# 2. Highlights of Triterpene Research in *Helvetica Chimica Acta* 1918–1992

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**1. Introduction.** – It is the aim of this contribution to comment on some selected topics of triterpene research in a historical context in order to make the non-expert aware of the efforts and accomplishments in this area as documented in *Helvetica Chimica Acta* in the last 75 years.

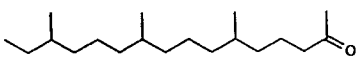
It seems that research in triterpene chemistry has been started and carried on for quite some time simply as a matter of curiosity in natural-product chemistry, since, already during the first decade of research, it became obvious that the triterpenes would never approach the significance of the other terpenoids with respect to the therapeutic use (steroids) or olfactory application (mono- and sesquiterpenoids). However, from the purely scientific point of view, the significance of triterpene research is undisputed. The systemic investigation of these compounds had a strong impact on the structure elucidation of the steroids carried out at the same time. The structural correlation of these two classes of compounds also initiated conformational analysis and led to the recognition of stereospecific '*Wagner-Meerwein*'-type rearrangements for explaining Me and H shifts on a rigid template. Furthermore, a biosynthetic scheme evolved for the formation of triterpenes from the acyclic squalene involving carbenium-ion-initiated stereospecific ring closure [1].

The discovery of this enzymatic reaction had a 'long-range' effect on synthetic organic chemistry, since it proved to be very useful to mimic such cyclizations employing *Lewis* acids [2]. And last but not least, in the course of these studies the schematic 'isoprene rule', originally suggested by *Wallach* as early as 1887 [3], became 'biogenetic' [4]. Accordingly, terpenes were defined as compounds that could be derived by cyclization and rearrangement from an aliphatic precursor synthesized from isoprene units. These ideas encouraged thousands of investigations in the terpene field to uncover nature's pathways producing these molecules [5].

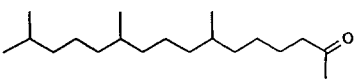
Contributions to the chemistry of triterpenes started to appear in *Helvetica Chimica Acta* in the early thirties. To understand the experimental facilities at this time, one has to remember that laboratories were devoid of IR, NMR, and mass spectrometers. Therefore, the characterization of compounds rested mainly on measuring m.p./b.p., $\alpha_D$, *d*, $n_D$, and using combustion analysis. Structure elucidation was largely accomplished by oxidative degradations, and the most important of all was the pyrolysis in the presence of sulfur or preferably selenium. These reactions had already served a great deal to determine the structures of cyclic sesquiterpenes and diterpenes, so that it could be estimated which substructures would yield certain substituted naphthalenes or phenanthrenes (see [6]). This experience together with employing the 'isoprene rule' as a connective guide-line [7] led in many cases to establish the correct constitutions of the triterpenoids. Even the relative configuration of the frameworks' substituents were determined without spectroscopy by correlation to known diterpenes, and as soon as the significance of conforma-

tional analysis was recognized, for fused ring systems [8]. From the early beginning, the compulsive reader of *HCA* has witnessed a great part of the history of triterpene chemistry, last but not least, because most contributions of this research area were accomplished in Swiss laboratories.

**Acyclic Triterpenes.** – One of the first milestones of triterpene chemistry was published in *HCA* by ***Paul Karrer*** in 1930 [9]. Analyzing the degradation products obtained from lycopine and $\beta$-carotine, he concluded, that both tetraterpenes have a symmetrical constitution (see [10]). *Karrer* realized that the same was true for *squalene*, re-investigating *Heilbron*'s experiments [11]. From the degradation of partially hydrogenated squalene, *Heilbron et al.* [11] had isolated a $C_{19}$ ketone for which he suggested the structure **1**.



**1**

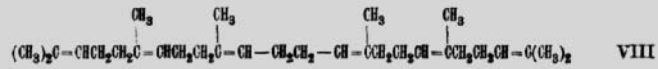


**2**

By synthesis, *Karrer* demonstrated that this was incorrect, and that the $C_{19}$ ketone was in fact **2**, leading to the conclusion, that squalene should have structure **VIII** (*Fig. 1*) [9].

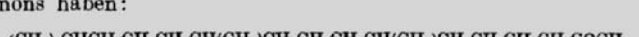
*Fig. 1*

Wenn Squalen nicht Formel VII, sondern die symmetrische Formel VIII, die den symmetrischen Lycopin- und Carotinformeln V und VI analog gebaut wäre, besitzt:

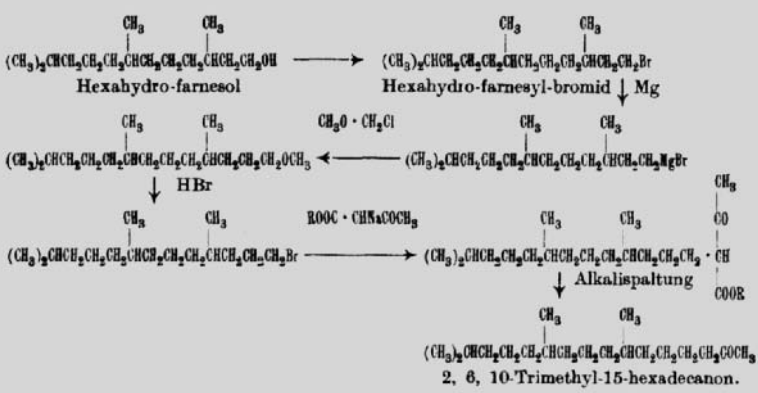


VIII

kann neben den Oxydationsprodukten Methyl-isohexyl-keton, Hexahydro-$\psi$-jonon, $\gamma$-Methyl-valeriansäure und 4,8-Dimethyl-nonansäure nur ein Keton $C_{19}H_{38}O$ entstehen (nicht $C_{18}H_{36}O$), wie dies tatsächlich der Fall ist. Es müsste die Konstitution des 2,6,10-Trimethyl-15-hexadecanons haben:



Dieses 2,6,10-Trimethyl-15-hexadecanon haben wir auf folgendem Weg synthetisch aufgebaut:



Seemingly, this interpretation violated the 'isoprene rule'; however, *Karrer* suggested (*Fig. 2*) [9]:

*Fig. 2*

Man könnte sich Squalen etwa durch Vereinigung von zwei Farnesolresten, wie Lycopin aus zwei Phytolgruppen, entstanden denken.

and, in a following paper, he confirmed his idea by synthesis of squalene form farnesyl bromide (*Fig. 3*) [12], which was the first synthesis of a naturally occuring triterpene.

