemistry.



Supellapyrone (**1**), the sex pheromone of the brownbanded cockroach *Supella longipalpa*



Lurlenic acid (**2**), the sex pheromone of the green flagellate *Chlamydomonas allensworthii*

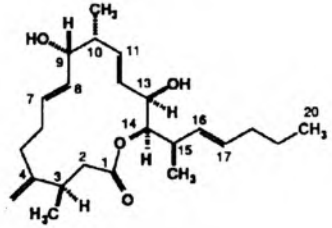


Phyllanthurinolactone (**3**), the leaf-closing factor of a nyctinastic plant *Phyllanthus urinaria*

Studies for the Synthesis of Marine Natural Products. New Developments for the Stereocontrolled Synthesis of Complex Macrocycles.

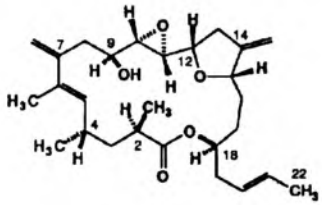
David R. Williams
Department of Chemistry, Indiana University, Bloomington, IN 47405, U.S.A.

The amphidinolides are a family of important biologically active macrolides isolated from the marine dinoflagellate *Amphidinium* sp., a symbiotic microalgae found in the Okinowan flatworm *Amphiscolops* sp. The amphidinolides have shown extraordinary activity against a variety of NCI tumor cell lines. Interestingly, this family of metabolites exhibits remarkable structural diversity with reported examples of amphidinolides A through P, illustrative of macrocycle formation ranging from fifteen-membered to twenty-six membered systems. Amphidinolide J was the first of the family in which the details of relative and absolute stereochemistry were defined. A route for total synthesis of Amphidinolide J will be presented. The discussion will focus on the applications of new methodologies which have afforded stereochemical control and efficient bond connections. Our efforts toward completion of the total synthesis of Amphidinolide K will be described. The presentation will explore asymmetric allylations in the context of enantioselective synthesis of a highly functionalized acyclic carbon framework.



Amphidinolide J

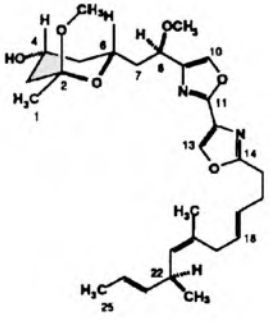
Kobayashi, J.; Sato, M.; Ishibashi, M.
J. Org. Chem. 1993, *58*, 2645.



Amphidinolide K

Ishibashi, M.; Sato, M.; Kobayashi, J.
J. Org. Chem. 1993, *58*, 6928.

These studies have led to an efficient synthesis of Hennoxazole A, a unique marine metabolite with antiviral activity. Finally, investigations toward the synthesis of the marine macrolide, Phorboxazole A, will illustrate a powerful strategy for stereocontrolled construction of tetrahydropyrans, and applications to C-linked nucleoside mimics.

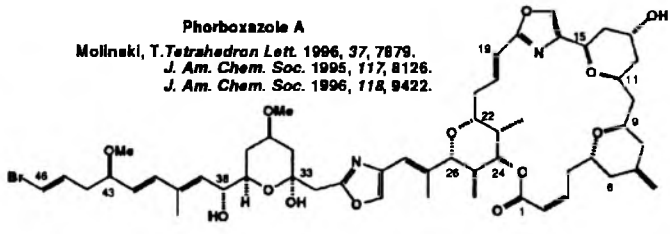


Hennoxazole A

Ichiba, T.; Yoshida, N.Y.;
Scheuer, P.J.; Higa, T.; Gravalos, D.G.
J. Am. Chem. Soc. 1991, *113*, 3173.

Phorboxazole A

Molinski, T. *Tetrahedron Lett.* 1996, *37*, 7879.
J. Am. Chem. Soc. 1995, *117*, 8126.
J. Am. Chem. Soc. 1996, *118*, 9422.

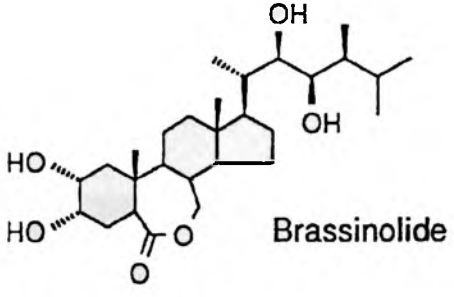


NEW DEVELOPMENTS IN THE CHEMISTRY OF BRASSINOSTEROIDS

Denise L. Baron,[1] Weide Luo,[1] Kazimierz Minksztym,[1] Suanne K. Nakajima,[1] Loeke Janzen,[2] Richard P. Pharis[2] and Thomas G. Back[1]

Departments of Chemistry[1] and Biological Sciences,[2] University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

A concise new synthesis of the plant growth-promoter brassinolide was achieved, in which the side chain with its four contiguous chiral centers was elaborated stereoselectively in just three steps. Variations of this approach provided access to a series of nuclear and side chain analogues, which were tested for bioactivity in the rice leaf lamina assay. They include derivatives designed to block metabolic deactivation in plants, with the objective of providing more persistent activity than offered by the naturally-occurring brassinosteroids. Observations concerning structure-activity relationships of these and other novel brassinosteroids will be reported.



Brassinolide

SYNTHESES VIA TERPENYLBORANES. 3(10)-CARENE, ALLYLIC ALCOHOLS, VINYLIC EPOXIDES AND DAMASCONES

Marek Zaidlewicz

Faculty of Chemistry, Nicolaus Copernicus University, Toruń, Poland

Several years ago we demonstrated that contrathermodynamic isomerization of olefins via allylic orgnoboranes is useful for the transformation of (+)-α-pinene into (+)-β-pinene without the loss of optical purity.[1)] The reaction sequence involves metalation – transmetalation – hydrolysis. This method has been extended for the transformation of (+)-2-carene into an elusive (+)-3(10)-carene and (–)-α-thujene into (+)-sabinene. The products are easily isolated in high purity and can also be selectively monodeuterated in the allylic position.

An allylic organoborane obtained from 1,3,3-trimethylcyclohexene was used as a key intermediate in the synthesis of γ-damascone. Short approaches to α-damascone via γ-pyronene and to β-damascenone via the Rupe rearrangement of 2,6,6-trimethyl-1-ethynyl-2-cyclohexenol have also been developed. The course of the rearrangement is strongly dependent on the reaction conditions. γ-Pyronene was prepared from β-pyronene by selective monoepoxidation, reduction of the epoxide with borane to 1,2,6,6-tetramethyl-2-cyclohexenol and its controlled dehydration.

Kinetic resolution of racemic vinylic epoxides derived from acyclic and cyclic 1,3-dienes by the reduction with terpenylboranes (Ipc_2BH, 2- and 4-Icr_2BH) was achieved.[2)] The isolation procedure is simple and both enantiomers of 40-55% ee can be obtained depending on the terpenylborane used. Absolute configuration of the optically active epoxides was readily established by the reduction with borane to the corresponding allylic alcohols of known configuration. The method provides epoxides of comparable or slightly lower enantiomeric excess to the products of catalytic monoepoxidation of 1,3-dienes developed recently by Jacobsen.[3)]

The terpenylboranes mentioned above of high optical purity were used for enantioselective synthesis of allylic cycloalkenols by monohydroboration of conjugated cycloalkadienes. An efficient procedure for the oxidation of allylic organoborane intermediates at low temperature was developed. The procedure provides a simple access to the product alcohols of 54-99 % ee.

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POSTER ABSTRACTS

LIGHT-INDUCED CAROTENOGENESIS IN *NEUROSPORA CRASSA*: COMPARISON OF CAROTENOID ACCUMULATION IN THE WILD TYPE AND IN THE TRANSPORT MUTANT *nap*.

T.A.Belozerskaya, Yu.V. Ershov, *T.V.Potapova
A.N.Bach Inst.Biochem., RAS, *A.N.Belozersky Inst. Physicochem. Biol., Moscow State Univesity, Moscow, Russia.

Excitation of a cryptochrome photoreceptor by light leads to the expression of carotenoid genes in *N.crassa* cells, and subsequently to the accumulation of neurosporaxanthin. Blue light treatment also brings about changes in ion permeability of the plasma membrane: decrease of membrane conductivity in first 2-5 min of illumination and plasma membrane hyperpolarization with the maximum on 25th-30th min of illumination. Previous investigations presented some prove that plasma membrane transport processes goverened by functioning of H^+-ATPase in the *N.crassa* cells are elements of the signal transduction chain leading to carotenoid biosynthesis (1). On the other hand electrophysiological investigation of different mutants has shown that the shift of the plasmalemma electrical properties can hardly be considered as an obligatory prerequisite for light-induced expression of carotenoid genes. To find out the role of plasma membrane transport shifts in carotenogenesis induced by light we performed a comparative investigation of ability to carotenoid accumulation in wild type and transport mutant *nap* (neutral and acidic amino acid permeability). After extraction and thin-layer chromatography carotenoids from both strains were identified spectroscopically. It was shown that a genetic damage of plasma membrane electrogenic mechanism and the impairment of membrane transport in *nap* provided accumulation twice as more carotenoids in comparison to the wild type. Neurosparaxanthin accumulated in larger quantities than the neutral carotenoids in both strains. Gamma-carotene, lycopene, 3,4-dehydrolycopene and torulene were identified in both strains. A presumed cause of the activated carotenogenesis in cells of the mutant *nap* is the increased ATP level resulting from the lowered plasma membrane H^+-ATPase activity.

1. T.A.Belozerskaya, M.S.Kritsky, V.Yu.Sokolovsky "Membrane Electrogenesis and the Problems of Cell Differentiation in Mycelial Fungi". Microbiologia, V. 64, N 3, pp. 245-249.

ESSENTIAL OIL OF *MINTHOSTACHYS SETOSA* (Briq.) Epl. (LAMIACEAE)

Felice Senatore

Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli "Federico II", Via D. Montesano, 49, 80131 Napoli, Italy

The genus *Minthostachys* (Lamiaceae) is a taxonomically complex genus of aromatic plants that comprises about twelve species and ranges belong the Andes from Venezuela to Argentina.[1] They are used as a condiment in foods, flavouring agent and, medicinally, in the treatment of respiratory diseases, as well as a stomachic, a digestive, a sedative, and as a topic anti parasitic and antimycotic.[2-4] *Minthostachys setosa* (Briq.) Epl., distributed in all the Peru and locally known as "*Arosh muña*", is an aromatic shrub, which grows wild along the roads and on slight slopes. The leaves and flower spikes are used as condiment in foods while in native folk medicine the decoction of the aerial parts is topically used for the scabies, as antimycotic and anti parasitic. Leaves are also used for medicinal tea with digestive, antidiarrhoic, vermifuge action, as antispasmodic for puerperal pains and for respiratory affections.[2] Therefore, in view of its local importance in traditional medicine the aim of this research is to increase the knowledge of the chemical composition of the essential oil of *M. setosa* aerial parts. The essential oil from the aerial parts of *M. setosa* collected near Lima, Perú, was obtained by hydrodistillation. Preliminary GC-MS analyses showed that monoterpene ketones are the main component of the oil.

1. C. Epling, C. Játiva, *Brittonia* **15**, 366 (1963).
2. V. De Feo, *Fitoterapia*, **63**, 417 (1992).
3. Girault, L. (1984) in: Kallawaya, Guérisseurs Itinérants des Andes, Ed. de l'ORSTOM, Paris.
4. White, D. (1985) in: Herbs of Ecuador, Ediciones Libri Mundi, Quito.

CHEMICAL COMPOSITION OF ARTEMISIA SUBCHRYSOLEPIS FILAT.

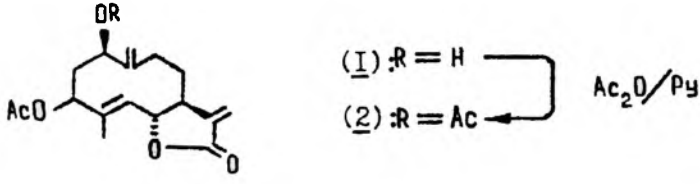
Arman T.Kulijasov[1], Talgat S.Seitembetov[1], Koblandy M.Turdybekov[2], Tanzila T.Edilbaeva[2], Sergazy M.Adekenov[1].

[1]Institute of Phytochemistry MS-AS RK, Karaganda, Rebublic of Kazakhstan

Fax (3212) 51 10 23. E-mail: kms @ phyto. karaganda. su

[2]Institute of Organic Synthesis and Coal Chemistry MS-AS RK,

From aerial part of Artemisia subchrysolepis Filat. three compounds were isolated and identified as β-sitosterine, α-santonin and a new sesquiterpene lactone-subchrysin (1).



Subchrysin (1) is a colourless crystalline compound (m.m.p.= 149-151° C, $[\alpha]_D$+140°) with composition $C_{17}H_{22}O_5$.

Treatment of (1) by Ac_2O/Py afforded acetate (2). (m.p. = 65-68°C, $[\alpha]_D$+200°).

The IR spectrum of (1) showed a γ–lactone band at 1760cm^{-1},ester band at 1720 cm^{-1}, OH band at 3460 cm^{-1}. The IR spectrum of (2) showed absense of OH band.

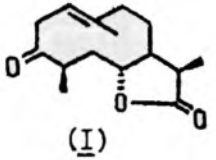
The ^{1}H NMR spectrum exhibited broad singlet of H-15 methyl protons at 1.72 ppm, acetate methyl group at 2.04 ppm. The lactone proton H-6 was at 4.41 ppm as triplet with J=10HZ. The broad doublet at 5.18ppm (J=10HZ) indicated to the proton H-3 being geminal to acetyl group. The protons H-14 appeared at 4.92ppm and 5.24 ppm as broad singlets. The olefinic proton H-5 was at 5.39 ppm as doublet with J=10HZ. The protons H-13, H-13^I appeared at 5.44ppm and 6.17 ppm as doublets with J=3,4 HZ.

Relative stereostructure of (1) was determined by X-ray analysis as 1β-hydroxy-3β-acetoxy-6β(H), 7α(H)-germacr-4(5), 10(14), 11(13)-triene-6,12-olide.

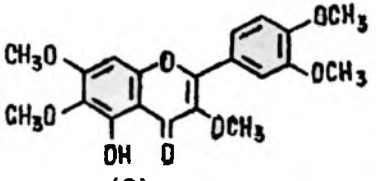
PHYTOCHEMICAL INVESTIGATION OF AJANIA FRUTICULOSA.

Arman T.Kulijasov, Talgat S.Seitembetov, Sergazy M.Adekenov.
Institute of phytochemistry MS-AS RK, Karaganda, Republic of Kazakhstan
E-mail: kms @ phyto. karaganda. su

From aerial part of Ajania fruticulosa according to procedure described by Yusupov M.I.[1], two substances were isolated and identified as sesquiterpene lactone - ketopelenolide "b" (1) and flavonoid - artemisetin (2).



(I)



(2)

The structure of (1) was determined on the basis of comparison the physical and spectral data with the ones from literature [2]. The structure of (2) has been proved by ^{1}H NMR-spectroscopy and by comparison of IR-and UV-spectra with literature ones [3].

LITERATURE:

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3. Belenovskaya L.M., Markova L.P., Nadezhina E.P.,Ligai U.// Chim. prirod. soedin.-1977.-№ 4, pp. 575-576.

NEW ISOLACTARANE SESQUITERPENES, THEIR STRUCTURE AND ANTIFEEDANT ACTIVITY

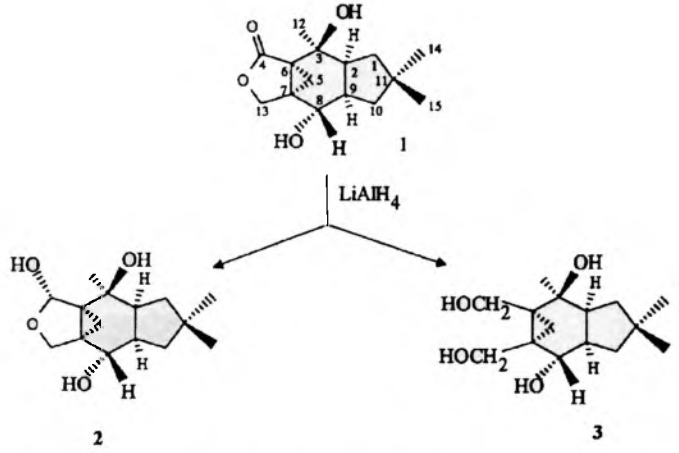
By W.M. Daniewski[1], M. Gumułka[1], E. Błoszyk[2], B. Drożdż[2], U. Jacobsson[3] and T. Norin[3].

[1]Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw Poland.

[2]Department of Medicinal Plants, Academy of Medicine, 60623 Poznań Poland.

[3]Royal Institute of Technology, Department of Chemistry, Organic Chemistry, SE-100 44 Stockholm Sweden

In seeking for antifeedants of natural origin we reduced Isolactarorufin (**1**) with $LiAlH_4$ and obtained two compounds (**2** and **3**) which were separated by chromatography. Structures of these compounds were established by exhaustive spectroscopic measurements and X-ray analysis.



Compound **2** possessed a hidden aldehyde group. Both compounds showed only moderate antifeedant activity against storage pests *Tribolium confusum*, *Trogoderma granarium* and *Sitophylus granarius.*

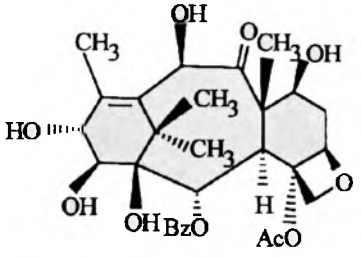
ANTIFEEDANT ACTIVITY OF CONSTITUENTS OF *TAXUS BACCATA*

By W. Anczewski[1], W.M. Daniewski[1], M. Gumułka[1], E. Błoszyk[2], B. Drożdż[2],

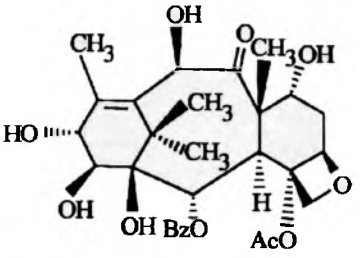
[1]Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw Poland.

[2]Department of Medicinal Plants, Academy of Medicine, 60623 Poznań Poland.

Known resistance to insect pests[1] of *Taxus baccata* prompted us to isolate its constituents of leaves and to check their antifeedant activity. The methylene chloride extract, which showed moderate activity against storage pests (*Tribolium confusum, Trogoderma granarium* and *Sitophylus granarius)*, was separated into various fractions whose activity was evaluated. From the most active fractions pure compounds were isolated and their structures identified. Subsequently the antifeedant activity of the compounds was measured, and among them the most active were the following:



10-deacetyl baccatin III



10-deacetyl baccatin V

Literature.

1. Fitoterapia Suppl.. al No. 1 - 1993 (vol. LXIV)

AN IN VITRO AND IN VIVO ANTIVIRAL ACTIVITY OF SESQUITERPENES, OF *LACTARIUS* ORIGIN

By M. Kobus[1], E. Piotrowska[1], M. Przybylski[1],
W.M. Daniewski[2], M. Gumułka[2], M. Łuczak[1].

[1]Department of Virology, Medical University, Chałubińskiego 5, 02-004 Warsaw, Poland
[2]Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw Poland.

Sesquiterpenes of *Lactarius* origin possessing marasmane, isolactarane and lactarane skeletons were isolated from mushrooms of *Lactarius* family by various techniques including extractions and preparative HPLC. Their antifeedant properties against storage pests were reported [1]. Now we would like to report antiviral activity of some of these compounds: isovelleral and isovellerol with marasmane skeleton, isolactarorufin and ketoisolactarorufin with isolactarane skeleton, 8,9-epifurandiol, lactarorufin A and lactarorufin B with lactarane skeleton. The toxicity of all these compounds was estimated using Vero and GMK cell lines. Sesquiterpenes with isolactarane and lactarane skeletons showed low toxicity. For in *vitro* assays of antiviral activity the following viruses were used: HSV 1, EMC and VSV. The activity of the above mentioned sesquiterpenes was estimated in three systems: before, during and after inoculation of the cell cultures with a virus. The results obtained indicated the inhibitory effect of isovellerol at the concentration of 0.005 μM against HSV 1 and lactarorufin A at the concentration of 1.9 mM against HSV 1 and EMC. NMRI mice were infected with HSV 1 for in *vivo* assays and the compounds were administered intraperitoneally every day. There has been a significant effect (decreased mortality, prolonged survival) after administration of sesquiterpenes with a marasmane skeleton. After intranasal infection of the 12-day old mice and daily administration of 5 μg of isovellerol mice mortality was 50%. After intraperitoneal inoculation of 6 weeks old mice and daily administration of 15 μg of isovelleral the mortality was 40% in comparison to 100% in the control groups. Considering the biology of sesquiterpenes and the results obtained to date in our own experiments one can presume with a high probability that these compounds are promising group with a potential antiviral activity.

[1] W.M. Daniewski, M. Gumułka, D. Przesmycka, K. Ptaszyńska, E. Błoszyk and B. Drożdż. *Phytochemistry* **38**, 1161 (1995).

A SESQUITERPENE LACTONE GLYCOSIDE FROM *LACTUCA TATARICA*

Wanda Kisiel and Barbara Barszcz

Department of Phytochemistry, Institute of Pharmacology,
Polish Academy of Sciences,
31-343 Kraków, Poland

Lactuca tatarica C. A. Meyer (*Asteraceae*) is widely distributed in central Asia. In previous paper [1], we reported on the occurrence of eleven sesquiterpene lactone aglycones and glycosides in the ethanol extract of the fresh roots of the plant.

A further study of the same extract allowed the isolation of another sesquiterpene lactone glycoside from the more polar chromatographic fractions. The compound was found to be a new plant constituent which was characterized as 3β,11β,14-trihydroxy-11,13-dihydrocostunolide-3-O-β-glucopyranoside on the basis of spectral analysis (ESMS, 500.13 MHz ^{1}H NMR, ^{1}H-^{1}H COSY).

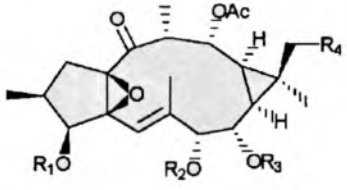
1. Kisiel W., Barszcz B., Szneler E., Phytochemistry 1997, 45, 365-368

NEW LATHYRANE POLYESTERS FROM THE LATEX OF *EUPHORBIA ABYSSINICA*

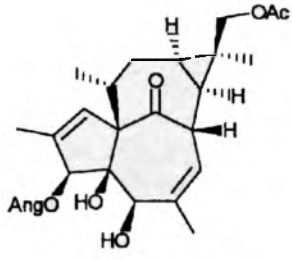
J.A. Marco, M. Carda, F.J. Ropero and F.J. Checa

Department of Organic Chemistry, University of Valencia, c/D. Moliner, 50, E-46100 Burjassot, Valencia, Spain; Tfn. No. +34-6-3864337; E-Mail: alberto.marco@uv.es

As a part of our current interest[1-3] in the chemistry of the genus *Euphorbia*, we have now investigated the composition of the irritant latex from the species *Euphorbia abyssinica* J.F. Gmel. By using a combination of various chromatographic methods, we were able to isolate copious amounts of widespread triterpenes (euphol, euphorbol) as well as small amounts of several lathyrane esters **1-5** of the ingol type, which bear acyl residues of various types attached to the different hydroxyl groups. Furthermore, the known ingenol derivative **6** was also found. The structures of these products have been established with the aid of spectroscopic methods, mainly one- and two-dimensional NMR spectroscopy.



1 $R_1 = R_3 = Ac$ $R_2 = Tigl$ $R_4 = H$
2 $R_1 = Ac$ $R_2 = H$ $R_3 = Tigl$ $R_4 = H$
3 $R_1 = Ac$ $R_2 = R_3 = Tigl$ $R_4 = OH$
4 $R_1 = Ac$ $R_2 = H$ $R_3 = Tigl$ $R_4 = OAc$
5 $R_1 = R_2 = H$ $R_3 = Tigl$ $R_4 = OAc$



6

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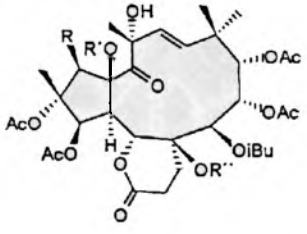
1.- J.A. Marco, J.F. Sanz-Cervera, A. Yuste, J. Jakupovic, J. Lex, *J.Org.Chem.* **1996**, *61*, 1707.
2.- J.A. Marco, J.F. Sanz-Cervera, A. Yuste, J. Jakupovic, *Phytochemistry* **1997**, in press.
3.- J.A. Marco, J.F. Sanz-Cervera, A. Yuste, *Phytochemistry* **1997**, in press.