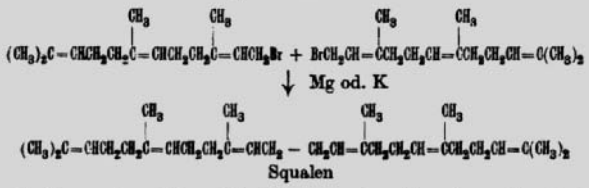
*Fig. 3*

**Synthese des Squalens**

von **P. Karrer** und **A. Helfenstein.**

(2. XII. 30.)

Diese Überlegungen sind nunmehr durch die Synthese des Squalens bestätigt worden. Wir erhielten diesen Kohlenwasserstoff durch Umsatz von Farnesyl-chlorid oder Farnesyl-bromid mit Kalium oder besser mit Magnesium:




Squalen

Dank der guten Charakterisierung des Squalens durch *Heilbron* und seine Schule war es leicht, den synthetischen Kohlenwasserstoff mit dem natürlichen genau zu identifizieren.

*Karrer* then elaborated on the consequences of this 'biomimetic' approach, and this seems to be the first step towards the extended and more general concept of the 'biogenetic isoprene rule', formulated much later by *Ruzicka* [4]. *Karrer* argued that the structures of mono-, sesqui-, and diterpenes, so far known, could all be explained as originating from a succesive condensation of 'isoprene units'; however, the higher molecular tri- and tetraterpenes are made from two identical halves of farnesol and phytol, respectively. Furthermore, *Karrer* predicted, that squalene may be the biosynthetic precursor of the steroids (*Fig. 4*) [12].

*Fig. 4*

Über die biologische Bedeutung des Squalens wissen wir noch wenig. Es besteht jedoch die Möglichkeit, dass in dem Kohlenwasserstoff die oder eine Muttersubstanz des Cholesterins und seiner Verwandten vorliegt. Die Konstitution des Cholesterins und der Gallensäuren ist zwar in wesentlichen Punkten noch ungeklärt[1]); so weit sich deren Formeln aber heute übersehen lassen, bestehen keine Schwierigkeiten, Strukturbilder, wie sie hier in Frage kommen, durch Aufrollen und vierfachen Ringschluss der Squalenmolekel, der unter gleichzeitiger Abspaltung von 3 Methylseitenketten verlaufen würde, zu konstruieren.

At this time, ***Leopold Ruzicka*** and coworkers were already involved in the research of the cyclic triterpenoids, an endeavour which continued for more than 25 years. The approach of this group can be best described in *Ruzicka*'s own words (*Fig. 5*) [13].

*Fig. 5*

Aus verschiedenen Gründen sahen wir uns veranlasst, die in der Literatur angegebenen Bruttoformeln von Triterpenen und Triterpenoiden[2]) einer möglichst genauen Nachprüfung zu unterziehen[3]).

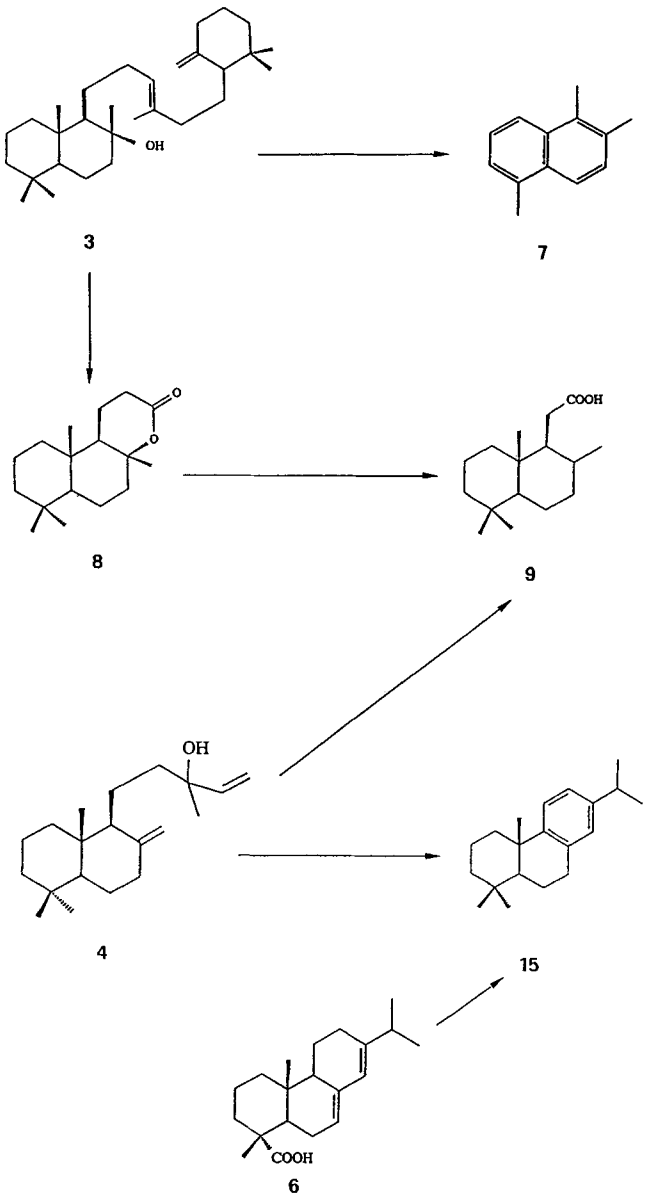
Accordingly, *Ruzicka* seemed to be interested more in the experimental and intellectual puzzle of structure elucidation rather than in achieving the first isolation of a triterpenoid. In the same paper, he gives a definition of the term triterpenoid (*Fig. 6*) [13], which links triterpenoids to the triterpenes and consequently to the isoprene rule. The recently edited '*Dictionary of Triterpenoids*' [14] reviews nearly 1500 cyclic compounds arranged in groups of structures with identical constitution of the carbon framework. In each of these chapters, contributions from *Ruzicka*'s laboratory can be found.

*Fig. 6*

[2]) Als „Triterpenoide" sollen Verbindungen verstanden werden, deren Kohlenstoffzahl nicht beträchtlich von 30 abweicht und deren Kohlenstoffgerüst dem der Triterpene ähnlich ist. Als Beispiele seien angeführt diejenigen Verbindungen, die beim Dehydrieren Sapotalin liefern (vgl. die Tabelle Helv. 15, 432 (1932) und ferner die Sterine.

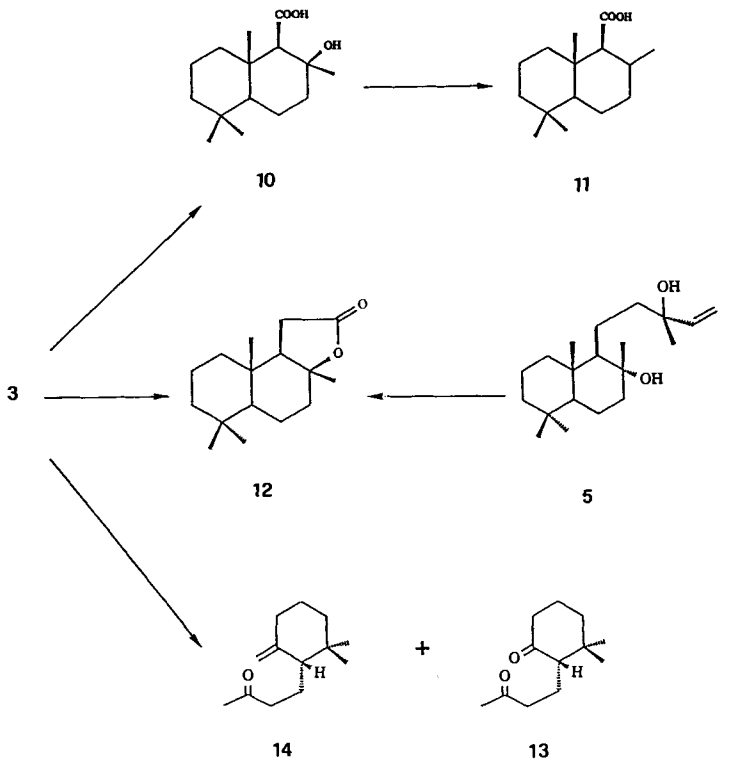
**Tricyclic Triterpenes.** – Structurally closely related to squalene is the tricyclic **ambrein** (**3**), which was first isolated by *Pelletier* and *Caventou* [15] from sperm whale excrements. In 1946, *Lederer et al.* [16] and *Ruzicka* and *Lardon* [17] idependently reported the first results concerning the structure of **3**. The whole story is a masterpiece of degredation of **3** to compounds which could be correlated to known diterpenes like manool (**4**) [18], sclareol (**5**) [19] [20], and abietic acid (**6**) [21] (*Scheme 1* and *2*).

*Scheme 1*




First insight into the substitution pattern at the *A*/*B*-ring system was gained by treatment of **3** with Se to yield a trimethylnaphthalene, agathalin (**7**); it was known that during this rough procedure angular Me groups as well as those at tertiary centers are lost. The ozonolysis of ambrein (**3**) gave *inter alia* ambreinolide (**8**) which, in three steps, could be converted to a saturated carboxylic acid **9**, also accessible by degradation of manool (**4**). A bicyclic hydroxy-acid **10**, obtained by $O_3$ treatment of **3**, was also very

*Scheme 2*

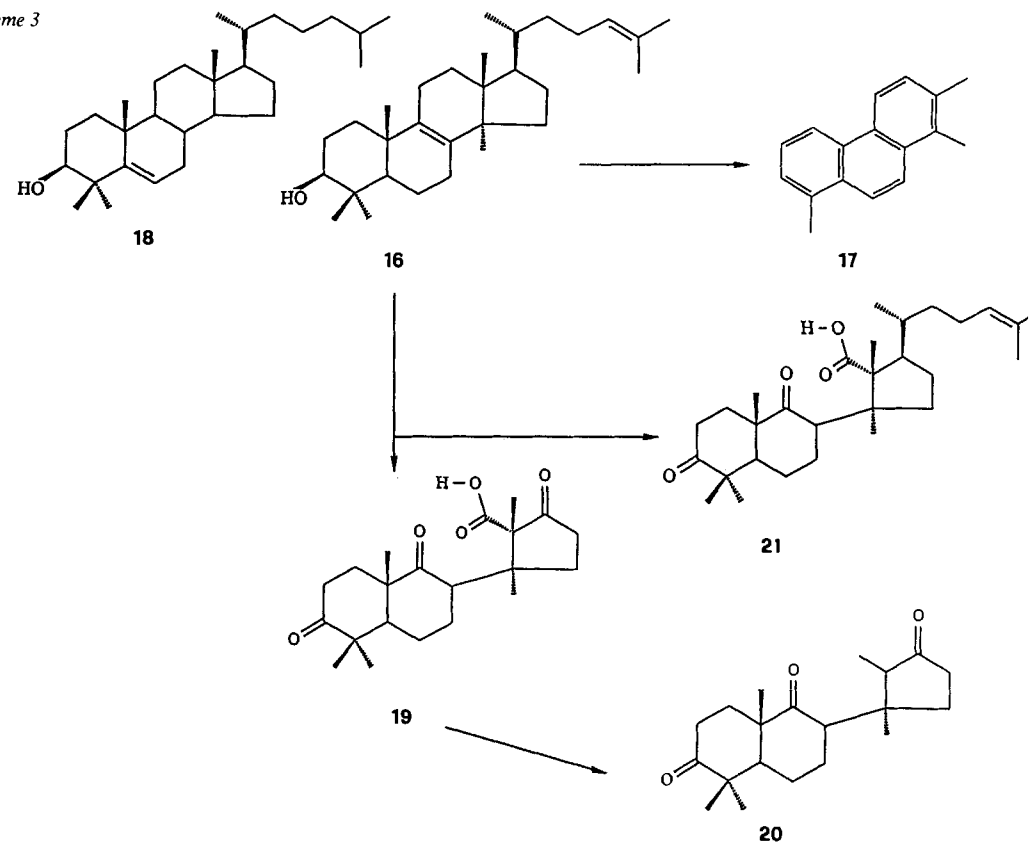



important, because dehydration and hydrogenation furnished the acid **11** which could be correlated to triterpenes belonging to the $\beta$-amyrin group, *vide infra*. Accordingly, both sequences starting from **8** and **10** established the constitution and relative configuration of the *A*/*B*-ring system, in particular the correlation of manool (**4**) with both **8** and abietic acid (**6**). The five-ring lactone **12**, another product of the ozonolysis of **3**, could also be obtained by degradation of sclareol (**5**) thus establishing the position and configuration of the *tert*-OH group in **3**. The remaining problems were the two C=C bonds and the substitution pattern at the ring *E*. From the neutral fraction obtained from the ozonolysis of **3**, two significant ketones **13** and **14** were isolated, and the latter was shown to be identical with the olfactorially interesting dihydro-$\gamma$-jonone (**14**) isolated from the volatile part of *Ambergis*. Final structure proof was provided by a short synthesis of racemic **14** and its easy degradation to the dione **13**.