NOVEL BISHOMODITERPENE LACTONES FROM *EUPHORBIA TERRACINA*

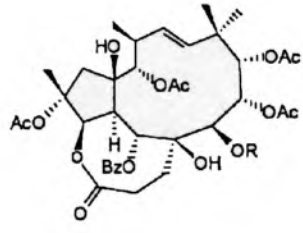
M. Carda, J.A. Marco, A. Yuste, J.-F. Sanz-Cervera and J. Jakupovic

Department of Inorganic and Organic Chemistry, University Jaume I, Campus Ctra. Borriol, E-12080 Castellón, Spain; Tfn. No. +34-64-345787; E-Mail: mcarda@qio.uji.es

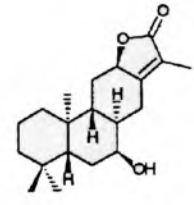
As a part of our current interest in the chemistry of the genus *Euphorbia*, we have recently published our initial results in the investigation of the Mediterranean species *Euphorbia terracina* L.[1-3] We described the isolation and structure elucidation of eleven new jatrophane derivatives, a novel rearranged jatrophane and seven bishomoditerpene lactones (terracinolides), which display the novel 17-ethyljatrophane framework. We now report the isolation of four further more highly oxygenated terracinolides **1-4**, two related eight-membered C_{22} lactones (isoterracinolides) **5-6**, and a new diterpene lactone **7** of the jolkinolide type. The structures of all these products have been established with the aid of spectroscopic methods, mainly one- and two-dimensional NMR spectroscopy.



1 R = R' = H R'' = Ac
2 R = H R' = R'' = Ac
3 R = R' = H R'' = Bz
4 R = OAc R' = H R'' = Ac



5 R = iBu
6 R = Prop



7

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2.- J.A. Marco, J.F. Sanz-Cervera, A. Yuste, J. Jakupovic, *Phytochemistry* **1997**, in press.

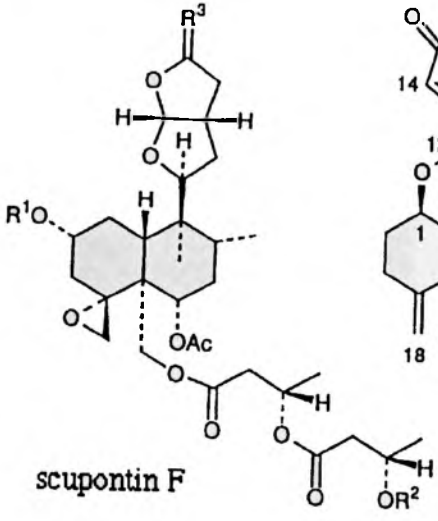
3.- J.A. Marco, J.F. Sanz-Cervera, A. Yuste, J. Jakupovic, F. Jeske, *Phytochemistry* **1997**, submitted.

NEOCLERODANE DITERPENOIDS FROM SCUTELLARIA PONTICA AND SCUTELLARIA POLYODON

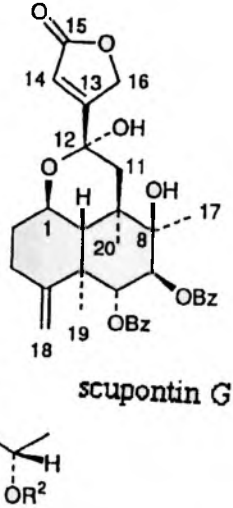
Franco Piozzi[1], Maurizio Bruno[1,2], Benjamin Rodriguez[3], Maria C.de la Torre[3], Maria L.Bondi[2] and N.Vassallo[2]

1. Dipartimento Chimica Organica, Università di Palermo, Italy
2 I.C.T.P.N.-C.N.R., Palermo, Italy
3 Instituto Quimica Organica General, C.S.I.C., Madrid, Spain

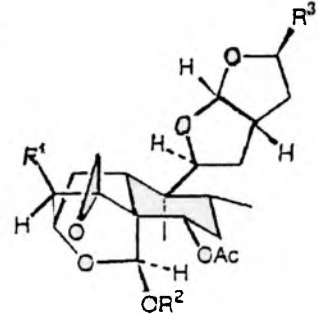
In continuation of our studies on *Scutellaria* plants for the search of neoclerodanes with insect antifeedant activity, we isolated from *S.pontica* seven novel products, scupontins A-G, and from *S.polyodon* nine new compounds, scupolins A-I.
The structure of scupontin F is remarkable for the occurrence of a long acylic chain at C-19, i.e.
(3'S, 3"S, 3"'S)-3'-[3"-(3"'-hydroxybutyryloxy)butyryloxy]butyryloxy).
The absolute configuration of scupontin G was established by the CD exciton chirality method.
Some of the scupolins show the 2α,19 hemiacetalic bridge already observed in other neoclerodanes from *Scutellaria* species.

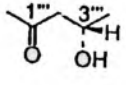


scupontin F



scupontin G



R¹	R²	R³
H		H,OH(*)

scupolin G

R¹	R²	R³
OH		H

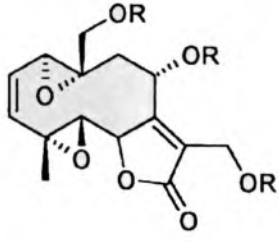
Bactericidal Sesquiterpene Lactones from *Vernonia fastigiata* (Asteraceae)

G. Roos, I. Klaiber, B. Vogler, U. Walter, W. Kraus

University of Hohenheim, Department of Chemistry, 70593 Stuttgart, Germany

Asteraceae are well known for their biological and pharmacological properties, often due to their content of sesquiterpene lactones. Considering this chemotaxonomic characteristics, 19 Asteraceae, collected in Namibia, were screened for their biological activities.

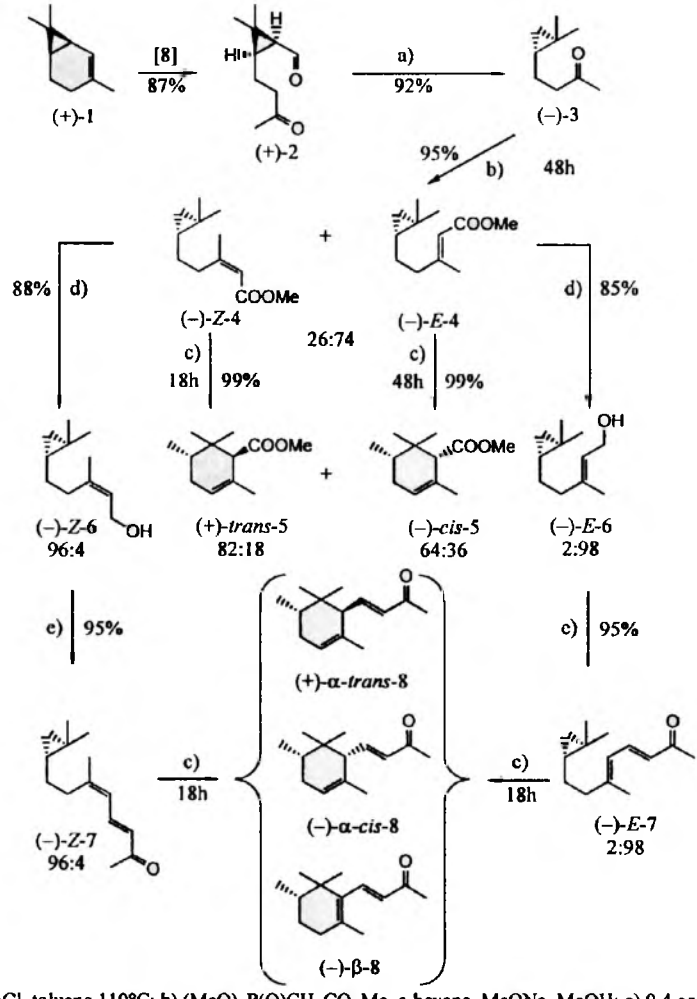
On the example of *Vernonia fastigiata* we demonstrate the efficacy of a bioassay guided isolation in combination with on-line spectroscopic methods like LC-MS and LC-NMR.
The preliminary purification via Rotational Locular Counter Current Chromatography (RLCCC) was the crucial step for the separation of the bactericidal compounds of the structure type shown below. Consecutively it was possible to assign the structures of nine sesquiterpene lactones responsible for the bactericidal activity of the crude extract against *Bacillus subtilis*, five of them not being described before.



OPTICALLY ACTIVE α-5-METHYLCYCLOGERANATE METHYL ESTERS AND IRONES FROM (+)-Δ^3 AND Δ^4-CARENE

by Christian Chapuis*, Michel Barthe, Wolfgang Giersch, Karl H. Schulte-Elte and Günther Ohloff
Firmenich SA, Corporate R&D, P.O.Box 239, CH-1211 Geneva 8

Scalemic methyl α-*cis*/*trans*-5-methyl-cyclogeranate **5** [1] and mixtures of α-*cis*/*trans*/β-irones **8** [2] were obtained with substantial racemisation (1-29 % e.e.) by $SnCl_4$ cyclisation of new optically pure acyclic precursors ((-)-Z or (-)-E-**4**; (-)-E, Z- or (-)-E, E-**7**). Similarly, the optically pure ketone (-)-**3**, available from (+)-Δ^4-carene by an ozonolysis, deformylation sequence, is also a new chiron. An alternative approach starting from (+)-Δ^3-carene is also presented.



a) $(Ph_3P)_3RhCl$, toluene 110°C; b) $(MeO)_2P(O)CH_2CO_2Me$, c-hexane, MeONa, MeOH; c) 0.4 equiv. $SnCl_4$, toluene 0°C; d) $LiAlH_4$, Et_2O; e) $Al(OiPr)_3$, acetone.

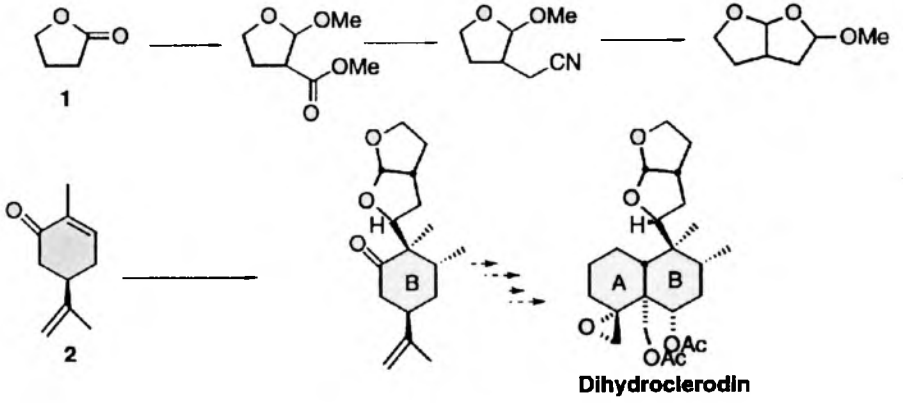
[1] C. Chapuis, K. H. Schulte-Elte, *Helv. Chim. Acta*, **1995**, *78*, 165.
[2] K. H. Schulte-Elte, H. Pamingle, A. P. Uijttewaal, R. L. Snowden, *Helv. Chim. Acta* **1992**, *75*, 759.

STUDIES TOWARDS THE TOTAL SYNTHESIS OF INSECT-ANTIFEEDANT DIHYDROCLERODIN

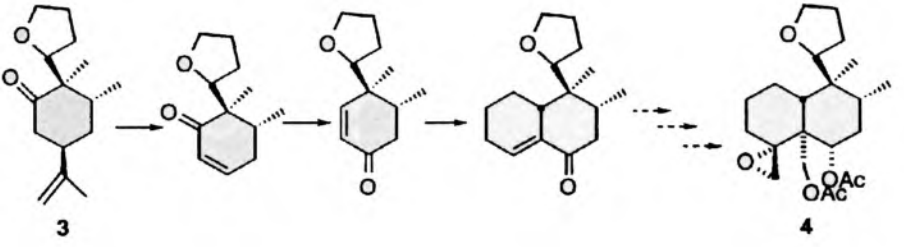
Tommi M. Meulemans, G. A. Stork, B. J. M. Jansen, and Æde de Groot

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

Clerodanes have a wide variety of biological activities. One of them, probably the best known, is the insect-antifeedant activity. Dihydroclerodin and similar clerodanes have been shown to be very potent antifeedants. The aim of this research project is the total synthesis of dihydroclerodin with R-(-)-carvone (**2**) as homochiral starting material. Starting from γ-butyrolactone (**1**) the furofuran part is synthesised and methods to couple this fragment to ring B have been devoleped. This pathway provides the right stereochemistry at all chiral centers obtained.



Also model compound **3** was synthesised in order to find a pathway to obtain a *trans* decalin system with chemical handles to synthesise model compound **4.**

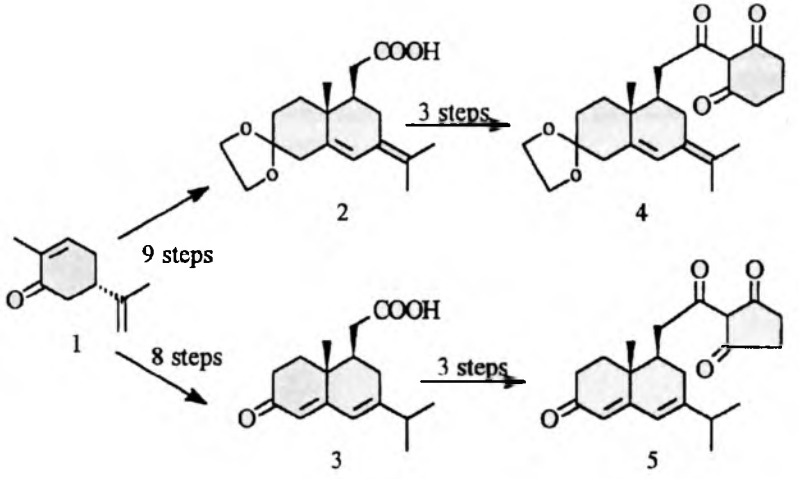


NEW SECO-STEROIDS OF β-TRICARBONYL STRUCTURE. TOTAL SYNTHESIS STARTING FROM S-(+)-CARVONE

Olga V GULYAKEVICH, Aede de GROOT*, Vladimir A. KHRIPACH

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus
* Wageningen Agricultural University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

New 8,14-seco-steroids of normal and D-homo-series having β-tricarbonyl moiety in their structure have been synthesised starting from S-(+)-carvone **1** *via* chiral decalones and their carboxylic derivatives **2** and **3** obtained in accordance with the approach elaborated earlier[1].



The transformations of **2** to **4** and **3** to **5** have been done *via* corresponding acid chlorides which were used as acylation agents in the reactions with cyclic diketones (1,3-cyclohexanedione and 1,3-cyclopentanedione). Resulting enolacylates of diketones were further rearranged into the triketones **4** and **5** under the action of 4-dimethylaminopyridine.

Reaction conditions, chemical, and spectral properties of the compounds synthesised will be discussed.

[1] A. A. Verstegen-Haaksma, H. J. Swarts, B. J. M. Jansen, A. de Groot, Tetrahedron, 1994, v. 50, p. 10095-10101.

BIOTRANSFORMATION OF GERMACRANE SYNTHONS BY CHICORY (*CICHORIUM INTYBUS*)

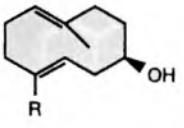
Dennis P. Piet, Maurice C.R. Franssen and Æde de Groot

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

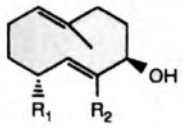
The edible sprouts of the chicory (witlof, *C. intybus*) are appreciated for their bitter taste. Guaiane lactones like lactucin (**1**), 8-deoxylactucin (**2**) and lactucopicrin (**3**) are responsible for this bitter taste. The roots are currently a waste product and mainly serve as cattle feed. This makes the root a cheap and interesting starting material for the elucidation of the biosynthesis of the bitter principles in chicory. In order to study the substrate specificity of cyclising enzymes in chicory, natural germacranes as well as germacrane synthons were exposed to a chicory root homogenate. By studying these model cyclisation reactions, parallels can be drawn to the biosynthesis of guaiane lactones and other bitter principles in chicory.

Studies (carried out by AB-DLO) using ^{3}H-labeled farnesylpyrophosphate (FPP,**4**) revealed that germacrene A (**5**) is an intermediate in the biosynthesis of bitter principles in *C. intybus*. Some examples of enzyme-mediated cyclisation reactions will be presented as well as a tentative biosynthesis of the bitter tasting guaiane lactones in the chicory.

Germacrane synthons:

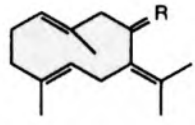


R = - H
R = - CH_3

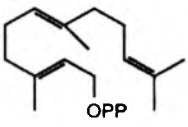


R_1 = - H; R_2 = - H
R_1 = - H; R_2 = - CH_3
R_1 = - CH_3; R_2 = - H

Germacrone derivatives:

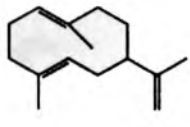


R = O
R = - H_2

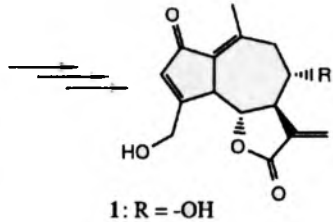


4

C. intybus



5



1: R = -OH
2: R = - H
3: R = *p*-OOCCH$_2$C$_6$H$_4$OH

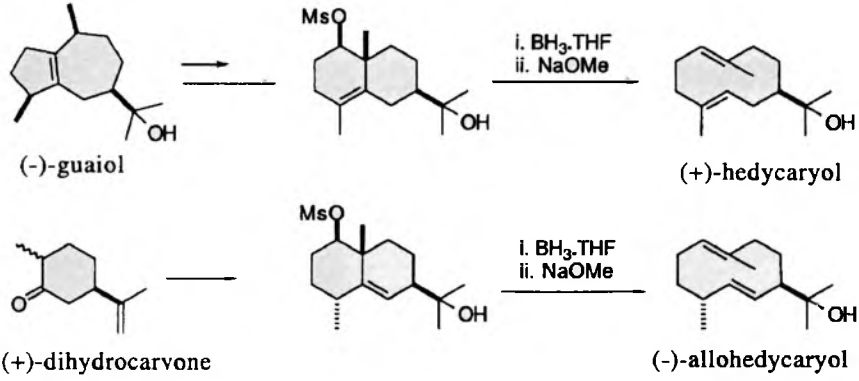
THE SYNTHESIS AND BEHAVIOUR OF GERMACRANES. SESQUITERPENES CONTAINING A TEN MEMBERED RING

A. J. Minnaard, J. B. P. A. Wijnberg, and Æde de Groot

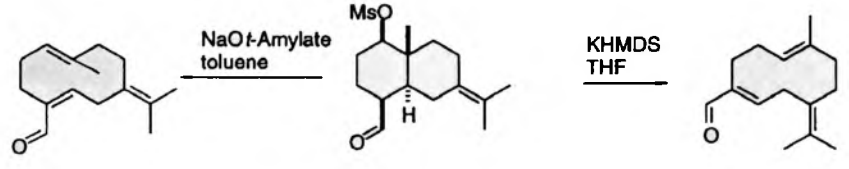
Laboratory of Organic Chemistry, Wageningen Agricultural University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

The germacranes make up one of the largest classes of sesquiterpenes and they are precursors in the biosynthesis of several other classes of sesquiterpenes. Germacranes possess a flexible but quite strained cyclodecadiene system as main characteristic.

We have developed new synthetic routes toward germacranes using various forms of the Grob-fragmentation (a 1,3-elimination). Applied to properly functionalised decalin systems, this reaction gives the desired cyclodecadienes. Using such a fragmentation, we have synthesised natural (+)-hedycaryol, starting from (-)-guaiol [1] and (-)-allohedycaryol starting from (+)-dihydrocarvone [2]. By studying the chemical behaviour of this compounds, a test hypothesis was proposed for biosynthetic routes of sesquiterpenes.



Grob-fragmentation of aldehyde-enolates leads to the *trans,trans*-germacrane skeleton in which the methyl group at C(4) is functionalised. It is known from the literature, and confirmed by us, that these systems are quite reactive and easily escape isolation from the reaction mixture. Depending on the structure of the C(7) side-chain, we have found conditions which allow the synthesis of either the *trans,trans*- or *trans,cis*-cyclodecadienes [3].



1) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, Ae., *Tetrahedron* **1994**, *50*, 4755.
2) Zhabinskii, V. N.; Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, Ae., *J.Org.Chem.* **1996**, *61*, 4022.
3) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, Ae., *J.Org.Chem.* (submitted).

A NEW APPROACH TO THE LACTARANE SKELETON. TOTAL SYNTHESIS OF FURANETHER B

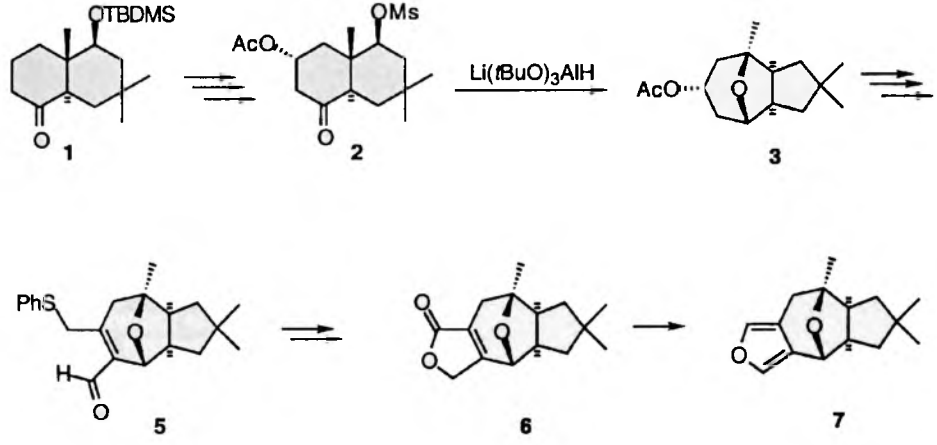
Roel P. L. Bell, Joannes B. P. A. Wijnberg, and Æde de Groot

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

Furanether B (**7**) a sesquiterpene possessing a lactarane skeleton, has been isolated from the mushroom *Lactarius scrobiculatus* in 1980 [1]. Furanether B and other lactarane sesquiterpenes are formed when the flesh of the mushroom is injured. These sesquiterpenes often possess interesting physiological activities like antifeedant, antifungal, antibacterial and insecticidal activity.

At our laboratory a new route toward [7+5] annulated ring systems has been developed via base-induced rearrangement of suitably functionalized decalin systems [2]. We haveused this method in the total synthesis of furanether B. The key step in this synthesis is the rearrangement of mesylate **2** to the cyclic ether **3** under the influence of $Li(tBuO)_3AlH$ in refluxing toluene

Conversion of the acetate function in **3** into annulated butenolides and furanes completes the total synthesis of furanether B (**7**).



[1] Battaglia, R.; DeBernardi, M.: Fronza, G.; Mellerio, G.; Vidari, G.; Vita-Finzi, P. *J. Nat. Prod.* **1980**, *43*, 319.

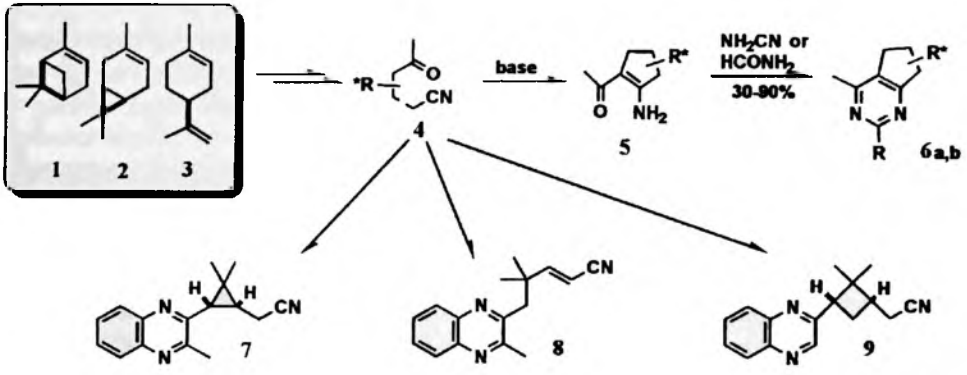
[2] Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, Æ. *J. Org. Chem.* **1990**, *55*, 941.

SYNTHESES OF CHIRAL FUSED PYRIMIDINE AND QUINOXALINE-TYPE HETEROCYCLES FROM NATURAL TERPENOIDS.