**Tetracyclic Triterpenes.** – Most fascinating is the history of **lanosterol (16)**, a triterpenoid, which can be isolated from wool fat [21], and which is now known to be the first cyclization product of squalene 2,3-epoxide in the animal kingdom and the biosynthetic prescursor of cholesterol (see [22]). Dehydrogenation of **16** with Se, yielding the trimethylphenanthrene **17**, and the empirical formula $C_{30}H_{50}O$ suggested that lanosterol

belonged to the triterpene family; however, the isobutenyl fragment in the side chain and the missing Me group at the *B*/*C*-junction induced *Ruzicka* to propose a relation of **16** to cholesterol (**18**) as early as 1950 [23] (*Scheme 3*).

*Scheme 3*




**18** **16** **17** **21** **19** **20**

After the structure of the side chain had been established, and the origin of the vicinal Me groups in **17** had become known, the most difficult problem remained to establish the attachment of the side chain to ring *D*. The basic difficulty was not only the lack of proper analytical methods – IR and UV spectrometers were already available, and *Klyne* had already developed rules for calculating the contribution of certain substructures to molecular rotation –, but the problem was that most people involved in this area were mentally still sticked to the conventional '*isoprene rule*'. Finally, it was shown in close competition between the Zurich group [24] and *D. H. R. Barton* [25], that ring *D* was five-membered, and there was only the choice of side-chain attachement between C(17) and C(15) [25], the latter being favored by the '*isoprene rule*'. In a decisive experiment by

*Ruzicka* [26], lanosterol (**16**) was sequentially degraded to yield a $\beta$-keto-acid **19** which spontaneously lost $CO_2$ to give the five-ring ketone **20** in contrast to **21**, which, under the same conditions, was not decarboxylated. These results clearly defined the side-chain being attached to C(17). At about the same time, the structure of **16** was confirmed by X-ray analysis of its iodo-acetate derivative [27], and, a few years later, by synthesis [28]. Regarding the structural similarity of lanosterol (**16**) and cholesterol, and considering experiments concerning the biosynthesis of the latter from acetate [29], *Ruzicka* proposed the *'biogenetic isoprene rule'* in 1953 [4], outlining a unified scheme for the formation of all known terpenes and in particular the biosynthesis of triterpenenes from squalene. This 'building-block' analysis was still devoid of stereochemical considerations; however, in the famous paper published in *HCA* in 1954 [20], co-authored by **Albert Eschenmoser**, **Duilio Arigoni**, and **Oskar Jeger**, one can find the complete stereochemical analysis including the most likely conformations of (all-*E*)-squalene to yield the different triterpene frameworks by acid-catalyzed cyclizations (*Figs. 7* and *8*) [30].

*Fig. 7*

**226. Zur Kenntnis der Triterpene.**

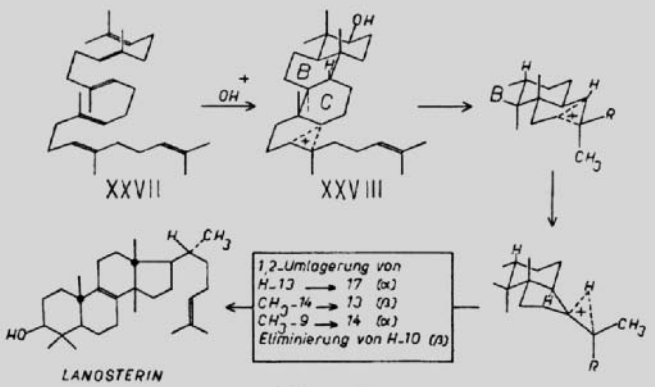
190. Mitteilung[1]).

**Eine stereochemische Interpretation der biogenetischen Isoprenregel bei den Triterpenen**

von **A. Eschenmoser, L. Ruzicka, O. Jeger** und **D. Arigoni.**

(13. X. 55.)

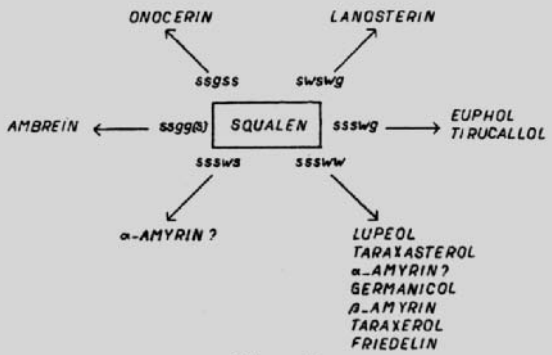
Die einzige mögliche Lösung (Schema 6) scheint darin zu bestehen, dass man von einer Faltung des Typus XXVII (Sessel-Wanne-Sessel-Wanne) ausgeht; der Vollzug einer genau gleichen Reaktionsfolge, wie sie bereits im Falle des Tirucallols angenommen worden ist, führt dann über XXVIII und weitere Zwischenstufen zwangslos und stereochemisch eindeutig zur Raumformel des Lanosterins.




Schema 6.

*Fig. 8*

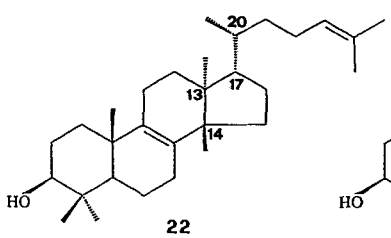
Im Rahmen der hier dargelegten Konzeption lässt sich die konstitutionelle Vielfalt der natürlichen Triterpenverbindungen zum Teil auf den Umstand zurückführen, dass bei der Entstehung dieser Verbindungen die Squalenkette in verschiedenen Konstellationen cyclisiert wird, und dass im besonderen, z. B. im Falle der steroiden, tetracyclischen Typen (Lanosterin, Euphol und Tirucallol), ein Teil der Squalenkette nicht gefaltet wird, sondern gestreckt bleibt. Im Schema 7 sind die oben diskutierten Cyclisationen unter Angabe der vorauszusetzenden Konstellationen des Squalens nochmals zusammen gefasst[2]).



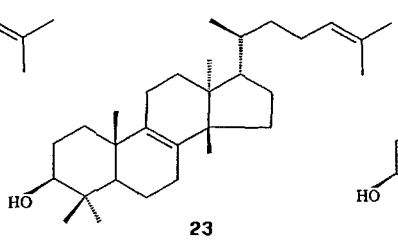

Schema 7.

[2]) s = Sesselfaltung; w = Wannenfaltung; g = gestreckte Anordnung der Squalen-Teilkette.

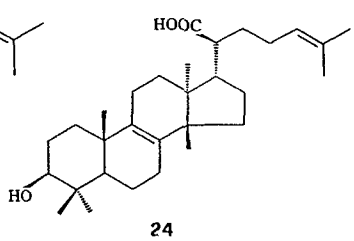
Structurally most similar to lanosterol **16** are the triterpenes belonging to the euphol group. The parent compound **euphol** (**22**), which can be isolated from various *Euphorbiaceae*, differs from **16** only with respect to the configuration at C(13), C(14), and C(17), indicating a squalene (*sswg*)-conformation (see *Fig. 8*), to account for the epimeric configurations at ring-*D* of **22**. **Tirucallol** (**23**) is just a C(20) epimer of **22** and **β-elemolic acid** (**24**) a C(21)-oxidized form of **23**.




**22**

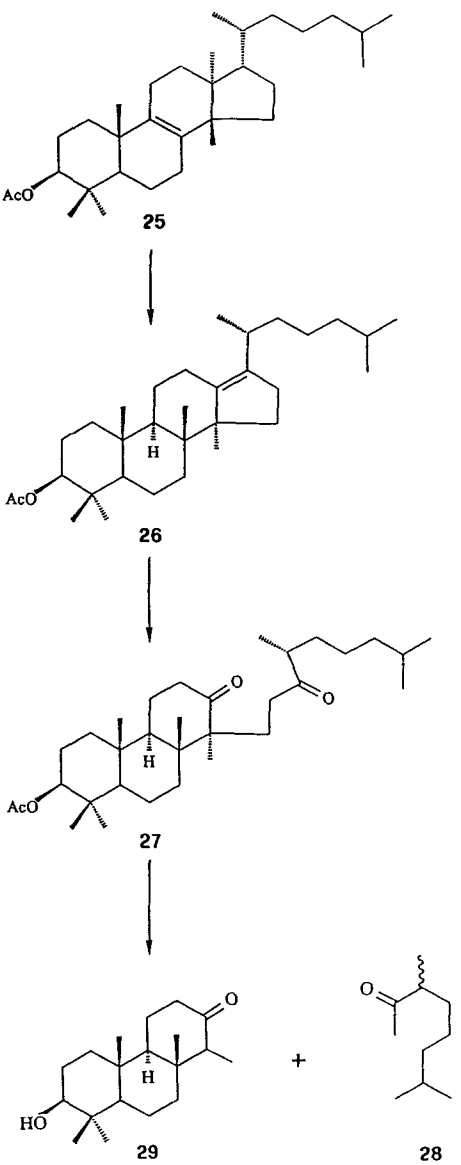



**23**




**24**

Besides the fact that euphol (**22**) and lanosterol (**16**), when treated with Se, gave the same hydrocarbon **17** (see *Scheme 3*), most important for the structure elucidation of the euphols was the acid-catalyzed, stereospecific isomerization of euphenol acetate **25** to isoeuphenol acetate (**26**) [31]. The structure of the corresponding alcohol was independently determined by *Barton et al.* [32]. *Ruzicka* and coworkers suggested a concerted mechanism [31], which, in contrast to similar experiments with lanosterol (**16**) [26] [33], involves two 1,2-Me shifts followed by eliminations (*Scheme 4*). The different behavior




*Scheme 4*

of the lanosterol and euphol framework under acidic conditions was rationalized by *Ruzicka* according to *Fig. 9* [31].

*Fig. 9*

**268. Zur Kenntnis der Triterpene.**

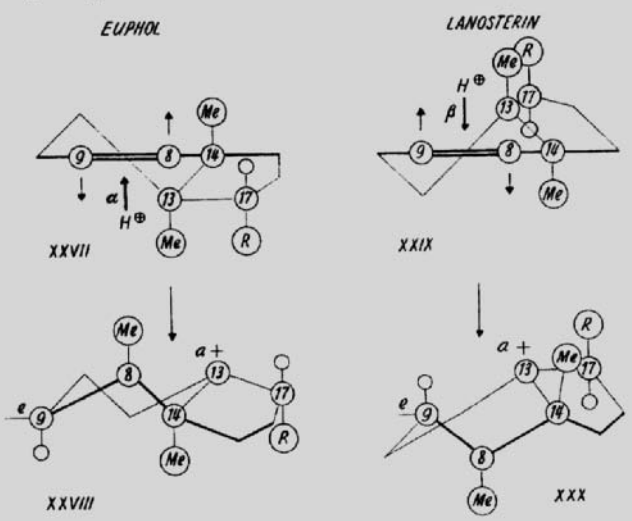
182. Mitteilung[2]).

**Konstitution und Konfiguration von Euphol und iso-Euphenol**

von **D. Arigoni, R. Viterbo, M. Dünnenberger, O. Jeger** und **L. Ruzicka.**

(13. X. 54.)

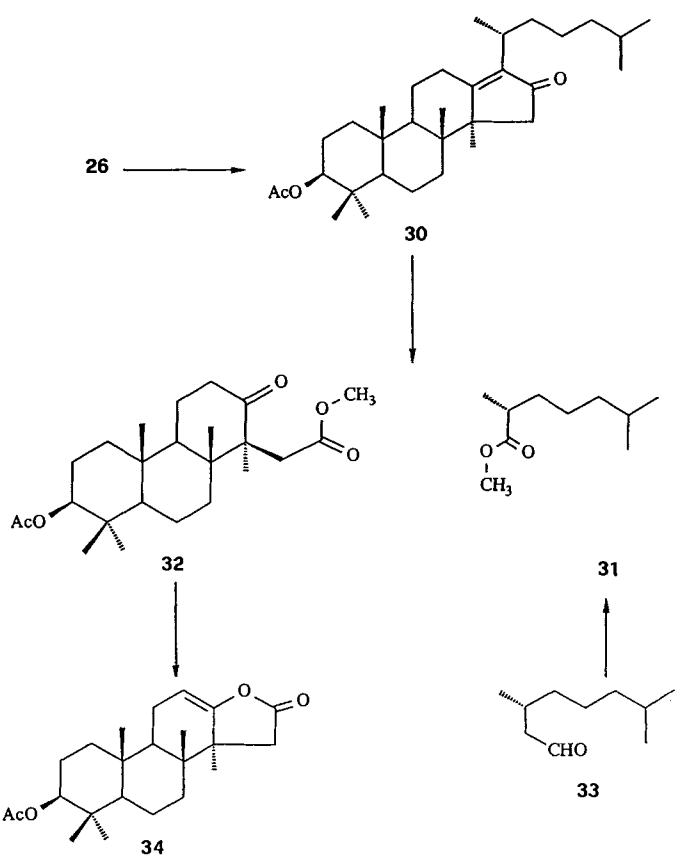
Besonders klar wird der Unterschied zwischen Euphol und Lanosterin, wenn man die Verhältnisse an Hand der Projektionsformeln der Ringe C/D betrachtet (XXVII und XXIX). Bei Lanosterin (XXIX) wurde der Angriff des Protons von der stärker gehinderten Vorderseite ($\beta$) dargestellt, der nach Wanderung der beiden Methyl-Gruppen zum Zwischenzustand XXX führen würde, worin der Wasserstoff am C-9 die ungünstige $\beta$-Konfiguration und der Ring C die Wannenkonstellation aufweisen müsste, damit die Bindung 9/10 in die äquatoriale Lage kommt[3]). Daher bleibt diese Umlagerung aus. Beim Euphol (XXVII) (bzw. Euphenol) dagegen ist der analoge Zwischenzustand XXVIII in jeder Beziehung günstig, und daher geht die Umlagerung zum iso-Zustand ausserordentlich glatt vor sich.