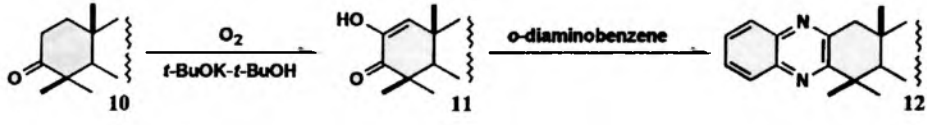
Sergey A. Popov, Alexander V. Korovin, Alexey V. Rukavishnikov, Aexev V. Tkachev

Novosibirsk Institute of Organic Chemistry, Novosibirsk 630090, Russia

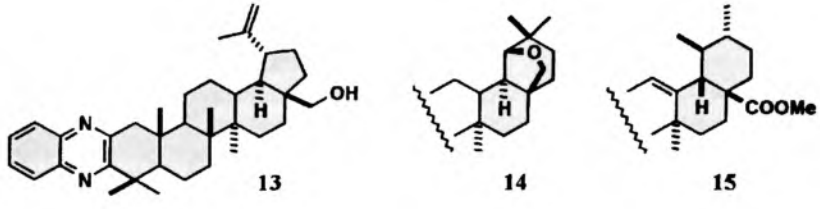
Natural monoterpenes α-pinene (**1**), 3-carene (**2**) and limonene (**3**) were transformed to the *seco*-derivatives **4** by known method. Keto nitriles **4** undergo intramolecular cyclization to give enaminones **5** that can be easily converted to pyrimidine (**6a**, R=H) or aminopyrimidine (**6b**, R=NH_2) derivatives. Bromination of ketonitriles **4** followed by treatment with *o*-diaminobenzene results in the formation of quinoxaline derivatives **7-9** in 36-50%:



3-Keto derivatives of pentacyclic triterpenoids may be also converted to fused quinoxaline-type compounds by the following reaction sequence:



According to this scheme, betulin, allobetulin and ursolic acid methyl ester were transformed to quinoxalines **13**, **14** and **15** respectively.



SYNTHESIS OF (3*R*) AND (3*S*)-GERANYLLINALOOL

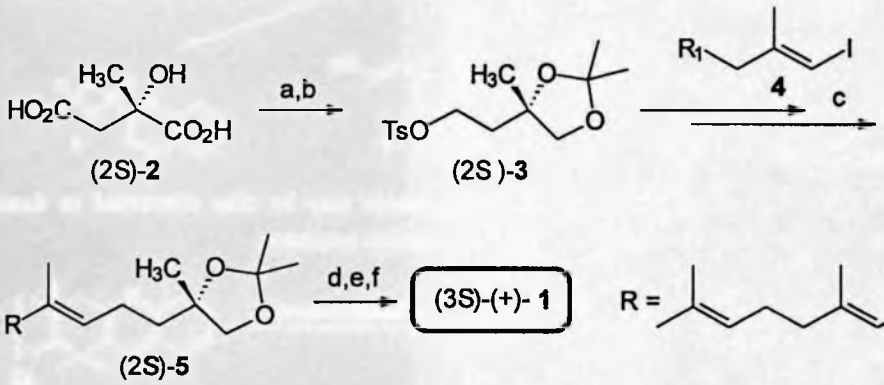
Aleš Svatoš, Klára Urbanová, and Irena Valterová

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic.

A diterpenic alcohol geranyllinalool (**1**) is one of compounds present in labial gland secretions of males' bumble bees. Males use this secretion (a marking pheromone) for marking theirs territories during patrolling flights to attract conspecific females for mating.

(3*S*)-(+)-**1**: $R_1 = CH_3$, $R_2 = OH$ (3*R*)-(-)-**1**: $R_1 = OH$, $R_2 = CH_3$

The presented synthesis of geranyllinalool enantiomers were performed in 7 steps from commercially available enantiomers of citramalic acid (**2**) which was converted to protected tosylate (**3**). Another synthon, the 1-alkenyl-1-iodide (**4**) was prepared from geranyl bromide according previously published procedure[1]. The synthons **2** and **4** were coupled using higher-ordered cuprate chemistry affording **5** which after deprotection, Swern oxidation and Wittig reaction yielded pure enantiomers of geranyllinalool.



a) $BH_3.Me_2S$ /THF; acetone/$CuSO_4$/TsOH; b) TsCl, KOH, c) CuCN, (2-thienyl)Li; *t*-BuLi (2 equiv.), **3**; d) PPTS, CH_3OH, e) ethyldiisopropylamine, DMSO, Py.SO_3 complex, f) H_3CPPh_3Br, *n*-BuLi

The synthesis allowed to assign the absolute configurations of previously isolated samples of **1** from a pine. Currently we are working on the determination of the absolute configurations of **1** in bumble bees marking pheromone.

1. Valterová I., Svatoš A., Hovorka O.: Collect. Czech. Chem. Commun. *61*, 1501 (1996).

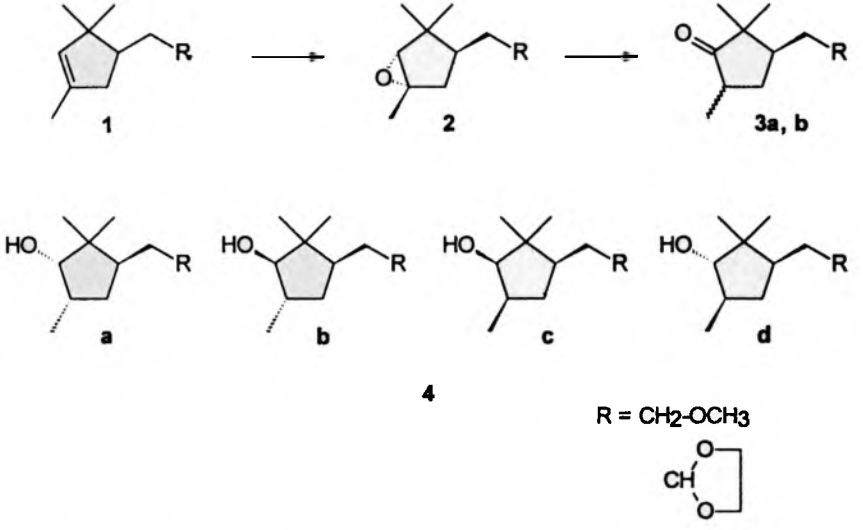
Financial support: Grant Agency of the Czech Republic, grant No. 203/95/0269.

REDUCTIONS OF FENCHOLENIC EPOXIDES

I. Sprung, K. Anhalt, K. Schulze

Institute of Organic Chemistry, University of Leipzig,
Talstraße 35, D-04103 Leipzig, Germany

In context with structure-activity relationship of sandalwood odorants we achieved the preparation of fencholenic compounds **(1)** [1]. Especially, we are interested in oxygen functionality of the five membered rings of fencholenic derivatives.
With different methods of epoxidation fencholenic system **(1)** afforded the *trans*-epoxides **(2)**.
Epoxides are extremely useful for further elaboration since their ring opening allows the formation of oxygen functionalized five membered rings. Therefore, we studied the rearrangement and the reduction of the *trans*-epoxy derivatives **(2)**. As a result of the rearrangement we got the two diastereomeric ketones **3a,b** [2]. Furthermore, the alcoholes **4a** are accessable by reduction [3].



The corresponding diastereomeric alcoholes **4b-d** were prepared by reduction of the ketones **3a,b** and by hydroboration of the fencholenic compounds **(1)**.

[1] K. Schulze, A.-K. Habermann, H. Uhlig, L. Weber, R. Kempe; Liebigs Ann. Chem. **1993**, 987
[2] K. Schulze, A.-K. Habermann, H. Uhlig, K. Wyßuwa, U. Himmelreich; Journ. Prakt. Chem. **1993**, 335, 363
[3] M.N. Rerick and E.L. Eliel; J. Am. Chem. Soc. **1962**, 84, 2356

TERPENIC ALCOHOLS - SOURCE OF CHIRALITY IN CONDENSING REAGENTS*

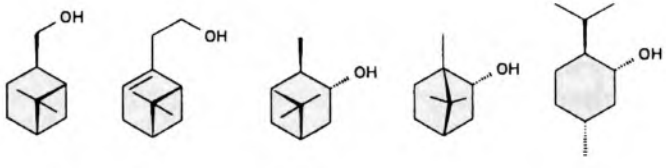
Z. J. Kaminski[a], B. Kolesińska[a], S. W. Markowicz[a], K. Pokrzeptowicz[a] and M. L. Główka[b], D. Martynowski[b].

[a] *Institute of Organic Chemistry;* [b] *Institute of General and Ecological Chemistry*
Technical University Of Łódź, Żwirki 36, 90-924 Łódź, POLAND

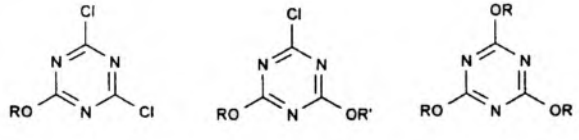
The presence of three chlorine atoms makes cyanuric chloride an interesting template for attachment of chiral residue, affording chiral auxiliaries prone to react with various kinds of nucleophilic reagents.

Achiral alkoxychloro-1,3,5-triazines are recognized as effective coupling agents[1] in forming of the ester- or amide- type bonds through the "superactive[2] triazine esters". Their analogs - derivatives of chiral alcohols, may appear promising reagents being of a great use for stereodifferentiating syntheses.

Using several easily available alcohols (**1** ÷ **5**) as the sources of chirality, we have obtained and fully characterized 1,3,5-triazines of types **I** and **II**. We have also obtained sterically hindered trimentoxy-1,3,5-triazine **III**. The X-ray analysis of its crystal established the arrangement of the menthoxy residues towards the triazine ring.



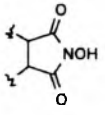
1 **2** **3** **4** **5**



I **II a,b** **III**

I: ROH = 1,2,3,4,5; III: ROH = 5

II: a) ROH = R'OH = 1,2,3,4,5; b) ROH = 1,2,3,4,5; R'OH = Alkyl-OH,



In the specific case of peptide synthesis chloro-terpenoxy-1,3,5-triazines **I** and **II** has been found good coupling agents for the selective introduction of only one enantiomer of racemic aminoacid.

Literature:

[1] a) Kamiński, Z.J. (1985) *Tetrahedron Lett.* **26**, 2901-2904. b) Cronin, J.S.; Ginah, F.O.; Murray, A.R.; Copp. J.D. (1996) *Synth. Commun.* **26**, 3491-3494 and ref. cited therein. c) Taylor, E.C.; Dowling, J.E. (1997*) J.Org. Chem.* **62**, 1599-1603.....

[2] Kaminski, Z.J., (1994) *Int. J. Peptide Protein Res.* **43**, 312-319.

*) Preliminary communication was presented at the 16th Conference on Isoprenoids, Prague 1995.

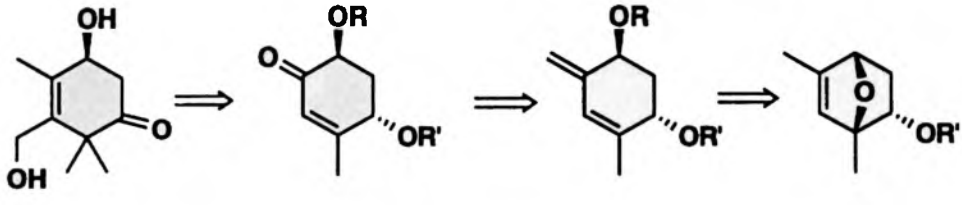
Supported by the State Committee for Scientific Research (KBN) grant 3 T09 A06708 and Technical University of Łódź grant I-18/18/96-97/Dz.S.

SYNTHETIC APPROACH TO TAXOL A RING FROM 7-OXANORBORNENIC SYSTEMS

Odón Arjona, Marisa León, Joaquín Plumet.

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

The bridge cleavage of 7-oxanorbornenic system constitutes a key step in the transformation of this bicyclic skeleton into functionalized cyclohexenols[1]. In our laboratory we have developed a new ring opening methodology to produce cyclohexenediol **2** starting from the 7-oxanorbornenic derivative **1**[2] . This transformation prompts us to develope a new approach to Taxol A ring.



4 **3** **2** **1**

In this way, treatment of 7-oxanorbornene **1** with LDA rendered hydroxy diene **2** which upon oxidation produced the enone **3**. The 1,4 addition to this system would provide a convenient approach to the target molecule.

References

1. a) Aceña, J.L; Arjona, O; Fernández de la Pradilla, R; Plumet, J; Viso, A. *J. Org. Chem.* **1992**, *57*, 1945. b) Arjona, O; de Dios, A; Fernández de la Pradilla, R; Plumet, J; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906.

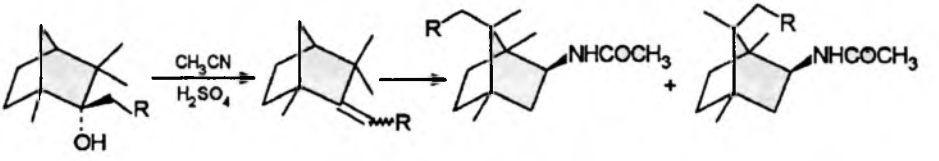
2. Arjona, O; Conde, S; Viso, A. *Tetrahedron Lett.* **1995**, *36*, 6157.

THE RITTER REACTION IN THE FENCHYL SYSTEM

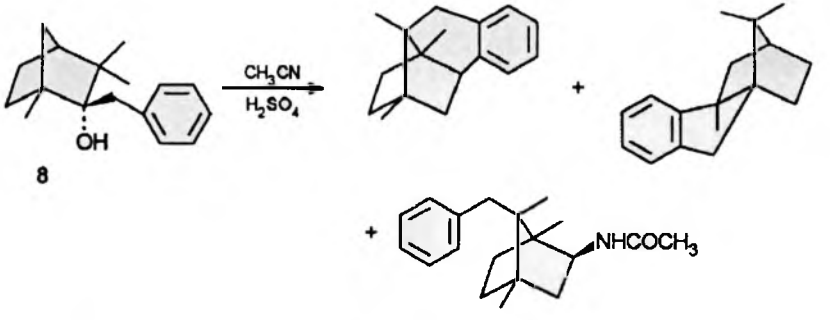
Mirosław Wełniak

Faculty of Chemistry, Nicolaus Copernicus University, Toruń, Poland

The Ritter reaction of ten fenchyl alcohols was investigated to give different products as a result of various types of rearrangements:



1 - 7 where R = H, Me, Et, Pr, Bu, *iso*-Pr and *iso*-Bu



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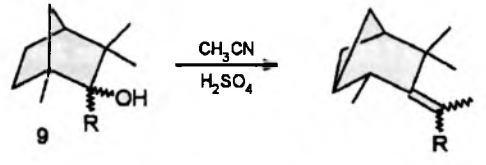
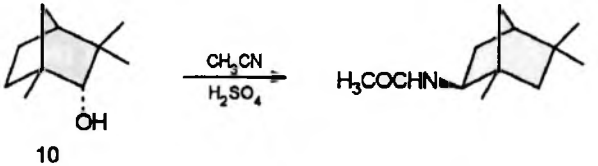


9

where R = Et or Pr



10

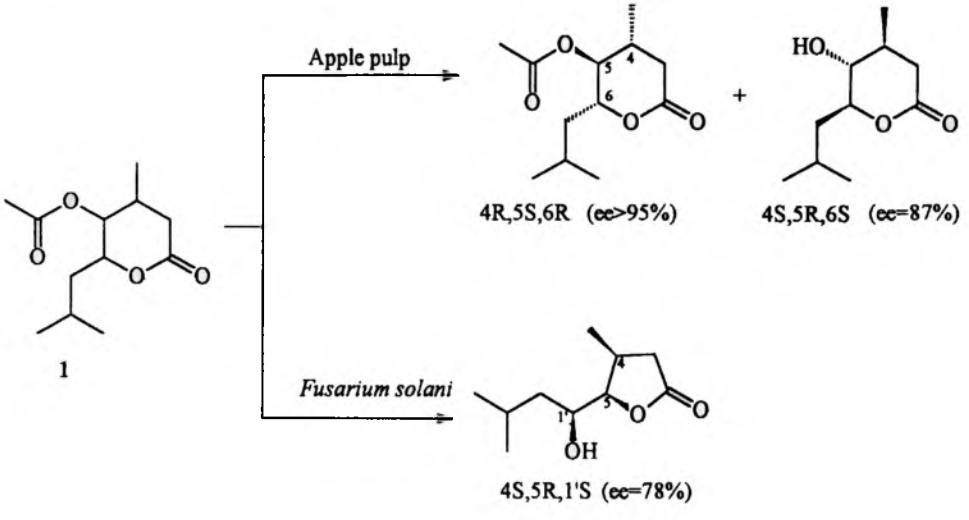
The proposed mechanisms of the reactions under investigation will be presented.

ENANTIOSELECTIVE HYDROLYSIS OF RACEMIC δ-HYDROXY LACTONE ACETATE BY MEANS OF *FUSARIUM SOLANI* AND APPLE PULP (*MALUS SILVESTRIS*)

Agnieszka Mironowicz, Teresa Olejniczak, Czesław Wawrzeńczyk

Institute of Fundamental Chemistry, Agricultural University, Norwida 25, 50-375 Wrocław, Poland

Studying the influence of the configuration of chiral centers on the feeding deterent activity of terpenoid lactones we were interested in obtaining pure enantiomers of some hydroxy lactones. We have found that we can reach them by the stereospecific hydrolysis of acetates of racemic hydroxy lactones. Here we present the enantioselective hydrolysis of acetate of racemic hydroxy δ lactone **1** by *Fusarium solani* or by enzymatic system of apple *Malus silvestris*. In the experiment with *Fusarium solani* the transformation of δ lactone to γ-lactone was observed.



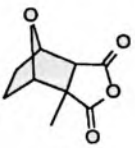
Bioassay Directed Determination of Natural Products with Anthelmintic Activity

G. Roos, I. Klaiber, B. Vogler, C.U. Walter, W. Kraus

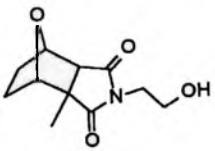
University of Hohenheim, Department of Chemistry, 70593 Stuttgart, Germany

The free-living soil nematode *Caenorhabditis elegans* serves as a model for detection of anthelmintic activity [1]. A suspension of worms is treated with extracts and after seven days of incubation assessed for increase in number of worms and their movement.

We report on the suitability of the assay for the activity directed isolation of the compounds **1-4** from *Butea monosperma* (Fabaceae), *Vernonia fastigiata* (Asteraceae) and *Thamnosma africana* (Rutaceae).



1



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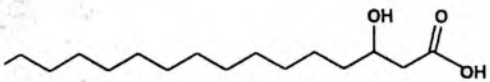

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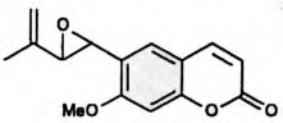

4

Furthermore we demonstrate the efficacy of a HPLC coupled evaluation of the assay in combination with on-line spectroscopy techniques such as LC-MS and LC-NMR. The active principle **4** of the root extract of *Thamnosma africana* (Rutaceae) could be found and determined using exclusively on-line techniques, thus circumventing time consuming isolation and identification of biologically inactive compounds.

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[1] K.G. Simpkin, G.C. Coles, *J. Chem. Tech. Biotechnol.* **31** (1981) 66-69.

SEPARATION AND APPLICATION OF THE TOAD POISON BUFADIENOLIDES AND RELATED COMPOUNDS BY DISPLACEMEN THIN-LAYER CHROMATOGRAPHY

Yoshiaki Kamano, Ayano Kotake and Toshihiko Nogawa
(Faculty of Science, Kanagawa University, Japan)
Machiko Tozawa
(Research Institute for Integrated Science, Kanagawa University, Japa

Recently, as the useful method of separation, displacement thin-laye chromatography(DP-TLC) have been reported in the field of bioactive natural products such as polymyxin, corticoids and ecdysteroids*.

In this presentation, the author describe about the novel and useful results on separation of the toad poison bufadienolides and related cardenolides by DP-TLC.

The report is including the followed experiments and results:

(1) Establishment of the essential method for separation of bufadienolides by use of resibufogenin, cinobufagin, bufalin, bufotalin, cinobufotalin, telocinobufagin and gamabufotalin.

(2) As the good solvents of development, hexane-acetone(7:3), hexane-ethyl acetate(6:4) and etc., which are containing ca. 3% of organic bases such as N,N-dimethyl-1,3-propanediamine, N,N-dimethyl-cyclo hexylamine and triethylamine, were selected.

(3) Application to separation of some derivatives and related cardenolides.

(4) Application to perfect separation on bufadienolides in the Chinese traditional drug Ch'an Su(Senso) by two dimensional DP-TLC.

Finally, the author would like to discuss about isolation and structur of three rare bufadienolides, 20(*S*),21-epoxyresibufogenin(X), 14β,15β-epoxydigitoxigenin and 19-oxo-desacetyl-cinobufotalin, from the Ch'an Su extract by the combination of DP-TLC separation and sephadex LH-20 isolation. Especially, configuration of the 20(*S*), 21-epoxy group of compound X was analyzed by the NOE experiment.

* For example: H. Kalász, Mária Báthori and I. Máthe,
J. Liquid Chromatogr., 18(5), 837-848 (1995).

MICROWAVE-ASSISTED DEACETYLATION AND ACYL MIGRATION OF STEROID ACETATES ON ALUMINA

A. Vass,[a] J. Wölfling,[b] P. Tapolcsányi [b] and Gy. Schneider[b]

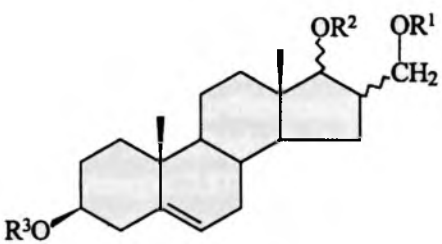
[a]Research Institute of Chemical Engineering Hungarian Academy of Sciences, H-8000 Veszprém, Hungary.
[b]Department of Organic Chemistry, József Attila University, H-6720 Szeged, Hungary.

Hydroxy group protection by acetylation is a common procedure and there are, therefore, numerous methods to achieve both protection and the deprotection sequence.

Recently we observed a facile and simple procedure to affect the deacetylation of a variety of acetylated steroid stereoisomers on alkaline alumina under solvent free conditions, reactions which can be accelerated safely using an unmodified common household microwave oven.

The 16α-acetoxymethyl-androst-5-ene-3ß,17ß-diacetate (**1a**) and its 16ß,17α isomers (**2a**) containing the 16,17-functional groups in *trans* orientation with respect to one another, lost its primary acetoxy group, while the secondary acetoxy groups remained intact to give 3,17-diacetates (**1b**, **2b**) after irradiation with 90 W within 6 minutes.

Under similar conditions, 16α-acetoxymethyl-androst-5-ene-3ß,17α-diacetate (**3a**) and its 16ß,17ß isomer (**4a**) containing the 16,17 functional groups in *cis* orientation underwent deacetylation to give 16-hydroxymethyl-androst-5-ene-3,17-diacetates (**3b**, **4b**). However compounds **3b** and **4b** transformed further on the alkaline alumina to 16-acetoxymethyl-androst-5-ene-17-ol-3-acetates (**3c**, **4c**), by acyl migration, followed by cleavage of the newly formed primary acetoxy group to give 16-hydroxymethyl-androst-5-ene-17-ol-3-acetates (**3d**, **4d**).



1-4

	R^1	R^2	R^3
a	Ac	Ac	Ac
b	H	Ac	Ac
c	Ac	H	Ac
d	H	H	Ac

Evidence for the structure of compounds (**1-4**) is provided after chromatographic separation by their ^{1}H-, and ^{13}C-NMR spectra.

THE MITSUNOBU INVERSION REACTION OF STERICALLY HINDERED 17ß-STEROID ALCOHOLS

P. Tapolcsányi, J. Wölfling, M. Rózsa-Tarjáni and Gy. Schneider

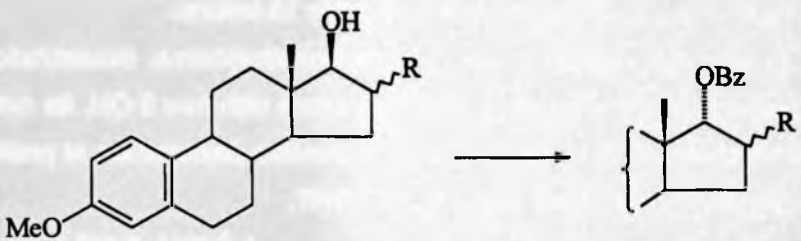
Department of Organic Chemistry, József Attila University, H-6720 Szeged, Hungary.

It is interesting from a structure-activity standpoint, that 17ß-steroid alcohols are readily accessible via selective reduction of the corresponding ketones, preparation of the 17α-alcohols has proved to be somewhat problematic. This is particularly true when Mitsunobu inversion conditions (diethylazodicarboxylate, PPh_3, RCO_2H) are employed.

It has been found that sterically encumbered alcohols can be easily inverted employing carboxylic acids of relatively high acidity such as 4-nitrobenzoic acid.

We found, that when 3-methoxy-estra-1,3,5(10)-triene-17ß-ol (**1a**) was subjected to modified Mitsunobu conditions (a mixture of 2.5 eq. 4-nitrobenzoic acid, PPh_3 and diethyl-azodicarboxylate was heated up to 90 °C for 30 min in chlorobenzene), the desired *p*-nitrobenzoate ester (**2a**) was isolated in a yield better than 90%.

In a similar manner, the sterically more hindered 16α-, and 16ß-methyl-3-methoxy-estra-1,3,5(10)-triene-17ß-ol (**1b,1c**) were converted into the corresponding p-nitrobenzoate esters (**2b,2c**) in good yields. In this case, however, by-products formed by elimination and rearrangement were also isolated, which were identical in all respect with authentic samples, prepared with other methods.



1 **2**

	R
a	H
b	α-CH_3
c	β–CH_3

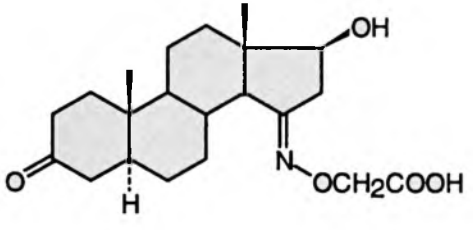
SYNTHESIS OF (15E)-17β-HYDROXY-5α-ANDROSTA-3,15-DIONE 15-(O-CARBOXYMETHYL)OXIME (15-CMO DHT).

Ivan ČERNÝ, Tereza SLAVÍKOVÁ, Vladimír POUZAR
Inst. Org. Chem. Biochem. ASCR, Flemingovo n. 2, 166 10 Prague 6, Czech Republic

After we had made 15β-hydroxyderivatives in androstane series available[1] we have prepared some haptens with connecting bridge at position 15 derived from testosterone[2]. We further modified this method for preparation derivatives with amino group in this position and we prepared 15β-succinamidoderivative of dihydrotestosterone[3]. Previous immunological studies revealed good sensitivity of antibodies generated using this hapten in tests with tritiated DHT. However, when the tracer was prepared from the same hapten, irreversible binding to antibody was observed[3]. For heterologous immunassays we needed another haptens: preparation of one of them is the subject of our contribution.

The synthesis is based on addition of 4-methoxybenzyl alcohol to 3β-hydroxy-5α-androst-15-en-17-one. The mixture of 15-methoxyphenymethyl derivatives of corresponding 3β,15β- and 3β,15α-diols with the former prevailing, was succesively acetylated, reduced at position 17, protected as 17-O-methoxymethyl derivatives, deprotected at position 15 with DDQ and finally by the Jones oxidation transformed into 15-ketone.

Subsequent oximation with O-(carboxymethyl)oxime, deacetylation and diazomethane methylation gave protected oxime with free 3-OH. Its oxidation gave corresponding DHT derivative and succesive deprotection at position 17 and at carboxy group led to final 15-CMO DHT.



1. Černý I., Fajkoš J., Pouzar V.: Steroids 61, 58 (1996).
2. Fajkoš J., Černý I., Pouzar V.: Steroids 61, 634 (1996).
3. Černý I., Pouzar V., Lapčík O., Hampl R.: Coll. Czech. Chem. Commun., in press.

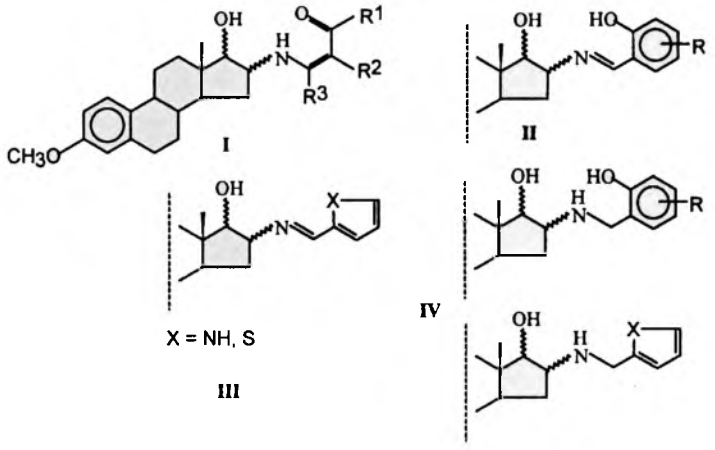
STEROIDS AS CHIRAL LIGANDS: SYNTHESIS OF 1-ENAMINO-3-OXO COMPOUNDS AND AZOMETHINES FROM STEROIDAL AMINO ALCOHOLS

Manuela DUBS[a], Reimar KRIEG[a], Helmar GÖRLS[b], Bruno SCHÖNECKER[a]

[a] Institut für Organische und Makromolekulare Chemie der Friedrich-Schiller-Universität Jena, Humboldtstr. 10, D-07743 Jena, Deutschland

[b] Institut für Anorganische und Analytische Chemie der Friedrich-Schiller-Universität Jena, August-Bebel-Str. 2, D-07743 Jena, Deutschland

For stereochemical and biological investigations new steroids were synthesized as chelating ligands. Condensation of the four 16-amino-17-hydroxy-3-methoxy-estra-1,3,5(10)-trienes with aliphatic 1,3-dioxo compounds (or derivatives), aromatic ortho-hydroxy aldehydes or heteroaromatic α-aldehydes gave 16-(1-enamino-3-oxo) compounds with a 17-hydroxy group (type **I**) or the corresponding 16-imines (types **II** and **III**), respectively. By reduction of compounds of the type **II** and **III** new N-substituted 16-amino-17-hydroxy compounds (type **IV**) have become available.



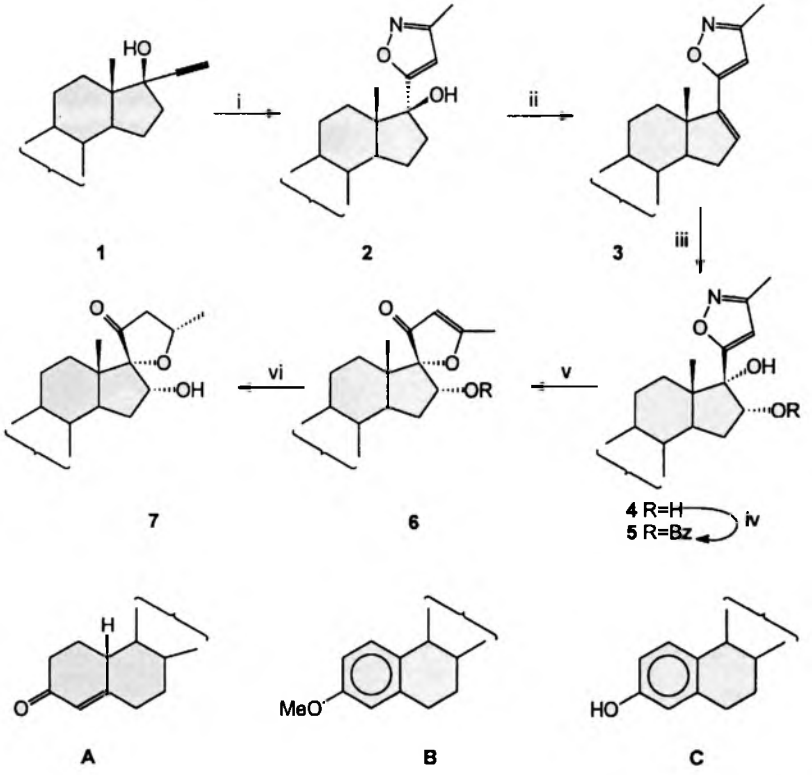
Two kinds of copper(II) complexes are described: steroid/copper(II) = 2 : 1 for 16,17-trans compounds, steroid/copper(II) = 1 : 1 for 16,17-cis compounds. X-ray data are presented.

SYNTHESIS OF STEROIDAL 17-SPIROFURANONES

A. V. Baranovsky, M.B. Groen*, Ae. de Groot, V.A. Khripach, R.P. Litvinovskaya, V.B. Sazanov**

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, 220141, Minsk, Zhodinskaya str., 5/2, Belarus
*Scientific Development Group, N.V.Organon, P.O.Box 20, 5340 BH, Oss, The Netherlands
**Department of Organic Chemistry, Wageningen Agricultural University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

A number of 19-norsteroids bearing an isoxazole or a spirofuranone ring at C-17 has been synthesized starting from propargyl alcohol **1.** Using the reaction sequence depicted in the scheme, a number of 17β-C steroid derivatives have been obtained. Reaction conditions and structure of the obtained compounds will be discussed.

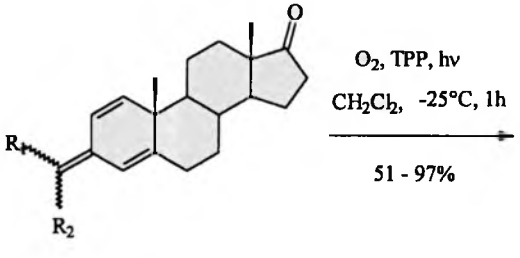


i: MeCHNOH, NCS, Et_3N, $CHCl_3$, rt, 48h; ii: $SOCl_2$, Py, THF, -50°C; iii: OsO_4(cat), NMO, Me_2CO, H_2O, rt, 4h; iv: BzCl, DMAP, CH_2Cl_2, rt, 48h; v: 1) $Mo(CO)_6$, MeCN, 80°C, 0,5h, 2)HCl, MeCN, rt, 2h; vi:LAH, THF, rt, 0,5h

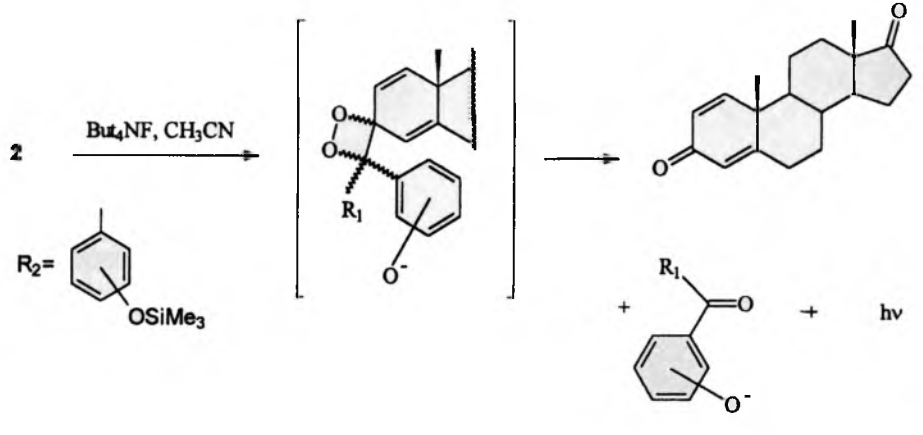
Steroid Substituted 1,2-Dioxetanes, a new Chance in Therapy

D. Weiß, B. Fiedler, R. Beckert
Institut für Organische und Makromolekulare Chemie
Friedrich-Schiller-Universität Jena
D-07743 Jena, Humboldtstr. 10
c5diwe@rz.uni-jena.de

The implication of 1,2-dioxetanes in photobiological processes is well investigated. This is expected in view of their unique ability to generate efficiently triplet excited carbonyl compounds on thermal decomposition. To use these high reactive derivatives as therapeutic/diagnostic agents it is necessary to find substituents which are able to stabilize the four-membered cyclic peroxide ring as well as to act as carrier to the action site. Both conditions were satisfied in a high degree by steroid substituted 1,2-dioxetanes. Thus, starting from unsaturated steroids of type **1** the 1,2-dioxetanes **2** were obtained by a regiospezific photodioxygenation reaction. Furthermore, we found that the half life times of **2** were between a few minutes and more than three days depending on the nature of the residues R_1 and R_2 . Some 1,2-dioxetanes as derivatives, bearing a silylated phenolic substructure, undergo a chemical induced decomposition, and thus constitute effective sources of luminescent light.



1 **2**

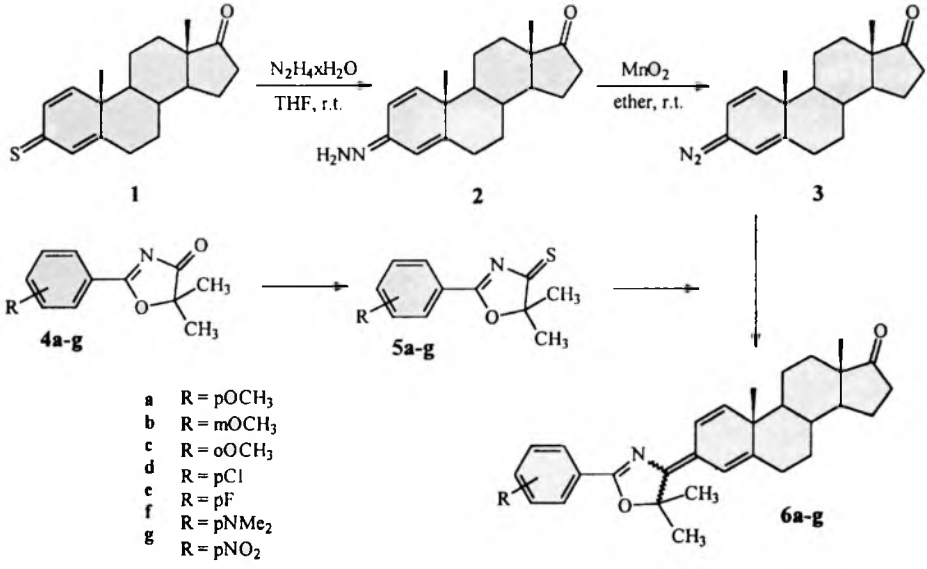


Synthesis and Properties of Highly Fluorescent Steroids

K.Wagner, D.Weiß, R. Beckert

Institute of Organic and Macromolecular Chemistry, Friedrich Schiller University of Jena
Humboldtstr. 10, D-07743 Jena, Germany

A very efficient and regiospecific synthesis of steroid substituted oxazolines of type **6** starting from 3-thioxoandrosta-1,4-dien-17-one **1** is described.
The 3-diazo-androsta-1,4-dien-17-one **3** is synthesized by oxidation of **2** with MnO_2 in diethylether. It is stable in solution for several hours by room temperature and could be characterized by spectroscopic methods (^1H and ^{13}C NMR, IR and UV/VIS spectroscopy). Only a few oxidations of steroidhydrazones are known in the literature. However in no case the corresponding diazocompound could be isolated or characterized.



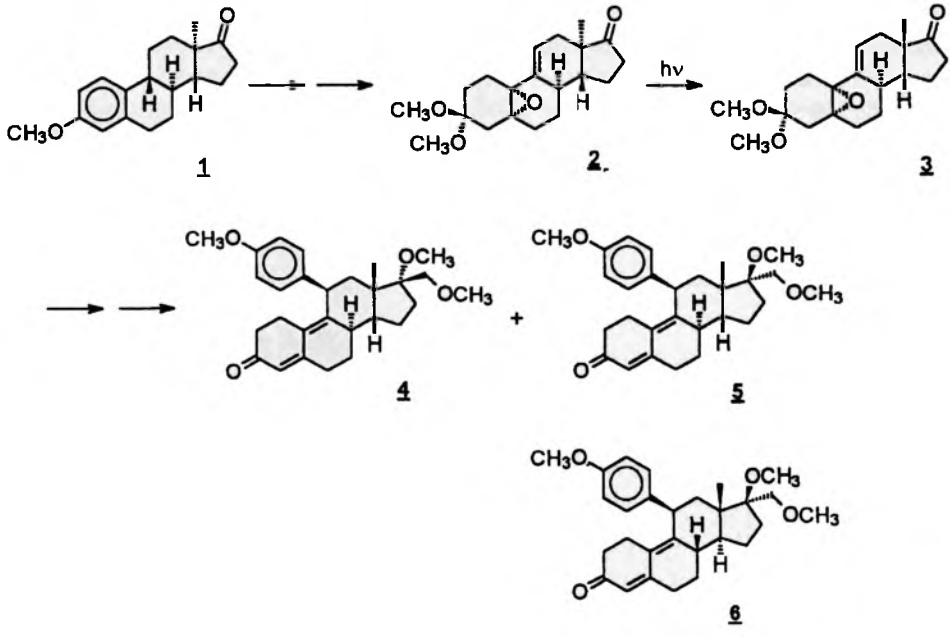
The diazosteroids **3** are able to react with thiones in a [2+3] cycloaddition reaction followed by elimination of nitrogen and sulfur (Barton-Kellogg-Olefination). Therefore **3** constitute a good starting material for A-ring substituted steroids.
The steroidolefines **6a-g** are formed in resonable yields between 25% and 90%. In contrast to the parent oxazolin-4-ones they are effective fluorescent dyes with quantum yields up to 80% and can be used as fluorophores in chemiluminescent systems.

A SYNTHETIC PATHWAY TO THE 8α,14β-ISOMER OF AN ANTIPROGESTIN

P. Droescher[1], B. Menzenbach[1], G. Kaufmann[1], M. Reichenbächer[2], C. Lange[2]

[1]Jenapharm GmbH & Co KG, Jena, Germany
[2]Friedrich-Schiller-Universität, Jena, Germany

Starting from the unnatural enantiomer **1** of estrone 3-methyl-ether, the 8α,14β-isomer **5** of the known antiprogestin **6** [1] was synthesised.
In the key step use was made of the known photochemical isomerisation of 17-oxo steroids [2, 3]. Thus, the epoxide **2** is directly transformed into the 8α,14β-isomer **3**, which was converted into the desired product **5** following the synthetic route known from naturally configurated antiprogestins [4] in 5 steps.



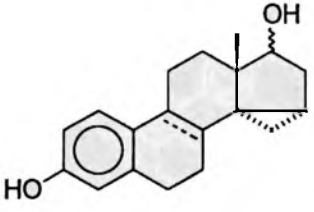
The isomeric structure of **5** seems to prevent any interaction with both the progesterone and the glucocorticoid receptor.

[1] H.Kasch, G.Schubert et al., EP 411 733 (publ. 06.02.91), C.A. **123** (1995) 112512h
[2] A.Butenandt et al., Ber. **74** (1941) 1308
[3] G.Neef et al., Steroids **44** (1984) 349
[4] A.Belanger et al., Steroids **37** (1981) 361

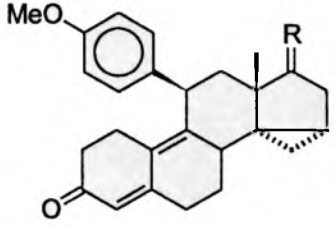
NOVEL CYCLOPROPANO STEROIDS WITH PROGESTATIONAL ACTIVITY. 14,15-METHYLENE BRIDGED DERIVATIVES OF THE 19-NOR-ANDROSTANE SERIES

Sigfrid Schwarz*, Gerd Schubert*, Walter Elger‡, Ina Thieme*, Birgit Schneider‡ and Bernd Undeutsch*
*Division of Research and Development, Jenapharm GmbH & Co.KG Jena (Germany)
‡EnTec GmbH Hamburg/Jena, Jena (Germany)

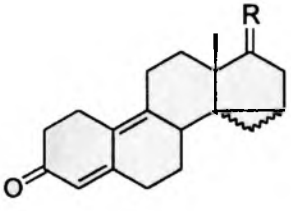
In the course of our search for novel estrogens 14α,15α-methylenestradiol (**J 824**) was found to be a highly active estrogen after oral administration[1]. **J 861**, another aromatic 14α,15α-methylene steroid[2], showed radical scavenging activity[3]. These promising results prompted us to study the influence of a 14,15-methylene bridge on the biological profile of 19-nor-androstane derivatives. We report here on the synthesis of selected 14,15-cyclopropano steroids **1** and **2** as well as on preliminary results of *in vitro* and *in vivo* tests. All compounds studied displayed a moderate binding to the progesterone receptor. The progesterone antagonistic activity in rats was negligible too. However, species of type **2** were found in mice to have a progestational activity as high as norethisterone acetate or even higher. The α-methylene bridge seems to be more effective than the β-oriented one.



J 824: 17β-OH
J 861: 17α-OH; Δ^8



1: R = H,OH; CH_2OH,OH; CH_2OMe, OMe; C_{17}-CH_2O-CMe_2-O-C_{17}



2: R = O; HO, H; HO, CH_2OH; HO, CH_2OMe; MeO, CH_2OMe; HO, Me; OCONHPh, H

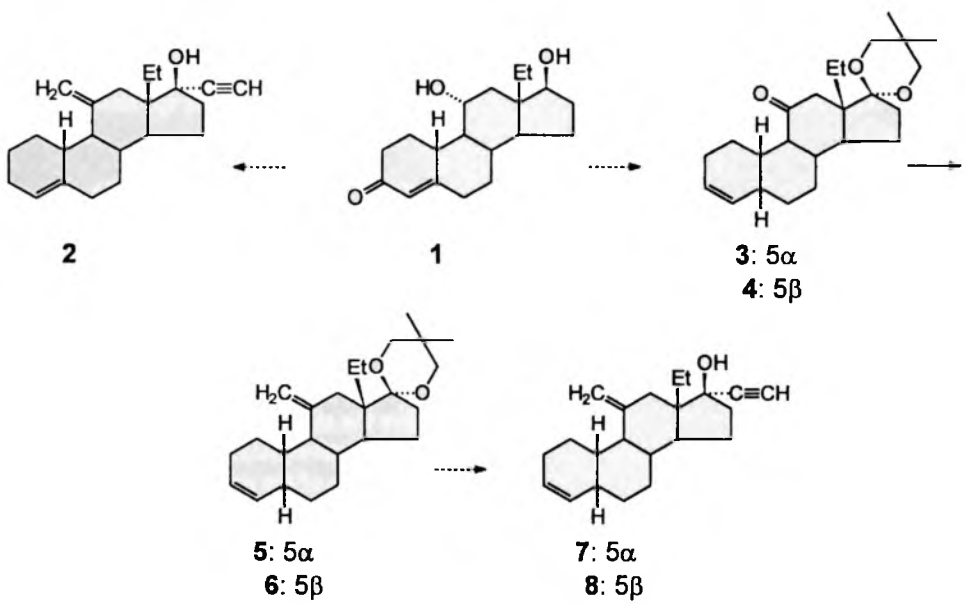
References
Ponsold K, Prousa R, Oettel M, Strecke J, Hoffmann H (1978) Ger. Patent DD 145 919. [2]Siemann H-J, Droescher P, Undeutsch B, Schwarz S (1995). *Steroids* **60**:308-315. [3]Römer W, Oettel M, Droescher P, Schwarz S (1997). *Steroids* **62**:304-310.

A REMARKABLE INFLUENCE OF STEROID A/B-RING JUNCTION ON THE WITTIG OLEFINATION REACTION OF THE 11-OXO GROUP. TOWARDS THE SYNTHESIS OF 5α- AND 5β-ORIENTED 3-DEHYDRO ISOMERS OF DESOGESTREL

Sven Ring*, Gisela Weber*, Alexander Hillisch‡ and Sigfrid Schwarz*
*Division of Research and Development, Jenapharm GmbH & Co.KG, Jena (Germany); ‡ Institute of Molecular Biology, Jena (Germany)

Recently, we realized a total synthetic approach to the widely used progestogen desogestrel (**2**) from the hydroxy steroid **1**[1]. Since the 3(4)-unsaturated isomers **7** and **8** proved to be potential impurities of **2**, we synthesized the title compounds from 11-hydroxy steroid **1** in 6 steps (Scheme). On this occasion, the compounds derived from the 5α-series differed markedly by their reaction rates from those of the 5β-series. In particular, this was true for the Wittig olefination reaction of the 5α-intermediate **3** by triphenylphosphino methanide to give methylene steroid **5** which proceeded much more slowly (108 h) than the olefination of the 5β-intermediate **4** affording compound **6** (1 h). The cause of this impressive difference will be discussed on the basis of computational studies.

The A/B-ring junction of the α- and β-series was established by x-ray analysis.



Reference

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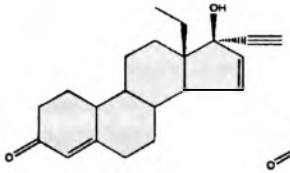
SYNTHESIS OF CONFORMATIONALLY RESTRICTED PROGESTATIONAL 13-ETHYL STEROIDS

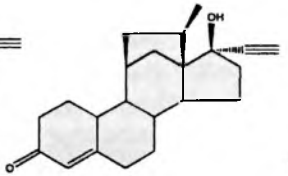
Arnold I.A. Broess, Hans Hamersma and Marinus B. Groen,

Department of Medicinal Chemistry I, Scientific Development Group,
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.

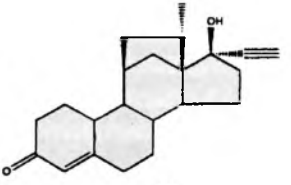
While in most progestational 13-ethyl steroids (e.g. levonorgestrel, desogestrel) the ethyl group occurs in a single conformation (i.e. the methyl group anti relative to C-14) in gestodene (**1**) it also can adopt an alternative conformation (the methyl group anti relative to C-12, pointing towards C-15). In order to assess the relative importance of these two conformers for biological activity we have devised a pair of compounds (**2a, 2b**) in which the the ethyl group is locked in either one of these conformations.



1

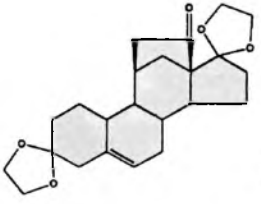


2a

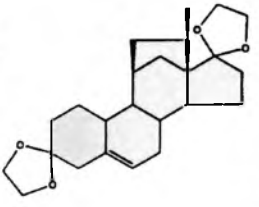


2b

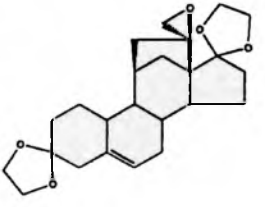
The synthesis of these compounds started with the ketone **3**, the synthesis of which is described elsewhere. Wittig reaction (methyl triphenylphosphonium bromide, *t*-BuOK, toluene), followed by hydrogenation afforded **4** as a single epimer. The conversion of **4** into **2a** was straightforward. Alternatively **3** could be converted into the epoxide **5** by modification of the method of Corey and Chaykovsky.