Evidence for the size of ring *D* and the Me shifts was provided by the sequence outlined in *Scheme 4*. Oxidative cleavage of the C=C bond in **26** gave the 1,5-dione **27**, which, under basic conditions, underwent a *retro-Michael* reaction to yield the ketone **28**

and the hydroxy-ketone **29.** The latter contained the complete framework of the *A/B/C*-ring system of euphol (**22**) but one additional Me group [31].

Oxidation of **26** with *tert*-butyl chromate furnished the $\alpha,\beta$-unsaturated ketone **30**, identified by characteristic IR bands, which could be cleaved on treatment with $O_3$ to yield the chiral side-chain fragment **31** and the $\gamma$-keto-ester **32** [31]. Compound **31** was correlated to (*R*)-citronellal (**33**) [34], and **32** could be cyclized to the enol lactone **34**, which firmly established the side-chain attachment at C(17) of **22** (*Scheme 5*).

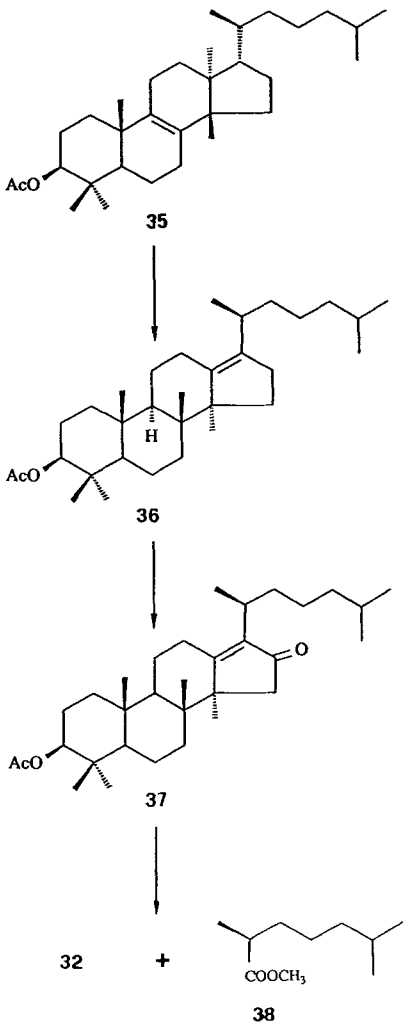



*Scheme 5*

After initial work by *Warren* [35], the structure of **tirucallol (23)**, a triterpene isolated together with **22** from *Euphorbia tirucalli* and *Euphornia triangularis* [36], was finally determined by *Ruzicka* and coworkers [37], using reactions already established for **euphol (22)**. Treatment of dihydrotirucallol acetate **35** with AcOH/HCl gave dihydroisotirucallol acetate **36** which, after $Cr^{VI}$ oxidation to the $\alpha,\beta$-unsaturated ketone **37**, was cleaved at the C(13)=C(17) bond to yield **32**, identical with the oxo-ester known from the degrada-

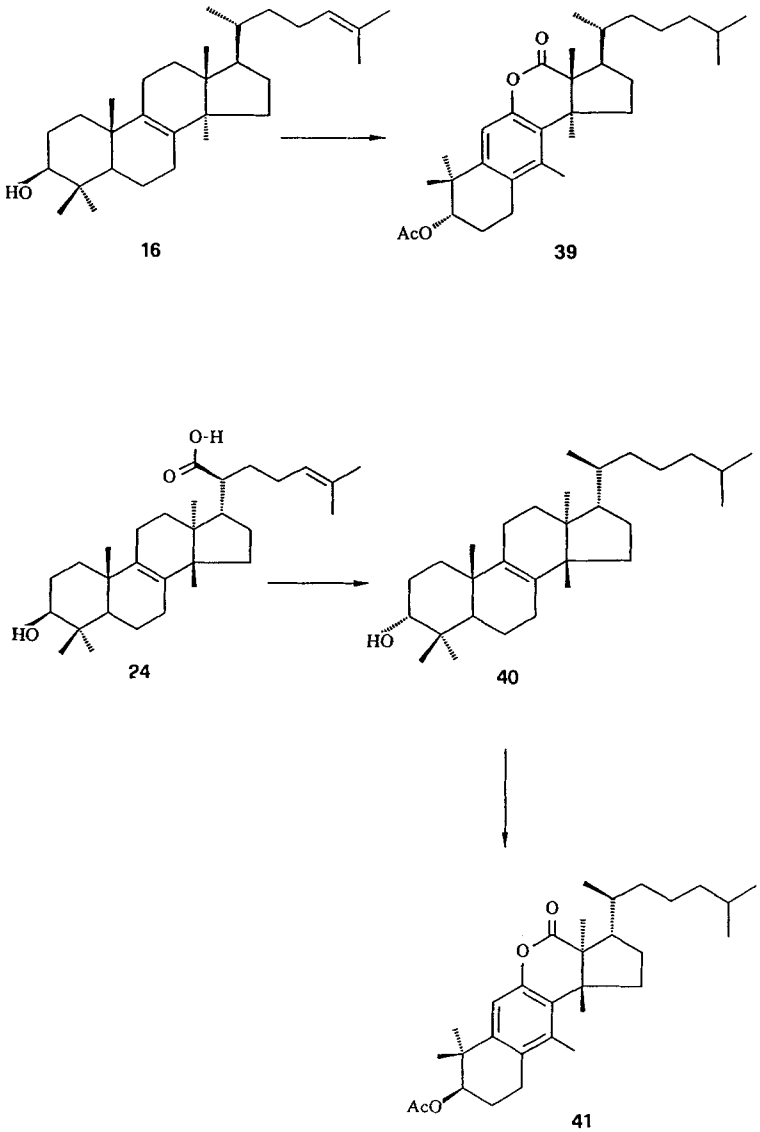
tion of euphol **22** (*Scheme 6*). The side-chain fragment was isolated as the ester **38** which was shown to be the enantiomer of **31** obtained from **22**. Accordingly, **22** and **23** have opposite configuration at C(20). Final proof of the identical configurations of the other six chiral centers of the euphol triterpenes, in particular with respect to the *C*/*D*-ring

*Scheme 6*



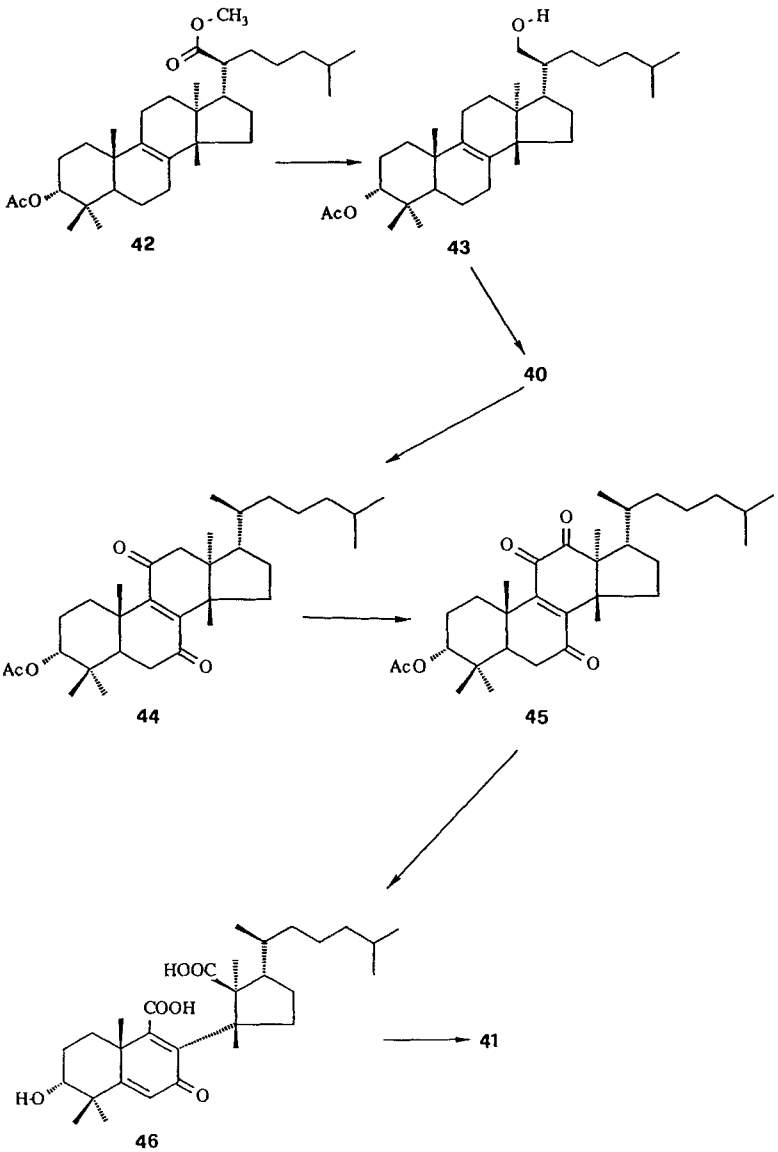

junction, was delivered by the experiments with **β-elemolic acid** (**24**). *Barton* and coworkers had already shown [38] that lanosterol (**16**) can be degraded to the lactone **39** (*Scheme 7*). Consequently, *Ruzicka* reasoned that, by the transformation β-elemolic acid (**24**)→3α-dihydrotirucallol acetate (**40**) → **41**, the enantiomer of **39** would provide unequivocal correlation of the euphols to lanosterol (**16**) [39].

*Scheme 7*




Starting with the ester **42**, conveniently available from $\beta$-elemolic acid (**24**), the acetoxy-alcohol **43** was prepared, which, in two further steps, gave the dihydrotirucallol acetate (**40**), the 3$\alpha$-epimer of **35**. Consecutive oxidations with $CrO_3$ and $SeO_2$ furnished **44**, and finally the 1,2-dione **45**, which was cleaved on treatment with alkaline $H_2O_2$ to yield the dicarboxylic acid **46**. The latter was heated at 260° in the presence of $Ac_2O$ to give the desired lactone **41**, the enantiomer of **39** (*Scheme 8*).

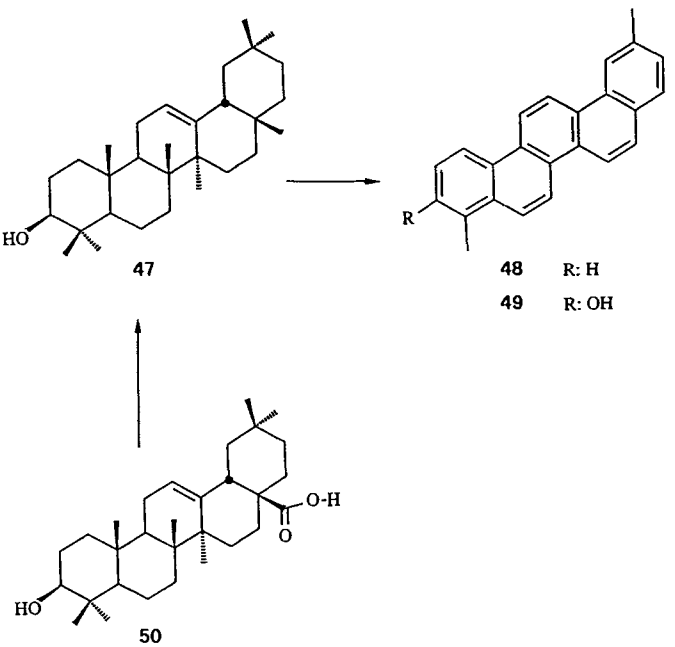
*Scheme 8*




**Pentacylic Triterpenes.** – The majority of the pentacyclic triterpenes has a common biosynthetic origin, (*sssww*)-squalene (see *Fig. 8*) and are structurally related to **β-amyrin** (**47**; *Scheme 9*). They display the same absolute configuration of the C framework but differ form the parent triterpene with respect to the number and sites of oxidations at **47**.