3

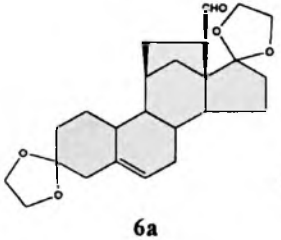


4

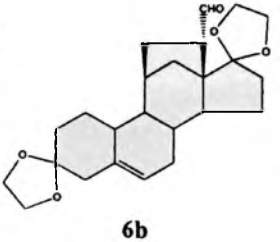


5

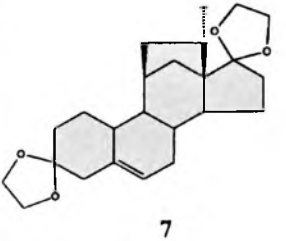
Brief treatment of **5** with Lewis acid ($BF_3.Et_2O$) gave the aldehyde **6a** which could be rearranged to the more stable epimer **6b** in nearly quantitative yield (KOH, methanol). Wolff-Kishner reduction of **6b** afforded **7** (along with some of the undesired epimer **4**), which was converted into **2b**.



6a



6b



7

STEROID HETEROCYCLES - QUEST FOR THE SEARCH OF BIOLOCICALLY ACTIVE LEAD STRUCTURES

Nguyen T.T.H[b], Urbanský M.[a], Černý I.[a], Pouzar V.[a], Protiva J.[b], Dražar P.[a]
Institute of Organic Chemistry and Biochemistry AS CR, 166 10 Prague 6, Department of Organic Chemistry, Faculty of Natural Sciences, Charles University, 128 40 Prague 2

Continuation[1] of the synthetic and biological experiments with the steroidal compounds possessing the heterocyclic moiety in the side chain or linked to the parent skeleton brings interesting results even on the interdisciplinary marketplace[2] as well as in the connection with endocrinology and neuroscience aspects.[3]

Several synthetic pathways leading to the title steroids (cf. e.g.[4,5]) brought us in front of a numerous data of their biological activity. Among the activities, the models were evaluated against several screening cell lines as e.g. A375 melanoma, A549 lung cancer, SW480 colon cancer, MCF-7 breast cancer, PC-3 prostate cancer, 8226 myeloma, P388 leukemia, HeLa S3 human crevix carcinoma, mouse leukemia L1210, and murine L-929, for anti HIV properties, and activity against *E. Coli*.

Mapping of the available heterocyclic steroids shows several interesting active structures. Heterocyclic ring, as it could be anticipated, brings into the molecule features that extend the classical biochemical properties of the steroid whereas the steroid moiety brings in the classic lipophillic aspect and rigidity which enables the regio- and stereo-controlled interaction with the receptor. This double feature character enables the chemist to design „linear molecules" where one end is lipophillic and the other polar. Thus, we can achieve even a „detergent-like" design which certainly has capability of influencing the cell metabolism as such.

There will be discussed steroidal heterocycles with five membered ring with different substitution and, also with another ring anelated to the heterocycle.

This work was accomplished with the partial support of the Czech Grant Agency within the projects Nos. 203/97/0695, 203/97/0302. The collaboration with dr. Kit S. Lam, AZ Cancer Ctr., dr. Michal Lebl, CSPS CA, and dr. Ivan Votruba IOCB Prague is highly appreciated.

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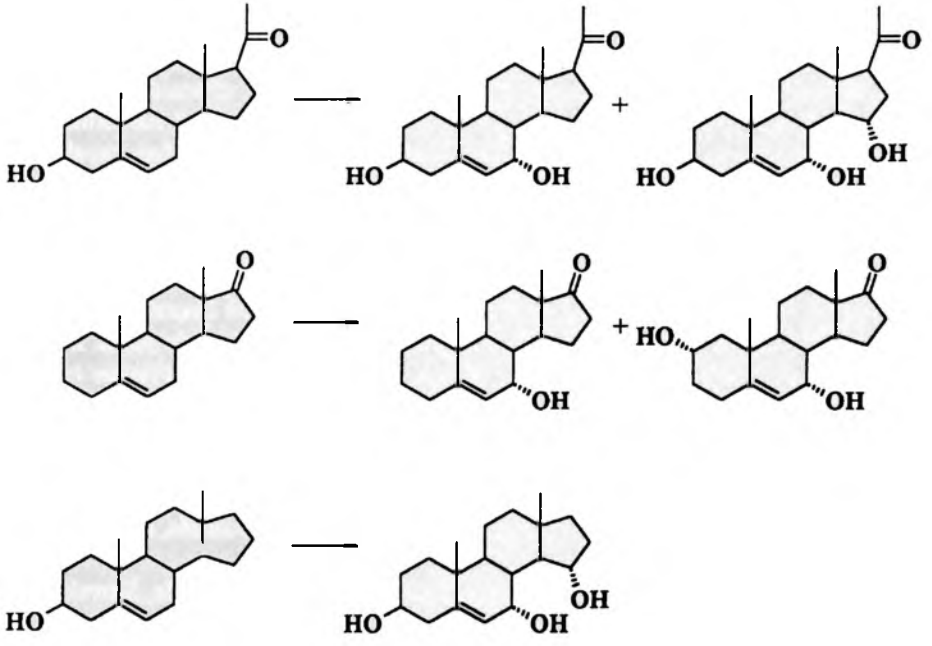
5 Urbanský M., Dražar P.: Synthetic Communications 23, 829 (1993).

HYDROXYLATION OF 5-ENE STEROIDS IN *FUSARIUM CULMORUM* CULTURE.

Teresa Kołek

Institute of Fundamental Chemistry Agricultural University, Norwida 25, 50-375 Wrocław Poland

The ability of the strain *Fusarium culmorum* to hydroxylate many steroidal substrates allowed to observe the influence of substrate structure on the position of hydroxylation. 5-Androsten-17-one, 5-androsten-3β,17β-diol and 17α-methyl-5--androsten-3β,17β-diol were hydroxylated entirely at the 7α-allylic position. The course of transformation of other substrates with C_5 - C_6 double bond and with various substituents at C-3 or C-17 is presented below.



SYNTHESIS OF 11,13-BRIDGED PROGESTATIONAL STEROIDS

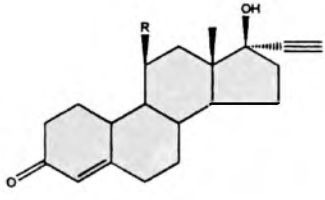
Arnold I.A. Broess, Hans Hamersma and Marinus B. Groen.

Department of Medicinal Chemistry I, Scientific Development Group,
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.

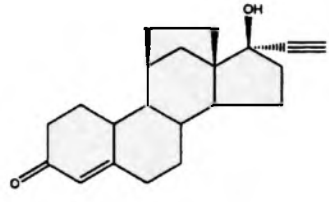
Substituents in the 11β-position of steroids are known to potentiate the hormonal, especially the progestagenic, activity of such steroids. A case in point is 11β-methyl norethisterone (**1b**) which is about ten times more progestagenic than norethisterone (**1a**). It has been hypothesized that the increased potency of **1b** relative to **1a** is due to the pronounced downward bending of the steroid skeleton caused by the steric repulsion between the 11β-substituent and the angular methyl group at C-13. It was believed that such bending would result in a better fit to the progesterone receptor.

To test this hypothesis we have prepared the closely related bridged analogue **2** which, due to the bond between the 11β- and C-13 methyl groups, is bent upward and -according to the hypothesis- should show **decreased affinity** for the progesterone receptor. This compound was prepared from the known lactone **3** which, in three steps, was converted into the ketol **4b.** Reduction afforded the ketone **4a** and subsequent Wolff-Kishner reduction the desired ethano bridged steroid **5.** The target compound **2** was obtained from **5** in a conventional manner.

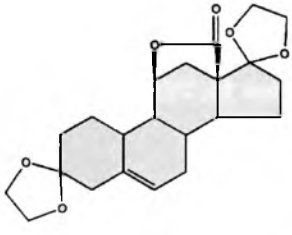
Compound **2** showed progestational activity comparable to **1b** and much higher than **1a** indicating the irrelevance of the bending of the steroid skeleton.



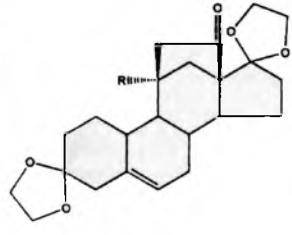
1a R = H
1b R = CH_3



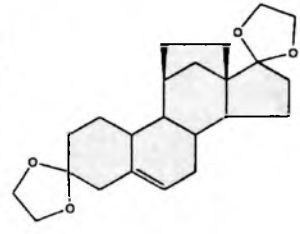
2



3



4a R = H
4b R = OH



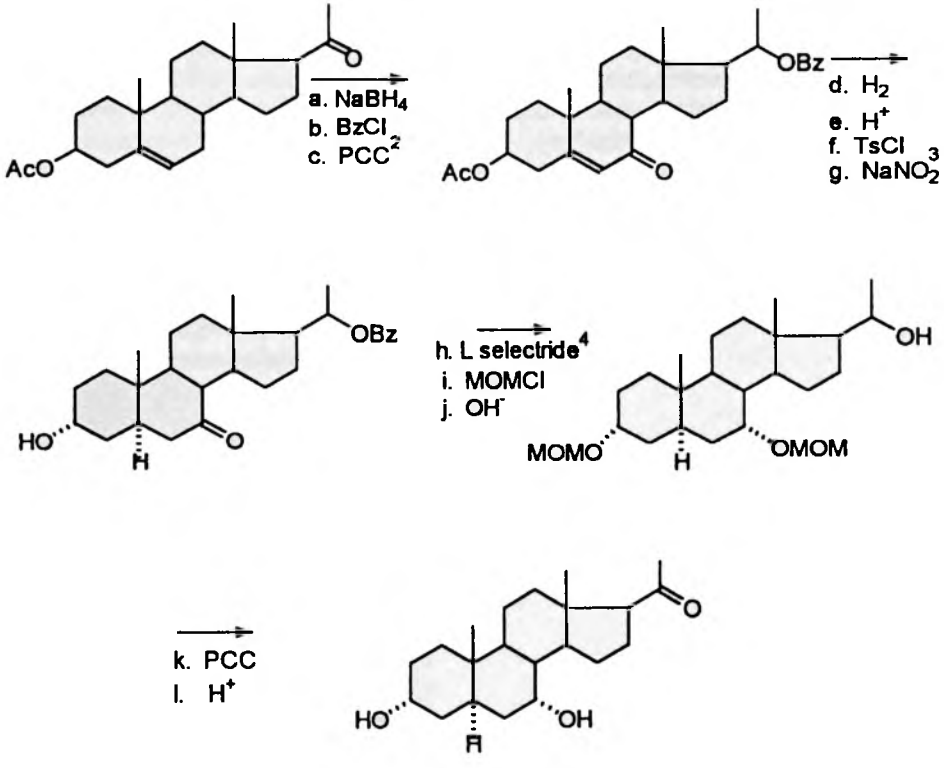
5

SYNTHESIS OF 3α,7α-DIHYDROXY-5α-PREGNANE-20-ONE

Chodounská Hana

Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

Title compound (i. e., an analogue of the most active neurosteroid positive allosteric modulator of $GABA_A$-benzodiazepine receptor complex[1]) was synthesised from pregnenolone acetate as follows:



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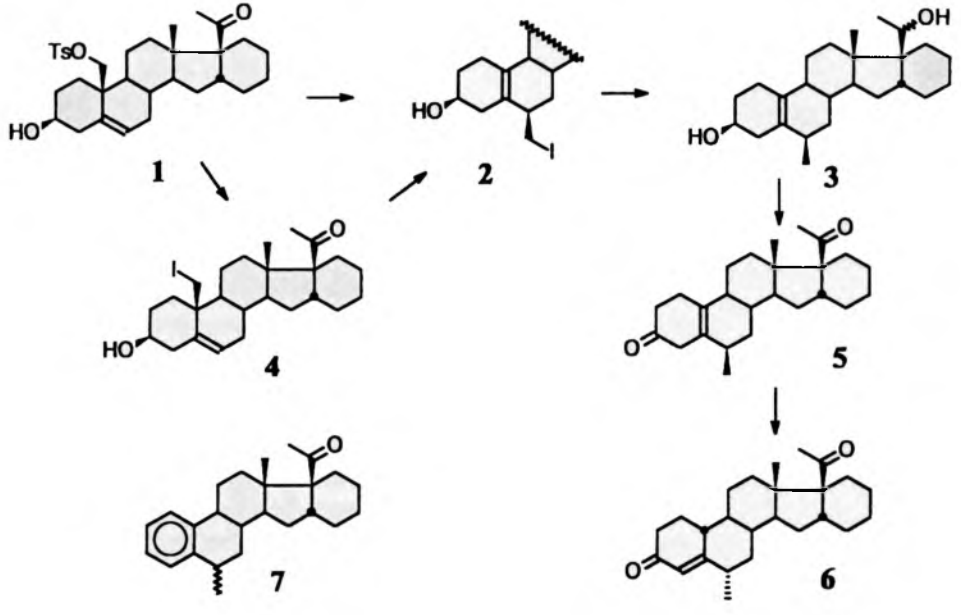
The project was supported by grants (GAČR 505/94/0009 and 203/95/1309)

SYNTHESIS OF 6α-METHYL-16α,17α-CYCLOHEXANO-19-NORPROGESTERONE FROM 19-METHYL-6-DESMETHYL PRECURSOR

I. S. Levina and L. E. Kulikova

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences Moscow, Russian Federation.

In search of the way to the synthesis of 6α-methyl-16α,17α-cyclohexano-19-norprogesterone **6** the homoallyic rearrangement of 10-iodomethyl derivative **4** was studied. The reaction of the tosylate **1** with excess of NaI in boiling Pr^iOH gave 6β-iodomethyl-5(10)-ene derivative **2**. The β-configuration to the C-6 substituent in **2** is assigned from the mode of formation of the rearrangement product *via* the homoallylic cation. Reduction of **2** resulted in the 3β,20ξ-dihydroxy-6β-methyl derivative **3**, which is oxidized to the diketone **5** followed by isomerization of 5(10)-double bond and epimerization of C-6 center into desired **6**. The compound **7** was isolated as a side product under the transformations.

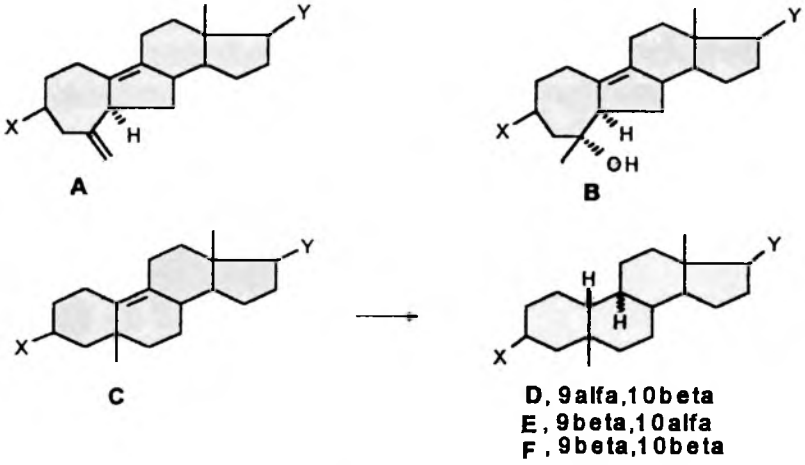


HYDROGENATION OF Δ^9-UNSATURATED 19-NORSTEROIDS

Alexander Kasal and Miloslav Buděšínský

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Fleming Sq. 2, CZ166 10 Prague 6, The Czech Republic

Three types of Δ^9-unsaturated compounds (**A** to **C**) were hydrogenated using a platinum catalyst in acetic acid. Products were separated and analysed by ^{1}H NMR spectroscopy. The hydrogenation of the five-membered ring olefins (compounds **A** and **B**) yielded products of cis addition of hydrogen[1,2,3]. The six-membered ring olefin **C** yielded mostly products of apparent trans addition of hydrogen[4,5]: 9α,10ß- and 9ß,10α-adducts **D** and **E** respectively. These results are interpreted in terms of isomerisation of compound **C** prior to hydrogenation.



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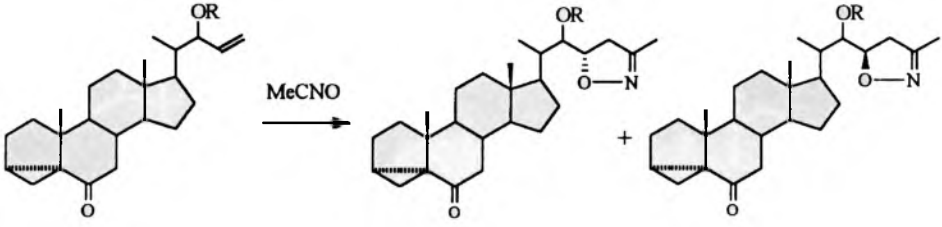
The project was supported by a grant (GACR 505/94/0009).

STEREOSELECTIVITY IN NITRILE OXIDE CYCLOADDITION TO 22-HYDROXY-23-ENE STEROIDS

Svetlana DRACH, Raissa LITVINOVSKAYA, Vladimir KHRIPACH

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus

In our studies on 1,3-dipolar cycloaddition of nitrile oxides with steroidal 23-olefines **1** we found that these reactions give the threo-isomer **3** as major product[1]. An investigation of cycloaddition of relating compounds **4** and **7** (R=H) showed the diminishing of stereoselectivity and its dependence on the character and configuration both the allylic and the homoallylic substituent. The use of the corresponding esters **1** and **4** (R=Ac) leads to the loss of stereoselectivity and decreases the conversion. In the case of bulky protected hydroxy function in **1** (R = $tBuMe_2Si$) the erythro-adduct **2** has been obtained as a single product with low yield.



1 20S,22R
4 20S,22S
7 20R,22S

2 20S,22R,23S
5 20S,22S,23S
8 20R,22S,23S

3 20S,22R,23R
6 20S,22S,23R
9 20R,22S,23R

These results are in contradiction with previous data[2] on the directing effect of an allylic hydroxy group.

Stereochemistry of the cycloadducts **3** (R=Ac) and **8** (R=H) derived from **1** and **7** was established by X-ray analysis. These data, in combination with NMR, were used for structural assignment of other Δ^2-isoxazolines.

Some chemical and spectral properties of the isoxazolinylsteroids and possible mechanism of stereocontrol will be discussed.

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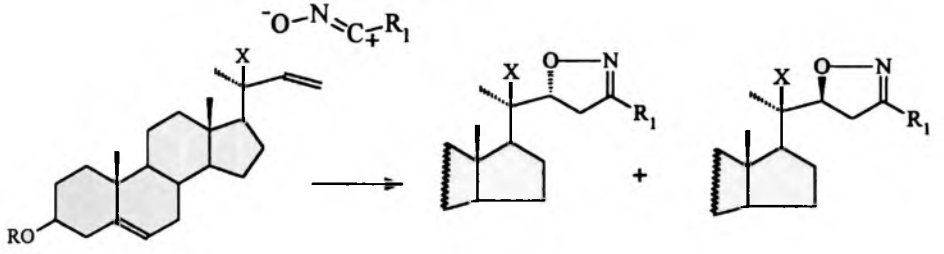
INTRAMOLECULAR HYDROGEN BONDING AND STEREOCHEMISTRY OF CYCLOADDUCTS OF NITRILE OXIDES WITH TERMINAL Δ^{22}- AND Δ^{23}-STEROIDS

Nikolai GARBUZ, Ludmila SOLOVEY, Raissa LITVINOVSKAYA, and Vladimir KHRIPACH

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus

Earlier we have shown that cycloaddition of nitrile oxides with terminal Δ^{22}-steroids proceeds stereoselectively to give mainly 22R-isomer **2**. The extent of selectivity is sensitive to the substituent at C-20 and the highest one was observed in the case of C-20 steroidal alcohols **1a**. The influence of C-20 hydroxy function on the stereoselectivity can be explained not only by directive steric effect of the substituent but also by effect of hydrogen bonding in intermediate complex.



1 a,b **2 a,b** **3 a,b**

R=H, OAc; R_1= Me, iPr; a: X = OH; X=H

We supposed that realisation of such specific electronic interaction in the process of attack of nitrile oxide on dipolarophyl can effect not just on the ratio of isomers formed but also on their parametres in IR-spectra showing intramolecular hydrogen bonding. Such difference between two types of isomers, really, has been found in the course of their IR-investigation, and it is important that stronger interaction in all cases was characteristic for the major isomers.

These data are important for better understanding of mechsnisms of stereocontrol in cycloadditions of nitrile oxides and can be used for determination of the structure of stereoisomeric products.

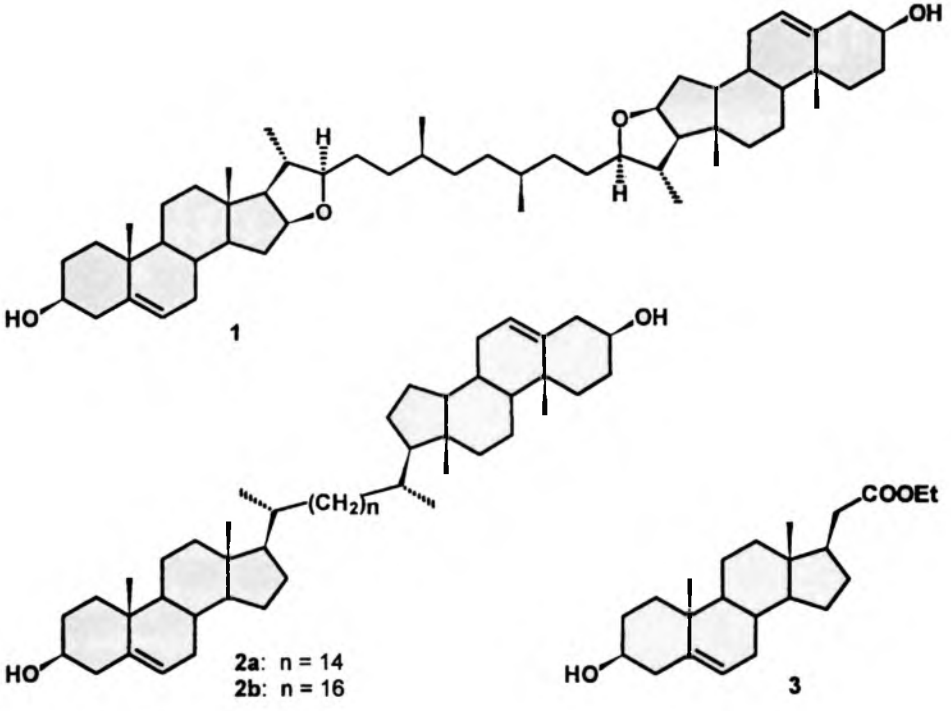
Spectral data and experimental conditions will be discussed.

SYNTHESIS OF DIMERIC STEROIDS AS COMPONENTS OF LIPID MEMBRANES

Agnieszka Z. Wilczewska, Zenon Łotowski, Joanna Rabiczko, and Jacek W. Morzycki

Institute of Chemistry, University of Warsaw, Bialystok Branch, 15-443 Bialystok, Poland

The synthesis of three dimeric steroids **1**, **2a** i **2b** is presented. Di(3β-hydroxyfurost-5-en-26-yl) (**1**) was obtained from diosgenin by reductive fission of ring F, substitution of -OH by -I and the Wurtz reaction. Two other dimers (**2a** i **2b**) were synthesized from the pregnanoic ester (**3**) by an "alkylation-reduction" procedure.



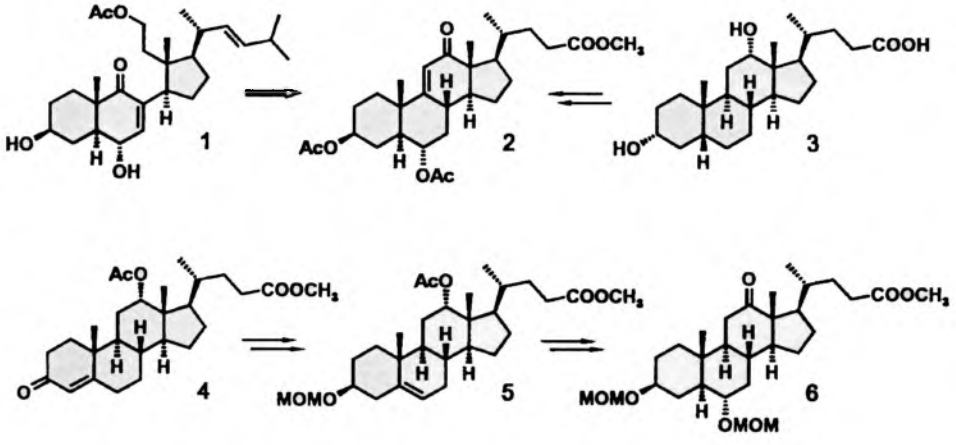
These dimers serve as components of artificial lipid bilayer membranes, formed from phosphatidylcholine by Mueller-Rudin method. The addition of the dimers increases rate of the bilayer formation, membranes stability, and their resistance to an electric breakdown.

PREPARATION OF 3β,6α-DIACETOXY-24-METHYL-12-OXO-5α-CHOL-9,11-EN-24-OATE, A CONCEIVABLE PRECURSOR FOR THE SYNTHESIS OF A MARINE SECOSTEROL FROM *GERSEMIA FRUTICOSA*.

Alexander Kuhl and Wolfgang Kreiser

Naturstoffchemie Universität Dortmund, Otto-Hahn-Straße 6, D-44221 Dortmund, Germany

For the envisaged synthesis of the cytotoxic effective constituent **1** from *gersemia fruticosa*, a north pacific soft coral, sterol **2** is considered a putative precursor. The preparation of **2** employing desoxycholic acid (**3**) as starting material is described herein.



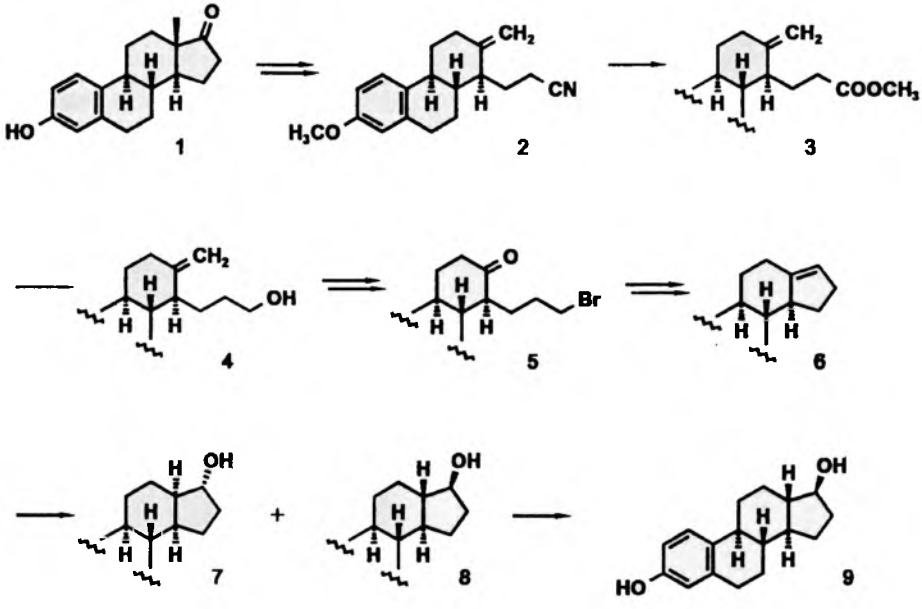
Enone **4** is obtained in five steps from **3** via selective protection, Jones oxidation and a bromination/dehydrobromination sequence. Reduction of the corresponding dienolacetate of **4** with $NaBH_4$ leads to the 3β-configurated homoallylalcohol, which is protected as methoxymethylether in order to ensure exclusive α-attack in the following hydroboration. For that purpose **5** is treated with $BH_3 \cdot S(CH_3)_2$ in THF. After oxidative work up and transacetalisation with $CH_2(OCH_3)_2/P_2O_5$ the selective deprotection of the 12α-acetate succeeds through methanolysis with $NaOCH_3$. Oxidation with PDC provides ketone **6**. Dehydrogenation of **6** is accomplished by SeO_2 in acetic acid under reflux and provides after acetylation **2** in 11 % total yield over 13 steps. In our point of view enone **2** may serve as a suitable intermediate for the synthesis of secosterol **1**, since the $\Delta^{9(11)}$-double bond allows further C-ring manipulation.

NEW SYNTHESIS OF 18-NORESTRADIOL

Alexander Kuhl[a], Heiko Karels[b] and Wolfgang Kreiser[a]

Naturstoffchemie Universität Dortmund, Otto-Hahn-Straße 6, D-44221 Dortmund, Germany[a] and Schering AG, Chemical Process Development, Enst-Schering-Straße 14, D-59179 Bergkamen, Germany[b]

Exemplified for the preparation of 18-norestradiol **(9)**, a new pathway for the synthesis of 18-norsteroids through intramolecular Wittig reaction as the key step is described. Starting from estrone **(1)** 18-norestradiol **(9)** is obtained in twelve steps with a total yield of 11 %.



After protection of **1** and transformation into the requisite oxime the δ-unsaturated seconitril **2** is obtained by Beckmann fragmention. Saponification of **2** and esterification of the raw acid with CH_2N_2, followed by reduction with $LiAlH_4$ leads to secosterol **4**. Formation of the primary bromide and its ozonolysis provides 13-keton **5**, which participates after preparation of the corresponding phosphonium salt as a suitable intermediate for an intramolecular Wittig reaction. Treatment of the alkene **6** with neat catecholborane under $LiBH_4$ promotion yielded a mixture of alcohols **7** and **8**. The desired norestradiolmethylether **(8)**, formed as the major diastereomer can be separated by HPLC and deprotected with an excess of DIBAH.

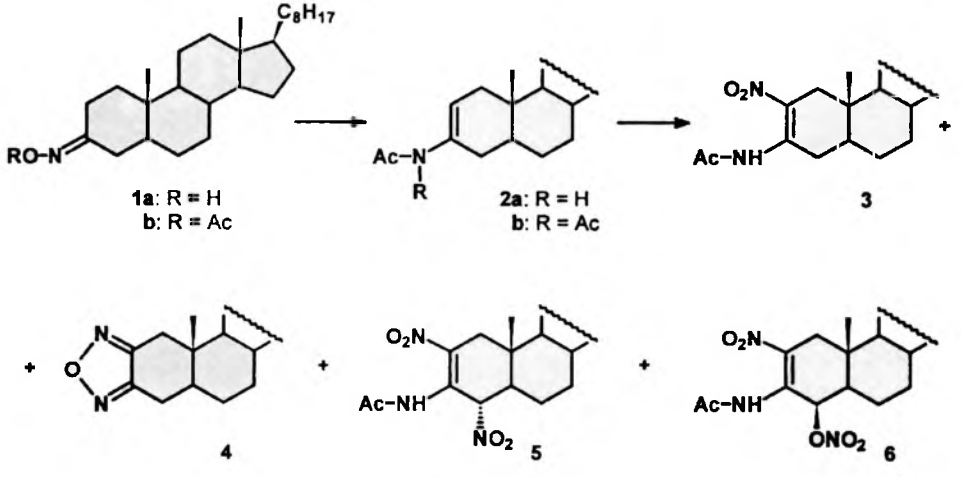
NITRATION OF N-ACETYL ENAMINES WITH ACETYL NITRATE

Agnieszka Z. Wilczewska, Zenon Łotowski, Monika Stępniowska, Agnieszka Gryszkiewicz, and Jacek W. Morzycki

Institute of Chemistry, University of Warsaw, Bialystok Branch, 15-443 Bialystok, Poland

The reactions of N-acetyl enamines with acetyl nitrate were studied. We have found that the reagent preferentially attacks on the terminal carbon atom of the double bond.

Nitration of N-acetylcholest-2-en-3-amine (**2a**) afforded the corresponding 2-nitro derivative (**3**), as the major product. Its structure is stabilized by intramolecular hydrogen bond. Other nitro enamides also showed strong hydrogen bonds except sterically hindered systems in steroid ring C.



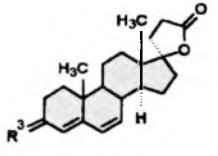
Products of further nitration and oxidation in an allylic position were also formed (e.g. **5** and **6**). An oxadiazole compound **4** was a minor product of N-acetyl enamine **2a** reaction.

An analysis of *enamide - N-acylimine* equilibrium in various systems was performed.

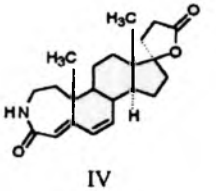
PARTIAL SYNTHETIC MODIFICATIONS OF CANRENONE

Rudolf Megges[a], Jürgen Weiland[a], Bernd Undeutsch[b],
Horst Büchting[a] and Rudolf Schön[a]
[a] Max-Delbrück-Center for Molecular Medicine, D-13122 Berlin-Buch, Germany,
[b]Jenapharm GmbH & Co. KG, D-07745 Jena, Germany

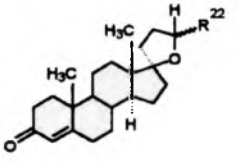
Canrenone (I) has been modified in order to test the possibility to increase its favourable but weak cardiac action. I is oximated ($NH_2OH{\cdot}HCl$/Py) to II. Its tosylation (TsCl/Py) to III, followed by BECKMANN rearrangement by heating on Al_2O_3 yields IV.- The lactol V reacts with Py·nHF at r.t. to give the epimeric 22-F derivatives VI and VII. - The 5β-H-tetrahydro-3β-canrenol (VIII) is transformed to the 3β-O-acetate IX (Ac_2O/Py), the 3β-O-trifluoroacetate X ($[CF_3CO]_2O$), the 3β-O-nitrite XI (t-BuONO) and the 3β-O-nitrate XII (Ac_2O/HNO_3). - The 5β-H-tetrahydrocanrenone (XIII) is 2α-hydroxylated by SeO_2 (XIV) and acetylated by Ac_2O/Py (XV). - Moreover, XIII is reacted to the 3-oxime XVI ($NH_2OH{\cdot}HCl$/Py). Its reduction (Al-Hg) leads to the mixture of the 3-amines XVII and XVIII (ca. 10:90). The reason for the excess formation of the *axial* epimer XVIII is not yet clear. Reaction with i-$PrSO_2Cl/NEt_3$ yields XIX and XX. ^{1}H-NMR of XX shows a narrow multiplet at 3.78 ppm (1H, 3α-H). ^{13}C-NMR of XX shows a signal at 24.0 ppm (DEPT: 3 H, 19-CH_3), indicating 5β-H configuration.. - The inhibitory potency on Na^+/K^+-ATPase from human heart or kidney is determined as an equivalent of digitalis-like cardiac activity. Compared to I, compounds X-XIII are the *least potent* inhibitors. The *greatest increases* are found (in increasing order) for IV, XIX, VI and VII. VII is nearly 20 times as active as I. For XX, the activity of XIX at least is to be expected, but the low solubility (15 µmol/l) of XX prevents the determination. The other compounds act about as strong as I. The results show that the activity of I may be increased by partial synthetic modifications at different points of the molecule.



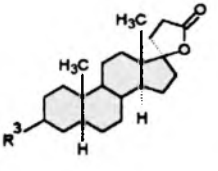
I: $R^3 = O$
II: $R^3 = NOH$
III: $R^3 = NOTs$



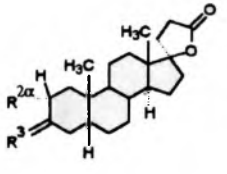
IV



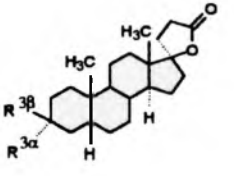
V: $R^{22} = OH$
VI: $R^{22} = F$ (apolar isomer)
VII: $R^{22} = F$ (polar isomer)



VIII: $R^3 = OH$
IX: $R^3 = OAc$
X: $R^3 = OCOCF_3$
XI: $R^3 = ONO$
XII: $R^3 = ONO_2$



XIII: $R^{2\alpha} = H$; $R^3 = O$
XIV: $R^{2\alpha} = OH$; $R^3 = O$
XV: $R^{2\alpha} = OAc$; $R^3 = O$
XVI: $R^{2\alpha} = H$; $R^3 = NOH$



XVII: $R^{3\alpha} = NH_2$; $R^{3\beta} = H$
XVIII: $R^{3\alpha} = H$; $R^{3\beta} = NH_2$
XIX: $R^{3\alpha} = NHSO_2iPr$; $R^{3\beta} = H$
XX: $R^{3\alpha} = H$; $R^{3\beta} = NHSO_2iPr$

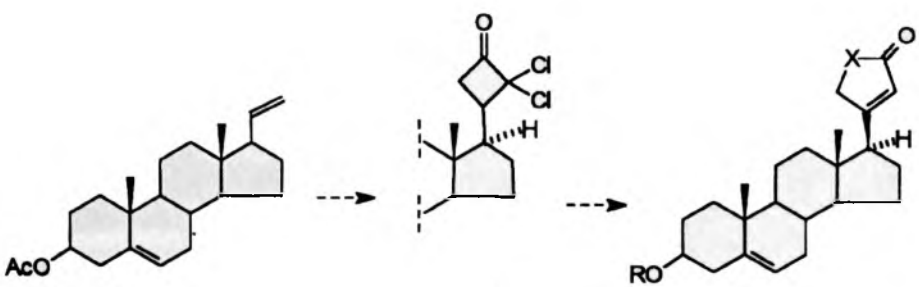
A NOVEL APPROACH TO BUTENOLIDE RING OF CARDENOLIDES

K. Blaszczyk and Z. Paryzek
Faculty of Chemistry, A. Mickiewicz University, Poznań, Poland

The cardenolides make a group of steroids of great medicinal importance. Among the naturally occuring cardiac glycosides, the 17β-lactone rings are considered as responsible for their pharmacological activity. However, active are also compounds with the lactone ring substituted with other groups. Therefore, synthetic efforts are directed toward derivatives with the modified side chains.

The aim of our work is to employ steroidal cyclobutanones as the key intermediates for the synthesis of the butenolide moiety of cardenolides and compounds with other 17β-substituent of potential utility.

In the model studies, 3β-acetoxypregna-5,20-diene **1**, prepared in four steps from the commercially available 3β-acetoxy-5-pregnen-20-one, was used as the starting material. The cycloaddition reaction of the diene **1** and dichloroketene gave cyclobutanone **2**, which was transformed to the steroidal butenolide **3a**. The Beckmann rearrangement of the cyclobutanone oxime, derivative of **2**, led to the aza anolog **3b**. Other synthetic possibilities with **2** will also be discussed.



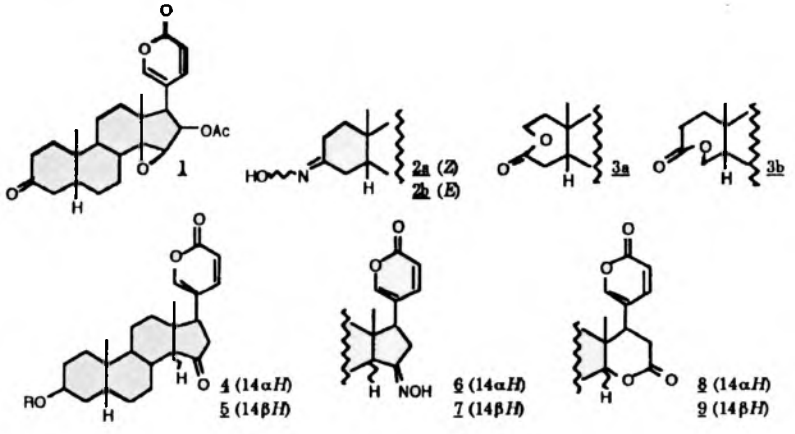
1 **2** **3a** X = O **3b** X = N

SYNTHESIS AND ANTINEOPLASTIC ACTIVITIES OF THE TOAD POISON BUFADIENOLIDE OXIMES AND CARBOLACTONES

Yoshiaki Kamano, Hirofumi Hashima and Ayano Kotake
(Faculty of Science, Kanagawa University, Japan)
Haruhisa Kizu
(Faculty of Pharmacy, Hokuriku University, Japan)

In interest, natural bufadienolides (A/B *cis* and C/D *cis* structure having α-pyrone ring at C-17) have important biological activities, recently such as antiviral and anticancer activities in addition to classic cardiac activity etc.. In our continued studies on relationship between bufadienolide structures and antineoplastic activities[1], new both the 3- and 15-oximes and the 3- and 15-carbolacones of some bufadienolides were synthesized.

As a typical compound, 3-oxo-cinobufagin (1) was used as starting material for synthesis of 3-oxime and 3-carbolactone. Reaction of ketone 1 with $NH_2OH \cdot HCl$ and AcONa afforded a mixture of 3-*Z*- and 3-*E*-oximes(2a and 2b). mCPBA oxidation of ketone 1 gave 3-oxo-[2.3]- (3a) and [3,4] (3b)-lactones, respectively. Similarly, two natural 15-oxo-bufadienolides, 14α-artebufogenin (4) and 14β-artebufogenin (5) were utilized for synthesis of 15-oximes and 15-carbolactones. The resulting two oximes (6 and 7) were obtained by similar oximic reaction of 15-ketones (4 and 5). Also, mCPBA oxidation of 15-ketones (4 and 5) afforded 15-(14α*H*)-(8) and 15-(14β*H*)-carbolactones (8 and 9), respectively.



The bioassay on antineoplastic activities of bufadienolides was performed by use of the cancer cells such as Human Liver Cancer Cell(PLC/PRF/5), Human epidermoid carcinoma KB cell, Human peripheral blood cancer HL-60 cell, Lymphoid neoplasma P388 cell, Human Liver Cancer HepG2 cell, etc.. It was very interested that bufadienolides showed the inhibitory activities against these cells except P388 cell.

[1] 38th Symposium on The Chemistry of Natural Products, Symposium Paper pp349-354 (at Sendai, 1996)

THE EFFECT OF ELECTROSTATIC PROPERTIES AND FEASIBILITY TO FORM H-BONDS ON THE ACTIVITY OF BRASSINOSTEROID SIDE CHAIN ANALOGS

Carme BROSA[a], Ismael ZAMORA[a], Ladislav KOHOUT[b]

[a] C.E.T.S. Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta 390, E 08017-Barcelona, Spain

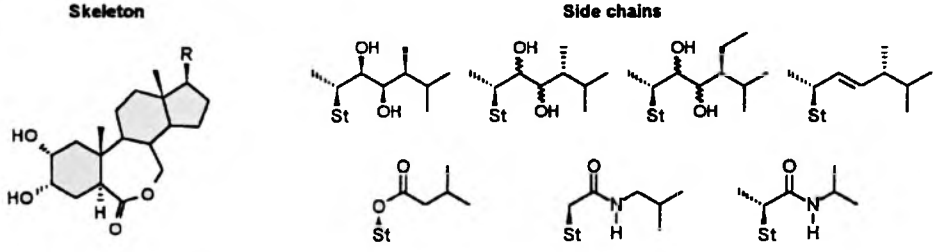
[b] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Praha 6, Czech Republic

Brassinosteroids, potent natural plant growth regulators, have an exciting potential use in agriculture due to their capability of improving crop yield and quality as well as overcoming environmental stress and herbicidal injury and controlling pathogenic diseases.[1]

With the aim of looking for other convenient analogs with a good activity/synthetic cost ratio for application in agriculture in an economic way, we have developed a methodology which allows us to establish a quantitative structure activity relationship (QSAR).[2] This methodology has been performed by means of molecular modeling calculations: we have found that the electrostatic charges of functional groups in a brassinosteroid as well as the feasibility to form H-bonds play an important role in the activity.[3]

In this communication the effect on the activity (modified rice lamina inclination test[4]) of a set of brassinosteroids differing only in the side chain will be discussed from two points of view: a) the electrostatic charges of the functional groups on each side chain studied and b) the feasibility to form hydrogen bonds.

Moreover, the conformational analysis of the amides and ester side chains[5,6] will be presented as well as their active conformer selection. These active conformations are essential for the evaluation of the similarity against brassinolide which is taken as reference.



LITERATURE

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* The work done by L. Kohout was supported by Grant N° 203/95/1309 of the Grant Agency of the Czech Republic

A HIGH SENSITIVE RICE LAMINA INCLINATION BIOASSAY FOR BRASSINOSTEROIDS

Carme BROSA, Emma TERRICABRAS, Lídia SOCA, Anna MODOLELL, Xavier TOMÁS

C.E.T.S. Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta 390, E 08017-Barcelona, Spain, brosa@iqs.url.es

Brassinosteroids, natural occurring potent plant growth regulators, have been evaluated as phytohormones in more than 20 bioassays typical for auxins, gibberellins or cytokinins.[1] From all of them, the rice lamina inclination test is one of the most specific for brassinosteroids and it is widely used for the evaluation of their activity.[2,3]

In our aim to found a quantitative structure-activity relationship (QSAR)[4] and due to the lack of homogeneity and the absence of statistical parameters on the activity data obtained from the literature we have developed a high sensitive modified rice lamina inclination test using *bahia* as cultivar.

The methodology employed in this bioassay as well as the selection of the most convenient cultivar will be presented and compared with our previous one following the procedure of Takeno and Pharis.[3] This procedure was applied to a set of brassinosteroids synthesized by us and the protocol essentially consists on:

a) germination: seeds were incubated in water in a growth chamber for 2 days at 30°C under white and UV fluorescent lamps (16 h light / 8 h darkness).

b) growth: selected germinated seeds were planted on the surface of 0.5 % aqueous agar and incubated under the above conditions for 4 days.

c) application: 95% ethanolic brassinosteroid solutions were applied to strictly selected seedlings by a microsyringe to the sheaths (rolled leave) up to the second lamina joint and they were kept for 2 days at 30°C in the dark in order to increase the seedlings sensibility.

d) evaluation: the angle between the unrolled second lamina and its sheath was measured using a circular protractor.

This procedure applied to *bahia* cultivar has shown a good reproducibility and repeatability and they are useful to be used as statistical parameters in the QSAR.

Moreover, the dose-dependent activity curves for some brassinosteroids will be presented as well as the procedure used to calculate the statistical parameters.

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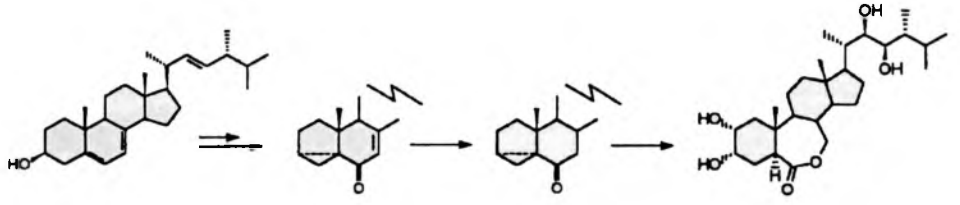
A NEW EFFICIENT PROCEDURE FOR THE REDUCTION OF Δ^7 ERGOSTAN DERIVATIVES

Carme BROSA, Carlos RODRÍGUEZ-SANTAMARTA

C.E.T.S. Institut Quimic de Sarrià, Universitat Ramon Llull, Via Augusta 390, E 08017- Barcelona, Spain, brosa@iqs.url.es

In the field of brassinosteroids, potent natural plant growth regulators,[1] most of synthetic efforts are focused to develop procedures to obtain the active compounds in an easier and economic way. One of the more interesting natural brassinosteroid to be applied in agriculture is 24-epibrassinolide since it has shown good results in different crops. In spite of 24-epibrassinolide having been synthesized in different ways, most of them involve a reduction step of Δ^7 double bond present in the ergosterol starting material.[2-10] This reduction is usually accomplished by treatment with lithium and liquid ammonia, being it the limiting step for large scale preparation.

On this communication we present an economic and mild alternative using sodium dithionite, a selective reagent for 1,4 reduction of conjugated ketones.[11] This reaction has been performed in the presence of a phase transfer catalyst.



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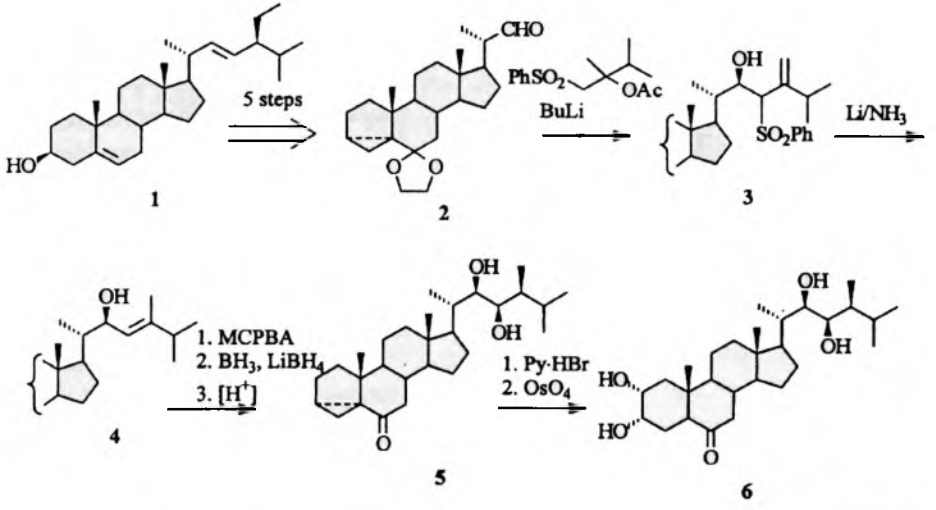
SYNTHESIS OF CASTASTERONE

Vladimir ZHABINSKII, Elena ZHERNOSEK, Vladimir KHRIPACH

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus

Brassinosteroids (BS) of 24S-series have been an attractive synthetic target since the first isolation of brassinolide[1]. This group of BS includes the most active hormones such as brassinolide and castasterone as well as their biosynthetic precursors[2]. Because of low availability of the starting material with the corresponding carbon skeleton of the side chain its construction is the most difficult part of BS synthesis[3].



The key stage of our synthesis of castasterone was the reaction[4] of the aldehyde **2** with the anion derived from the sulfon **3**. Treatment of the formed β-acetoxysulfone **4** with lithium in liquid ammonia led to the allylic alcohol **5** which was then transformed into the diol **5** and castasterone **6** by methods which are common[3] for this class of compounds.

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SYNTHETIC PATHWAYS TO 25-HYDROXY-BRASSINOSTEROIDS

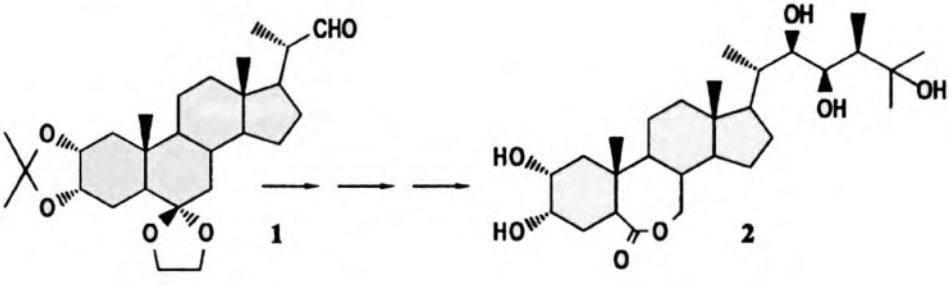
D. Lichtblau and G. Adam

Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle/S., Germany

Brassinolide and ist analogues, collectively known as brassinosteroids, are a new class of steroidal phytohormones with high growth promoting and anti-stress activity. Since the discovery of brassinolide in 1979, about 40 other naturally occurring brassinosteroids have been isolated and characterized from a broad variety of plants [1].

In cell suspension cultures of *Lycopersicon esculentum* 24-epibrassinolide was converted to 25-β-D-glucopyranosyloxy-24-epibrassinolide which afforded upon hydrolysis the pentahydroxylated brassinosteroid 25-hydroxy-24-epibrassinolide [2]. Such a hydroxylation at C-25 plays an important role also for other steroidal hormones, especially in the ecdysone and vitamin D metabolite series. A direct oxyfunctionalization of brassinosteroids at C-25 by C-H insertion with methyl(trifluoromethyl)dioxirane has been described [3].

Now we report a reaction sequence leading to 25-hydroxylated brassinosteroids of type **2** via side chain construction. As key intermediate the 22-aldehyd **1** was used, available from stigmasterol by functionalization of the A/B-ringsystem and side chain degradation. One of the most important and challenging problems in this synthesis is the stereoselective introduction of the contiguous chiral centres at C-22, -23 and -24 in the side chain moiety.



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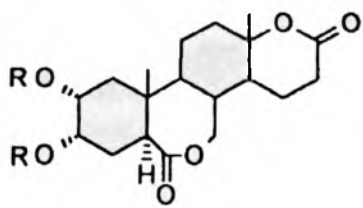
D-HOMO-17a-OXA-BRASSINOSTEROID ANALOGUES

Ladislav Kohout
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic
166 10 Prague 6, Czech Republic

In the course of our structure activity relationship studies on brassinosteroids (e.g. ref.[1-4]) we have synthesized a new type of brassinosteroids with an lactone group also in the D ring.



The synthesis starts from dehydroepiandosterone acetate. Introduction of the lactone grouping in the D ring has been carried out simultaneously with the synthesis of the lactone grouping in the B ring. The biological activity (the bean second internode bioassay) of the new compounds will be described.

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This work was supported by Grant No. 203/95/1309 of the Grant Agency of the Czech Republic.

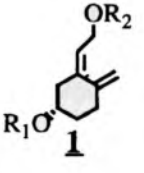
DEGRADATION TO AND TRANSFORMATIONS OF VITAMIN D A-RING FRAGMENTS

Wolfgang Reischl and Christian Hamon

Department of Organic Chemistry, University of Vienna, A-1090 Vienna, Austria

Continuous efforts in our laboratory is directed towards the synthesis of vitamin D analogs possessing unusual structural features. In this paper we like to disclose our studies upon degradation and transformations of vitamin D A-ring fragments, which are suitable for synthesizing further vitamin D analogs.

The A-ring fragment **1** is readily available by a literature known three step degradation sequence from vitamin D itself [1]. A method for further degradation to **2** will be presented as well as other approaches to this valuable synthon.



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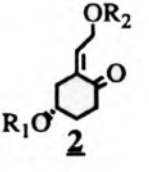

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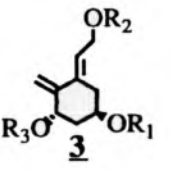

3

In addition a method for the direct introduction the 1α- hydroxyl group into fragment **1** will be presented.

Acknowledgement

Vitamin D_3 used in this study was generously provided by **SOLVAY DUPHAR**, Weesp, The Netherlands. Financial support by the **Österreichische Nationalbank** (Jubiläumsfondsprojekt Nr.: 4865) is gratefully acknowledged.

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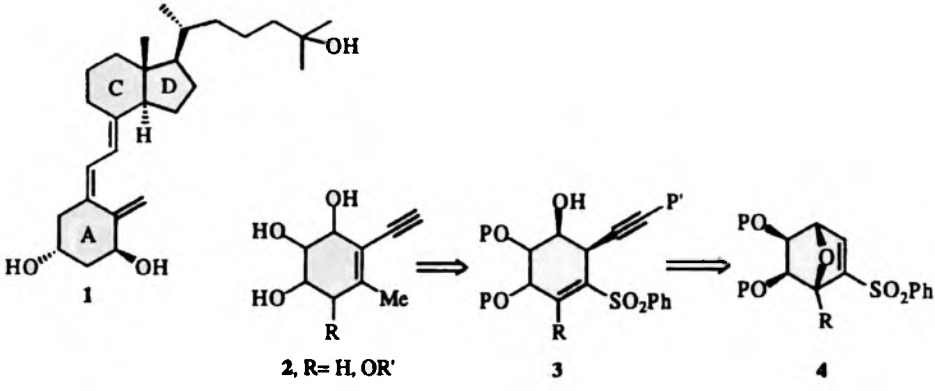
THE 7-OXABICYCLO[2.2.1]HEPTANE SYSTEM AS A VALUABLE STARTING MATERIAL FOR THE SYNTHESIS OF MODIFIED A RING VITAMIN D_3 ANALOGUES

Odón Arjona, Fátima Iradier, Joaquín Plumet.

Dpto. Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain.

The use of 7-oxanorbornene derivatives as starting material for the synthesis of complex molecules has been widely developed in our laboratory. In this context, we have studied two oxygen bridge opening reactions based on the deprotonation in α position to a 7-oxanorbornanic sulfone and on the nucleofilic addition to a 7-oxanorbornenic sulfone.[1]

In this communication, we wish to report the application of the alkylative oxa-bridge opening methodology to the vinylsulfones **4** in order to obtain highly functionalized vitamin D_3 **1** A ring analogues.[2]



In this way, addition of the appropriate acetylide to the vinylsulfones **4**[3] produce regio- and stereoselectively cyclohexenylsulfones **3**, which have been transformed succesfully in modified **A** rings **2**.

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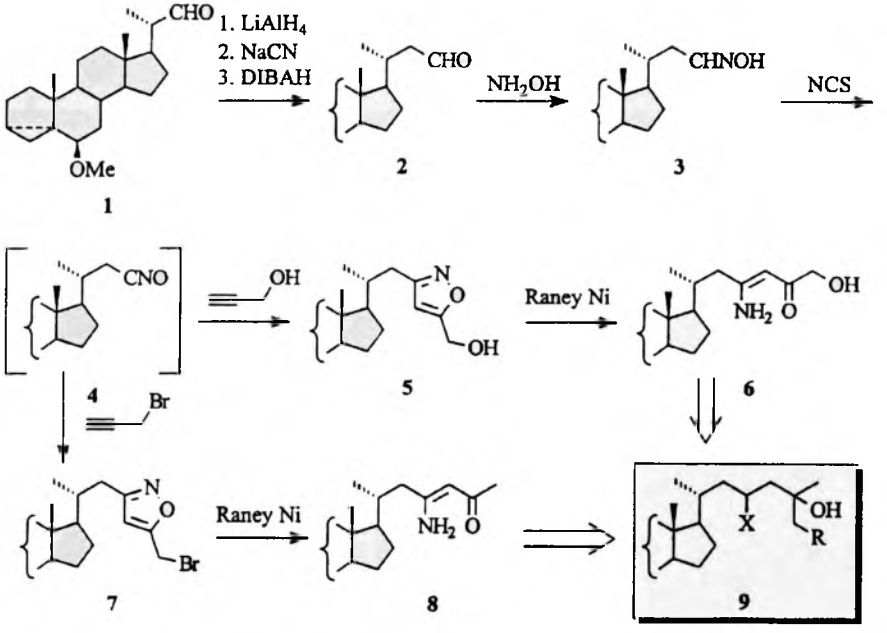
SYNTHESIS OF 23-ENAMINO-25-KETONES - POTENTIAL INTERMEDIATES FOR PREPARATION OF VITAMIN D ANALOGUES

Vladimir KHRIPACH, Vladimir ZHABINSKII, Nikolai PAVLOVSKII

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus

Synthesis of vitamin D analogues with modified side chains belongs to the most important tasks of the modern steroids chemistry[1]. It is concerned with the finding that $1\alpha,25\text{-}(OH)_2D_3$ possesses various types of hormonal activity apart from the regulation of calcium and phosphorous metabolism. In this respect investigation on synthesis of corresponding analogues is essential part in search for new compounds perspective as medicines, especially those without of an extra hypercalcemic activity.



Convenient intermediates for preparation of $1\alpha,25\text{-}(OH)_2D_3$ analogues functionalised at C-23 and C-26 could be enaminoketones like **6** and **8**. Their synthesis was performed starting from the aldehyde **1**. Its homologisation followed by oximation of the aldehyde **2** gave the oxime **3**. Oxidation of **3** with N-chlorosuccinimide produced the unstable nitrile oxide **4**, which on 1,3-dipolar cycloaddition reaction with propargyl alcohol or propargyl bromide led to the corresponding isoxasoles **5** and **7**. Their hydrogenation over Raney nickel furnished the enaminoketones **6** and **8**. The opening of the heterocycle of compound **7** was accompanied by debromination at C-26.

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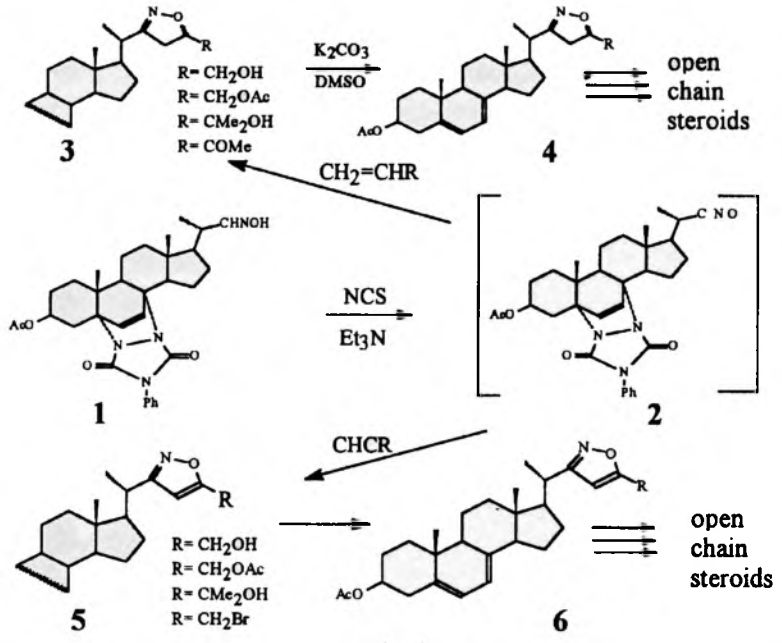
SYNTHESIS OF PROVITAMIN D ANALOGUES WITH ISOXAZOLE OR ISOXAZOLINE RING IN THE SIDE CHAIN

Raissa LITVINOVSKAYA, Nadezhda KOVAL, Vladimir KHRIPACH

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus

Synthetic approaches to steroid side chain construction using nitrile oxide methodology have been developed in our laboratory in the recent years. They were found to be efficient for the synthesis of side chains of biologically important natural polyhydroxysteroids such as brassinolide, some ecdysteroids, and marine sterols[1].



Here we are reporting a new application of this strategy to the synthesis of provitamin D analogues bearing isoxazole or isoxazoline cycle in the side chain. 1,3-Dipolar cycloaddition of the nitrile oxide **2** generated *in situ* from the oxime **1** to alkene or acetylene derivatives gave the adducts **3-6** in good yields. Their transformations into open-chain polyfunctionalized derivatives (24,25-dihydroxy-22-ketones, 24,26-dihydroxy-22-ketones, 25-hydroxy-22,24-diketones et all.) as well as chemical and spectral properties of synthesised compounds will be discussed.

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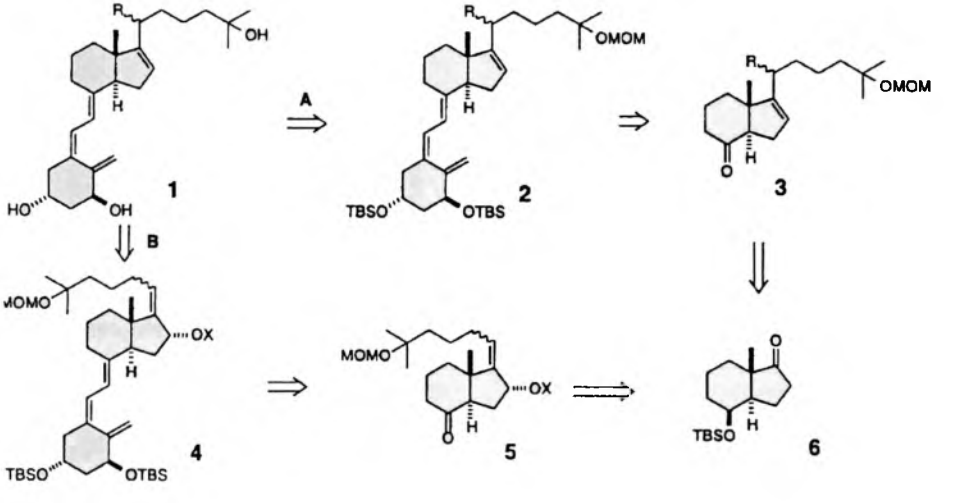
Efficient Copper-mediated Synthesis of C-20 and C-21 Modified Analogues of 16,17-Didehydrocalcitriol.

A. Mouriño, A. Rey, Y. Fall, J. Granja, and L. Castedo

Departamento de Química Orgánica y Unidad Asociada al CSIC, Facultad de Química, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain.

Two highly stereoselective synthetic routes to 16,17-didehydrocalcitriol and analogues modified at C-20 and C-21 have been developed both starting from ketone **6**. A key step in Route A is the construction of ketone **3** by S_N2' *syn* -displacement of allylic carbamates. Key steps in Route B are: (1) Wittig-Horner type coupling between ketone **5**, which bears an allylic ester group on the side chain, and the ylide derived from the Lythgoe-Roche phosphine oxide to form **4**; and (2) efficient S_N2' *syn*-displacement of the carbamate group of **4** by organocuprates without affecting the labile vitamin D triene system, to give, after deprotection, **1**. Route B is particularly attractive as an approach to diverse C-20 and C-21 vitamin D analogues for biological screening.

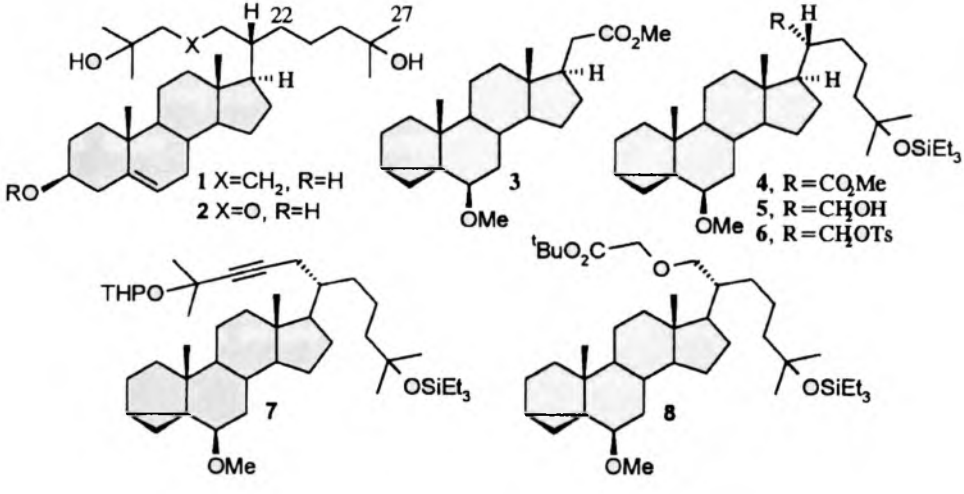


Synthesis of 21-(3-Methylbutyl)-cholest-5-ene-3β,3',25-triol and 21-(2-Methylpropoxy)-cholest-5-ene-2',3β,25-triol, the First "Double Side Chain" Cholesterol Analogues

Alicja Kurek-Tyrlik[a], Fliur Z. Makaev[a,§], Jerzy Wicha[a] and Martin J. Calverley[b]

Institute of Organic Chemistry, Polish Academy of Sciences[a],
POB 58, 01-224 Warsaw 42, Poland
Leo Pharmaceutical Products[b],
55, Industriparken, DK-2750 Ballerup, Denmark

A synthesis of 21-(3-hydroxy-3-methylbutyl)- and 21-(2-hydroxy-2-methylpropoxy)cholestane derivatives **1** and **2**, formally being double chain hybrid (20*R*)- and (20*S*)-cholesterol analogues, will be presented. The C-22 to C-27 section of the 25-hydroxycholestane side chain was established by stereoselective alkylation with 5-bromo-2-methyl-2-(triethylsilyl)oxypentane of the easily accessible pregnanoic ester **3**. Reduction of the ester **4** to the 21-alcohol **5** permitted elaboration of a second hydroxylated side chain, either via the tosylate **6** by alkynation yielding the intermediate **7** or by the alcohol **5** alkylation with bromoacetate (yielding **8**) followed by reaction with methyl magnesium bromide.



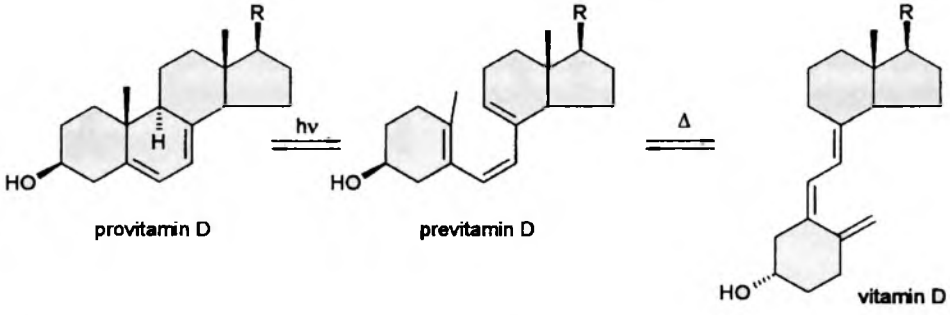
[§]On leave from Institute of Chemistry, Academy of Scineces of Republic of Moldova, Kishiniev, Moldova.

SYNTHESIS AND REARRANGEMENT OF PROVITAMIN D ANALOGS WITH ELECTRON-WITHDRAWING SUBSTITUENTS AT C-19

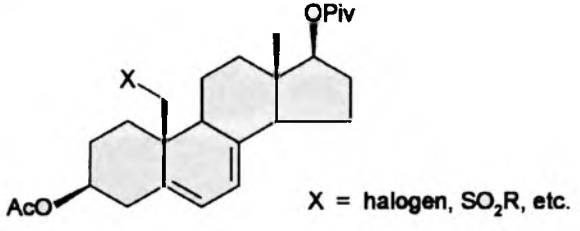
P. Grzegorzewski, I. Koładkiewicz and R. R. Siciński

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

Steroidal 5,7-dienes (provitamins D) are known to undergo a photochemical ring opening to the corresponding B-seco isomers, i.e. previtamins D. These, in turn, can be thermally converted to the vitamin D compounds possessing the 5,7,10(19)-triene moiety.



During these pericyclic isomerizations the 10β-methyl group in a provitamin D molecule undergoes a critical conversion into an exomethylene unit, which is a part of the vitamin D triene system. Consequently, analogous rearrangements in the series of 19-functionalized steroids seem to be a worthwhile research target and, as was indicated by our previous experience, effects of electron-withdrawing substituents could be of interest. The synthesis of 19-halogenated provitamins D, as well as other 5,7-dienes substituted at C-19 with electron-withdrawing groups, will be described and their rearrangement processes presented.



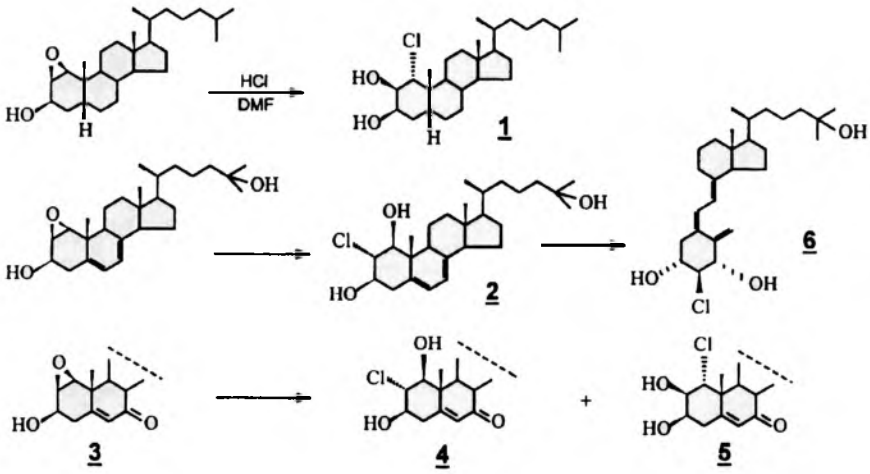
ANOMALOUS OPENING OF STEROIDAL 1β,2β-EPOXIDES - INFLUENCE OF THE B-RING STRUCTURE

Manuela GONSCHIOR[a], Wolfgang GÜNTHER[a], Christian ROBL[b], Bruno SCHÖNECKER[a]

[a] Institut für Organische und Makromolekulare Chemie der Friedrich-Schiller-Universität Jena, Humboldtstr. 10, D-07743 Jena, Deutschland

[b] Institut für Anorganische und Analytische Chemie der Friedrich-Schiller-Universität Jena, August-Bebel-Str. 2, D-07743 Jena, Deutschland

Reaction of hydrochloric acid with 1β,2β-epoxy-cholestan-3β-ol in N,N-dimethyl-formamide gives the normal trans-diaxial opening product (**1**), in agreement with other opening reactions. In contrast, the analogous reaction with 1β,2β-epoxy-cholesta-5,7-dien-3β,25-diol furnished the trans-diequatorial cleavage product (**2**). The opening of the 7-oxo-5-en-1β,2β-epoxide (**3**) proceeds in both directions to **4** and **5**. These results show that the unsaturated character of the B-ring is responsible for the anomalous cleavage of the epoxide ring.



^{1}H nmr data of the cleavage products and x-ray data of the epoxides are presented. Using this anomalous cleavage a route has been developed to the new class of 2α-substituted 1-epicalcitriols (**6**).

CHIRAL ANALOGS OF 1,25-DIHYDROXYCHOLECALCIFEROL

Odrzywolska, M[a]., Chodyński, M[a], Fitak, H[a]., Halkes S.J.,[b], van de Velde, J-P[b]., and Kutner, A[a]

[a]Pharmaceutical Research Institute, 8 Rydygiera, 01-793 Warszawa, Poland, and [b]Solvay Duphar B.V., 1381 Weesp, The Netherlands

Separation of the regulatory effect on calcium metabolism and antiproliferative activity of vitamin D compounds was recently obtained by synthetic modifications of the most active hormonal form of vitamin D [1,25-dihydroxycholecalciferol, 1,25-$(OH)_2D_3$]. The separation was obtained by modification of the 3D arrangement of hydroxyls located at C-1, C-3 and C-25 in the vitamin D molecule. This was achieved by several means, including lengthening of the aliphatic side-chain of the parent compound by one or two carbon units, placing the heteroatom at C-22 in the side-chain, and also by introducing a hydroxyalkyl substituent at C-2 in the A-ring. In our work on the most efficient antiproliferative agent from this group we have developed synthetic methods for introducing an additional chiral center in the extended aliphatic side-chain of 1,25-$(OH)_2D_3$. The goal was to test the enantioselective interaction of a chiral analog with the vitamin D receptor (VDR). In our convergent strategy for the synthesis of side-chain modified analogs of 1,25-$(OH)_2D_3$ we used a novel vitamin D synthon that might be also applied as an intermediate in the preparation of 1,25-$(OH)_2D_3$. Vitamin D synthon was coupled with homochiral side-chain fragments to give final analogs, after removal of activating and protecting groups. Both enantiomers of the chiral side-chain fragments were obtained from R-(+)- and S-(-)-methyl glycidols, respectively. In the key synthetic step the oxirane ring of the glycidol derivative was opened with the vitamin D synthon containing phenylsulfone as the carboanion stabilizing moiety. Analogs containing an additional hydroxyl at the terminal carbon atom in the side-chain were obtained to test the increased binding of the chiral analog to VDR. New chiral analogs are screened for binding affinity for the vitamin D proteins (VDR and DBP) and also, for the activity in stimulation of cell differentiation of malignant cells and human epidermal keratinocytes.

[1] Odrzywolska M., Chodyński, M., Halkes, S.J., van de Velde J-P., Kutner A., Pol. Pat. Appl. P-316696, 1996.

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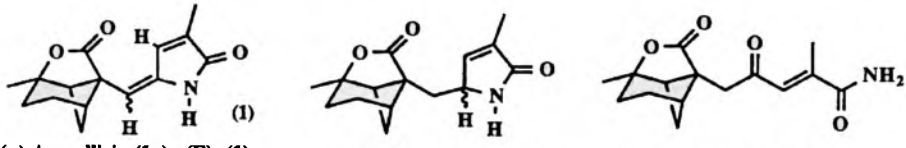
TOTAL SYNTHESES OF (+)-AMPULLICIN, (+)-ISOAMPULLICIN AND DIHYDROAMPULLICIN. THREE GROWTH REGULATORS FROM *Ampulliferina* Sp. No. 27.

Rosario Rico and Francisco Bermejo*. Departamento de Química Orgánica. Universidad de Salamanca, 37008 Salamanca, Spain.

Ampullicin (**1a**), Isoampullicin (**1b**), and Dihydroampullicin (**2**) (Fig.1) are sesquiterpene amides isolated from a culture filtrate of an *Ampulliferina*-like fungus sp. No. 27. by Kimura and col.[1] These sesquiterpene amides accelerate the root growth of lettuce seedlings by 200% at doses of 300 and 30 mg/L.

The structural arrangements of (**1a**), (**1b**) and (**2**) are closely related to Pinthunamide (**3**), also isolated from the same natural source, whose structure has been determined by single-crystal X-ray diffraction.[2]



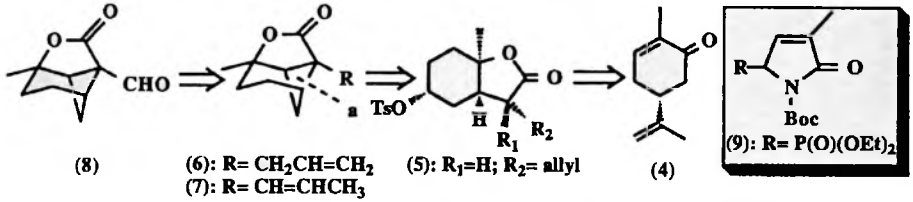
(+)-Ampullicin (1a)= (E)- (1)
(+)-Isoampullicin (1b)= (Z)- (1)

(+)-Dihydroampullicin (2)

(+)-Pinthunamide (3)

Fig.1

According to our retrosynthetic analysis the three natural products are envisaged to be accesssible by homologation of aldehyde (**8**), easily prepared using the "type a" disconnection from the bicyclic tosyloxy lactone (**5**), which can be obtained enantiomerically pure from both enantiomers of carvone (Scheme1)[3].



(8)

(6): R= $CH_2CH=CH_2$
(7): R= $CH=CHCH_3$

(5): R_1=H; R_2= allyl

(4)

(9): R= $P(O)(OEt)_2$

Scheme1

Access to the bicyclic lactone (**5**) from R-(-)-carvone (**4**) was accomplished by application of a 14-step sequence in 12% overall yield. Isomerization of the allylic fragment of (**6**) to the internal olefin (**7**) followed by ozonolysis allowed us to isolate the carbaldehyde (**8**) in excellent yield (85%).

Treatment of the phosphonate (**9**) with NaH in THF followed by the addition of carbaldehyde (**8**) led to the exclusive formation of the N-Boc-ampullicin in 76% yield. N-Boc deprotection by treatment with trifluoroacetic acid led to (**1a**) in quantitative yields. The thermodynamically more stable isomer (**1b**) was prepared quantitatively by isomerizing (**1a**) with iodine in refluxing benzene.

Selective reduction of the γ,δ-double bond of either (**1a**) or (**1b**) by hydrogenation over nickel on alumina afforded (**2**) with excellent yields (85%).

References:

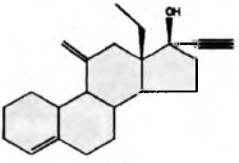
1. Kimura, Y.; Nakajima, H.; Hamasaki, T.; Matsumoto, T.; Matsuda, Y.; Tsuneda, A.; *Agric. Biol. Chem.*, **1990**, *54*, 813-814.
2. Kimura, Y.; Nakajima, H.; Hamasaki, T.; Sugawara, F.; Parkanyi, L.; Clardy, J. *Tetrahedron Lett.*, **1989**, *30*, 1267-1270.
3. Rico, R.; Bermejo, F. *Tetrahedron Lett.*, **1995**, *36*, 7889-7892. *ibid.* **1996**,*37*, 5809-5812

TOTAL SYNTHESIS OF DESOGESTREL

Johannes Leemhuis and Marinus B. Groen,

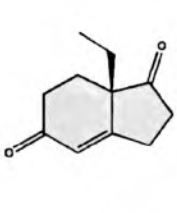
Department of Medicinal Chemistry I, Scientific Development Group,
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.

Desogestrel (**1**) is a potent progestagen widely used for contraception. The current technical synthesis of **1** is based on diosgenin, using a lengthy route (approx. 24 steps).



1

We have been exploring various total syntheses of desogestrel as alternatives to the current partial synthesis. A promising approach starts with the Hajos-Parrish diketone **2** which can be readily obtained in optically pure form. The known sulphone **3**, obtained from **2** in 4 steps was condensed with the keto-ester **4**, which was easily synthesized from cheap starting materials (tetrahydrofuran, ethyl acetoacetate). The resulting product **5** gave, upon treatment with base and heating, the tricyclic product **6**.



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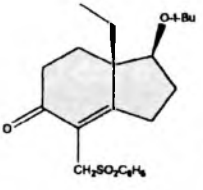

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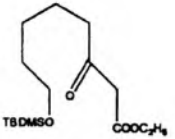

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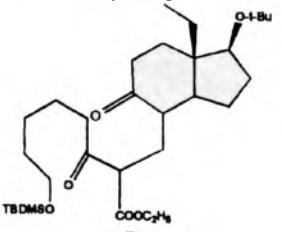
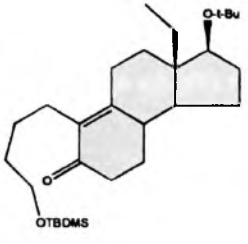


5

Allylic oxidation of **6** (SeO_2, then H_2CrO_4), followed by catalytic hydrogenation, gave the ketone **7** which was converted into the phosphonium salt **8.** Intramolecular Wittig reaction, with concomitant epimerization at C-10, gave the known steroid **9.** The conversion of **9** into **1** was carried out in a straightforward fashion.



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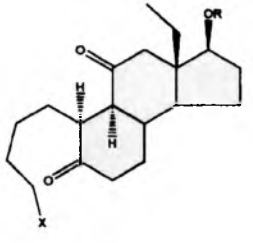
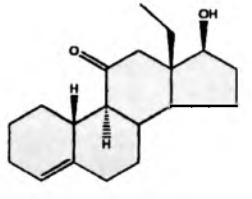


7 R = t-Bu X = OTBDMS
8 R = H X = $(C_6H_5)_3P^+$ I^-



9

Use of the New Alkenation in the Synthesis of Vitamin D_3

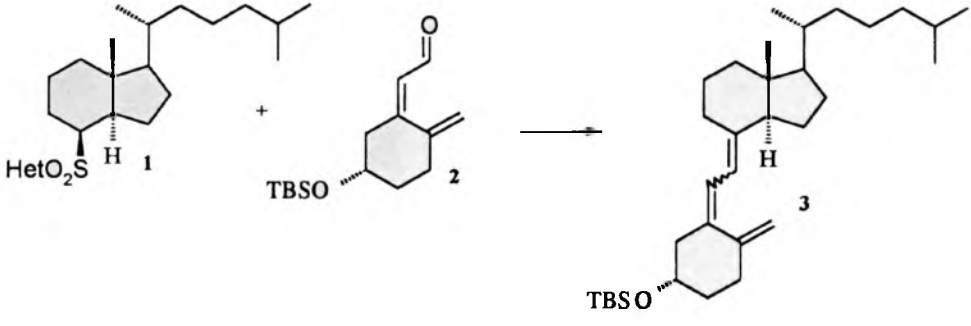
P. Blakemore, P. J. Kocieński

Department of Organic Chemistry, University of Glasgow, G12 8QQ Glasgow, UK

S. Marczak, J. Wicha

Institute of Organic Chemistry, Polish Academy of Sciences, 01224 Warsaw, Poland

A new approach to the Vitamin D_3 synthesis will be presented which involves one step coupling of aldehyde **2** and heterocyclic sulfones **1** accordingly to a new method developed by Sylvestre Julia *et al.*[1]. The effect of base counter-ion (Li, Na, K, Mg) and solvent on the outcome of this one pot procedure will be discussed.



1. a. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc Chim. Fr.* **1993**, 130, 336-357.
b. Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc Chim. Fr.* **1993**, 130, 856-878.

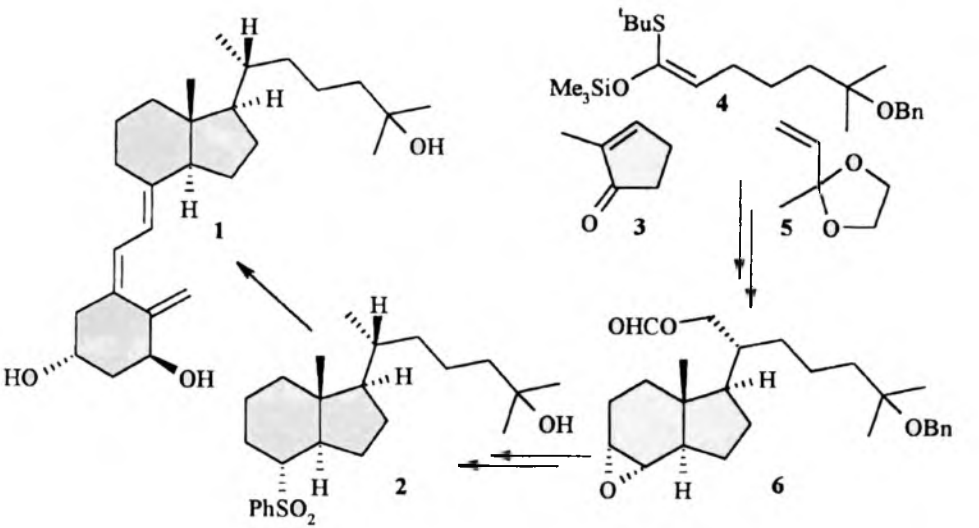
Short Diastereoselective Synthesis of 4-Benzenesulfonyl-1-(1,5-dimethyl-hexyl)-7a-methyl-octahydro-indene, a Building Block for the Vitamin D Synthesis

S. Marczak, K. Michalak, J. Wicha

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

Recent discoveries of new biological functions of 1α,25-dihydroksyvitamin D_3 **1** and congeners have renewed and further stimulated interest in a synthesis of de-AB-cholestane derivatives and related precursors of the vitamin D northern segment.

A new approach to sulfone **2** will be presented which involves tandem Michael-Mukaiyama addition **3**, **4** and **5** for the carbon skeleton formation, the trans-hydrinadane unit construction by hydrogenolysis of the respective allilic formate, sulfonyl group introduction *via* epoxide **6**.



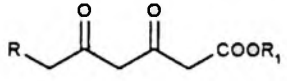
Enantioselective Hydrogenation of Multicarbonyl Systems

Jarosław Kiegiel[a], Aldona Cybulska[a], Julita Jóźwik[a], Grzegorz Juszkiewicz[a], Jolanta Polkowska[a], and Janusz Jurczak[a,b]

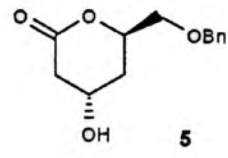
a) Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland
b) Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

Enantioselective hydrogenation of ketones was proved to be an effective tool in the synthesis of natural products. High enantiomeric excesses and high yields are obtained using ruthenium-diphosphine chiral catalysts and 3-oxoesters as substrates. This is the case because effective hydrogenation requires chelation of the central metal atom in the transition state.

However, a presence of additional keto groups in the substrate molecule may be an advantage in designing new syntheses of natural products based on asymmetric hydrogenation. The problem is how this additional keto groups interfere with ketoester chelation system, and consequently how they affect the enantioselectivity of hydrogenation.



1 R = H
2 R = OBn
3 R = $COOR_1$
R_1 = Me or tBu



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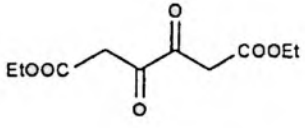

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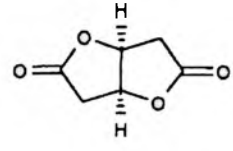


6

In this communication we present the results of asymmetric hydrogenation of some multicarbonyl systems in the presence of {RuCl[(R)- or (S)-BINAP][*p*-cymene]}Cl catalyst. We tested simple model molecules **1**, **2**, **3** and **4** as substrates for hydrogenation. In general, enantiomeric excesses were high to very high. Optically pure compounds **5** and **6**, intermediates in the synthesis of some natural products were obtained after transformation of hydrogenation products of **2** and **4**.

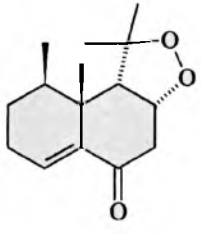
Circular Dichroism of Steroidal and Related Cisoid α,β-Unsaturated Ketones. Octant rule *versus* helicity rule for nπ* transition?

Jadwiga Frelek [a], Wojciech J. Szczepek [b], Hans Peter Weiβ [c], Guido J. Reiβ [d], Walter Frank [d]

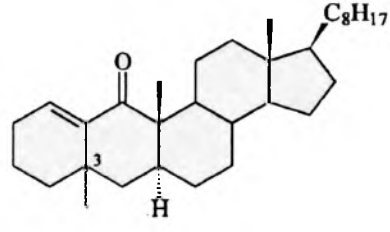
[a] Institute of Organic Chemistry of the Polish Academy of Sciences, PL-01-224 Warszawa, Kasprzaka 44
[b] Pharmaceutical Research Institute, PL-01-793 Warszawa, Rydygiera 8
[c] Department of Chemistry, Ruhr-University Bochum, D-44780 Bochum, Universitätstr. 150
[d] Department of Chemistry, University of Kaiserslautern, D-67663 Kaiserslautern, Erwin-Schrödinger-Straße

Recently[1] we have found that the sign of the enone torsion angle for unsubstituted as well as substituted cisoid enones correlates with the sign of the nπ* Cotton effect (CE) if it is monosignate. In the case of bisignate curve within nπ* transition, the enone helicity corresponds to the sign of the long wavelength branch of the nπ* CD. However, one of the nardosinone derivatives - compound **1** - does not follow the rule giving a positive nπ* CE although its conformational analysis by molecular mechanics calculations indicates a negative enone helicity.

To explain this exception to the rule we decided to synthesize suitable model cisoid enones **2** and **3**, which differ in geometry of cycloheksanone moiety, to determine their geometries by MMX calculations and X-ray analysis, and to compare the structural parameters with the CD data.



1 nπ* CE: +0.75 (343)



2 3α nπ* CE: –0.76 (326), +0.16 (286)
3 3β nπ* CE: –2.08 (321)

The enones **2** and **3** were obtained in four-step synthesis from readily available 5α-cholest-1-en-3-one. Their X-ray data support the results of conformational analysis by MMX calculations showing a negative enone torsion angle and nearly symmetrical chair conformation of cyclohexanone unit for **2** as well as a positive enone helicity and distorted non-symmetrical boat conformation of cyclohexanone unit in the case of **3**.

The nπ* CD band of **2** in acetonitrile is bisignate and according to the rule[1] the stronger negative long wavelength branch of the CE correlates with the sign of the enone helicity. Enone **3** exhibits in all solvents studied, as well as in the whole temperature range, strong negative nπ* CD band in contradiction to the positive one expected on the basis of the positive enone helicity. The explanation of this exception will be proposed.

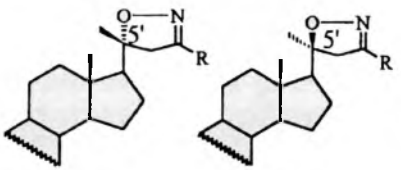
1. J. Frelek, W.J. Szczepek, and H.P. Weiβ, *Tetrahedron Asymm.* **6**, 1419 (1995).

CIRCULAR DICHROISM IN DETERMINATION OF CONFIGURATION OF STEROID SIDE CHAINS MODIFIED BY FRAGMENT OF Δ^2-ISOXAZOLINES

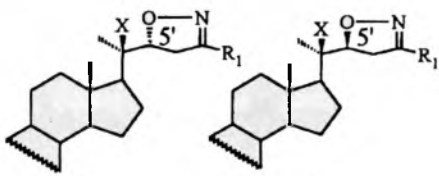
Nikolai GARBUZ, Raissa LITVINOVSKAYA, Galina YANKOVSKAYA, Vladimir KHRIPACH

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, Zhodinskaya 5/2, 220141 Minsk, Belarus

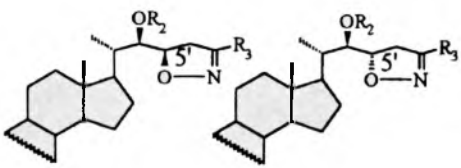
A simple method for configuration assignment of new chiral center (C-5') resulting from 1,3-dipolar cycloaddition of nitrile oxides with terminal steroidal olefines (Δ^{20}, Δ^{22}, and Δ^{23}) has been elaborated. It is based on study of CD-spectral parametres of corresponding adducts: 17- , 20-, and 22-isoxazolinylsteroids **1-4**. Compounds of this type are known as synthetic intermediates of some biologically impotant natural steroids[1,2].



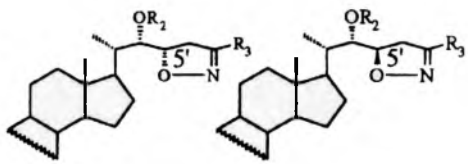
1a **1b**



2a **2b**



3a **3b**



4a **4b**

An examination of their CD curves showed that the negative Cotton effect at 212-224 nm is characteristic of 5'R-epimers, and positive Cotton effect is the specific feature of 5'S epimers.

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[1]Baranovskii A.V., Litvinovskaya R.P, Khripach V.A., Rus.Chem.Rev. **62**(7), 661 (1993).

[2] Litvinovskaya R., Drach S., Khripach V., Mend. Comm., 215 (1995).

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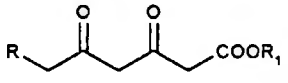

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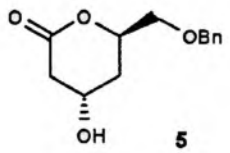

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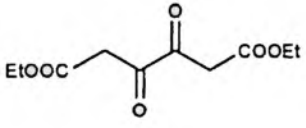

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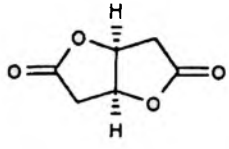

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In this communication we present the results of asymmetric hydrogenation of some multicarbonyl systems in the presence of {RuCl[(R)- or (S)-BINAP][*p*-cymene]}Cl catalyst. We tested simple model molecules **1**, **2**, **3** and **4** as substrates for hydrogenation. In general, enantiomeric excesses were high to very high. Optically pure compounds **5** and **6**, intermediates in the synthesis of some natural products were obtained after transformation of hydrogenation products of **2** and **4**.

Preparation of α-Hydroxyketones, β-Hydroxyesters and Homoallylic Alcohols Using Metals on Solid Supports

Mieczysław Mąkosza, Karol Grela, Piotr Nieczypor

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

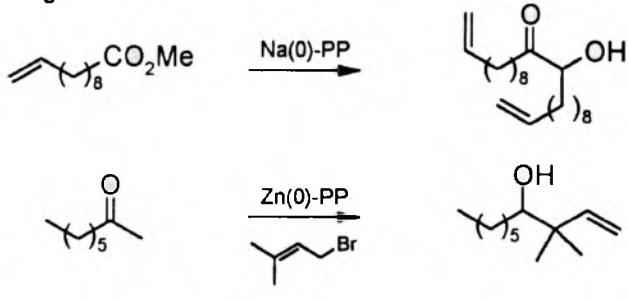
Reagents adsorbed on solid supports are widely used in organic synthesis. They offer some significant advantages such as high activity often connected with better selectivity, simplicity of handling of active reagents, and easy work-up. Among reagents of particular interest is 'high-surface sodium' - metallic sodium deposited on solid support (alumina, titanium dioxide, sodium chloride).

The common methods of preparation of supported sodium consist in vigorous mixing/grinding of the support with melted sodium metal in inert atmosphere at 180 - 190°C or in boiling solvent (toluene, xylenes).

We have found that 'high-surface metals' can be conveniently prepared *via* deposition of alkali or alkaline metals on solid support from its solution in liquid ammonia. In this procedure support materials such as powdered NaCl, glass beads or poly(propylene) were used. 'High-surface alkali metals' could be applied for the preparation of other supported metals (*e.g.* Zn) - *via* reduction of corresponding metal salts.

These reagents were used *inter alia* for the acyloin reaction, Reformatski and Barbier type reactions to give the corresponding α-hydroxyketones, β-hydroxyesters and homoallylic alcohols in good to excellent yields.

e.g.



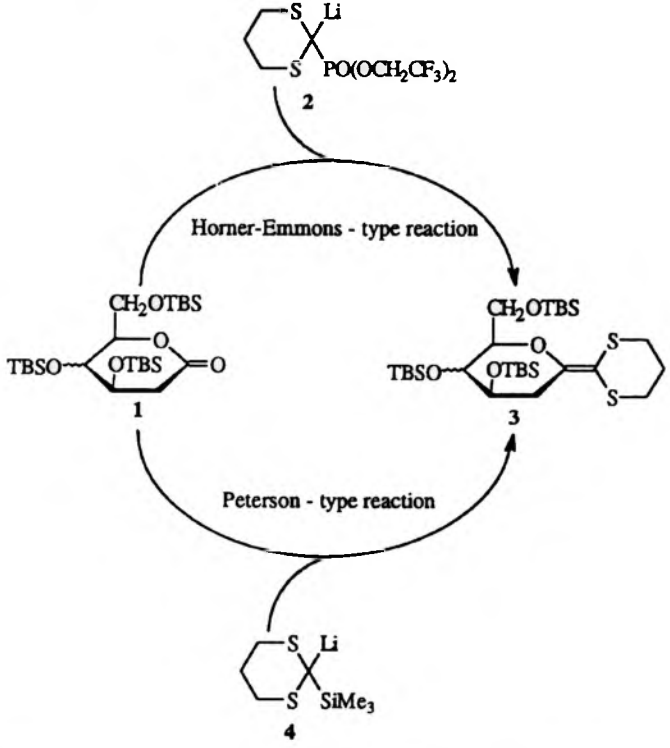
PP = poly(propylene)

KETENE THIOACETALS SYNTHESIS FROM SUGAR LACTONES: ONE CARBON HOMOLOGATION OF 2-DEOXY-HEXOPYRANOSES AT C-1

JACEK MŁYNARSKI AND ANNA BANASZEK

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, POLAND

The reaction of the *O*-silylated 2-deoxy lactones **1** with phosphonate **2** [1] furnished the ketene thioacetals **3** as sole products. The same compounds **3** were achieved using 2-lithio-2-trimethylsilyl-1,3-dithiane (**4**) [2] as a reagent.



The olefinic linkage in the ketene thioacetals undegoes the reduction with Et_3SiH / CF_3CO_2H in a protonation-hydride transfer process. The products thus obtained can serve as versatile synthetic synthons. This can be illustrated by one example: methanolysis of the above thioacetals promoted by HgO / $HgCl_2$ in MeOH provides methyl ester of 2,3-dideoxy-hept-2-ulosonic acids belonging to the modified sialic acid type sugars.

References:

[1] M. Mikołajczyk, P.P. Graczyk, M.W. Wieczorek; *J. Org. Chem.*, 59 (1994) 1672-1693.

[2] F.A. Carey and A.S. Court; *J. Org. Chem.*, 37 (1972) 1926-1929.

AUTHOR INDEX