The decisive experiments concerning the structure elucidation of these complex molecules were carried out in the late thirties by identifying 1,8-dimethylpicene (**48**) and

*Scheme 9*




1,8-dimethyl-2-hydroxypicene (**49**) as products of dehydrogenation with Se [40], and moreover correlating $\beta$-amyrin (**47**) and its C(28)-oxidized congener **oleanic acid** (**50**; *Scheme 9*). A very simple and elegant four-step sequence, as depicted in *Scheme 9*, was used to prepare $\beta$-amyrin (**47**) from oleanic acids (**50**) as early as 1937 [41], demonstrating clearly, that both compounds only differ at the oxidation level of one C-atom; however, the position of individual Me groups and of the C=C bond was a matter of dispute between the Zurich group and its competitors for many years. After several wrong suggestions concerning the structure of **50**, *Ruzicka* [42] finally took advantage of the work of *Kitasato* [43] who had shown that ring-*C* of **50** can be cleaved, when the corresponding acetoxy-ketone **51** is treated with $CrO_3$ in $AcOH/H_2SO_4$ (*Scheme 10*). *Ruzicka* realized that the resulting lactone ester **52** was an ideal candidate to separate the pentacyclic system into two parts, if one would be able to cleave the highly substituted C(8)–C(14) bond. This was indeed possible, when the corresponding ketone **53** was pyrolyzed and fragments of the *A*/*B*- and *D*/*E*-ring system could be identified as the keto-esters **54** and **55** (*Fig. 10*) [44].

*Wolff-Kishner* reduction of **55** followed by hydrolysis generated the bicyclic carboxylic acid **11** already known from the degradation of ambrein **3** (see *Scheme 2*). Since ambrein (**3**) has been related to the diterpenes manool (**4**) sclareol (**5**), and abietic acid (**6**), it became evident that diterpenes and the triterpenes of amyrin descent have the same configuration with respect to the *A*/*B*-ring system [45]. That is also valid for cholesterol (**18**) [28] and lanosterol (**16**); the latter was correlated to manool (**4**) [46]. Quite a number of pentacyclic triterpenecarboxylic acids have been isolated from plants. The structure of **glycyrrhetic acid** (**56**) was a challenging problem for more then a decade mainly because of the position of the COOH group. The $\alpha,\beta$-unsaturated ketone substructure in **56** was easily recognized by its UV spectrum and, fortunately, the C=O group could be smoothly

*Scheme 10*

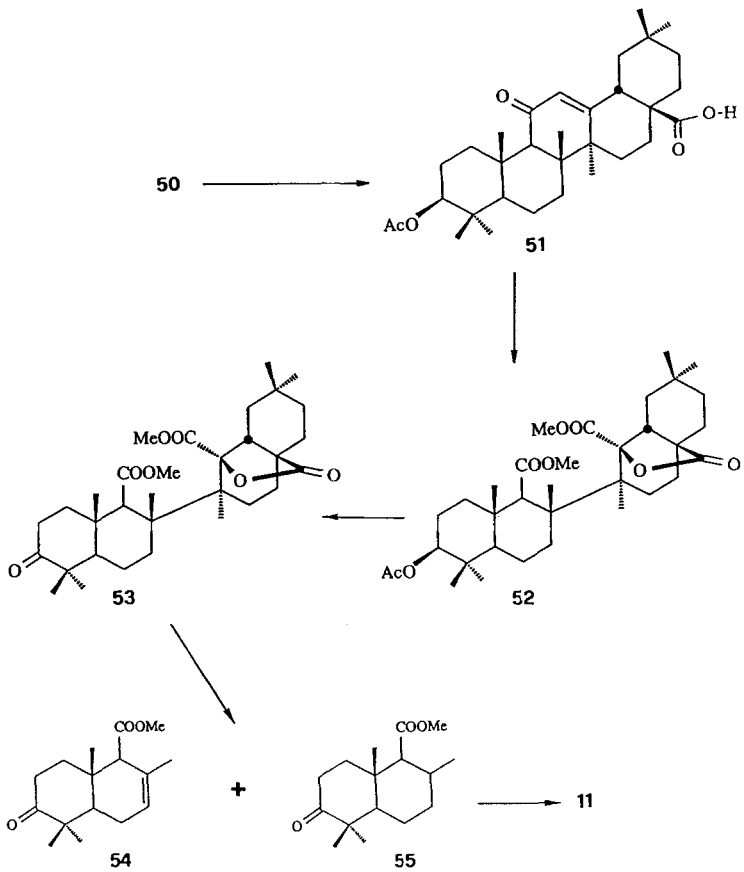



*Fig. 10*

231. Zur Kenntnis der Triterpene.

132. Mitteilung[1]).

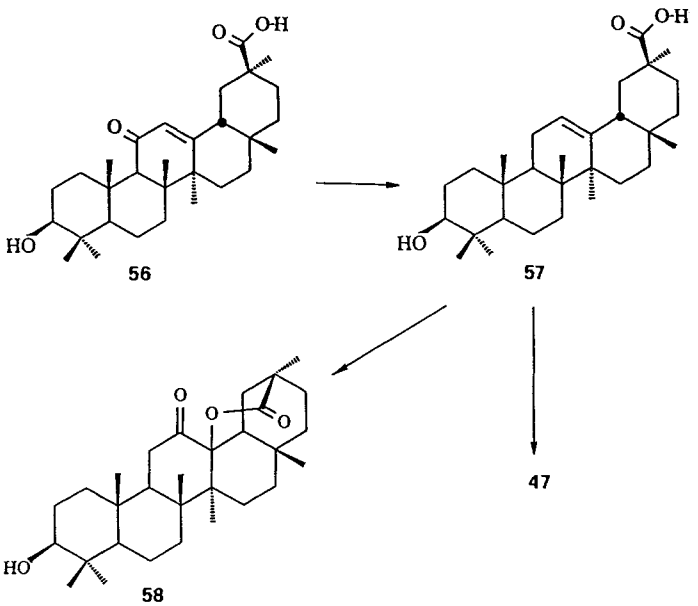
**Über die Zusammenhänge der Oleanolsäure mit dem Triterpen Ambreïn und den Diterpenen Abietinsäure und Manool[2])**

von L. Ruzicka, H. Gutmann, O. Jeger und E. Lederer.

(2. IX. 48.)

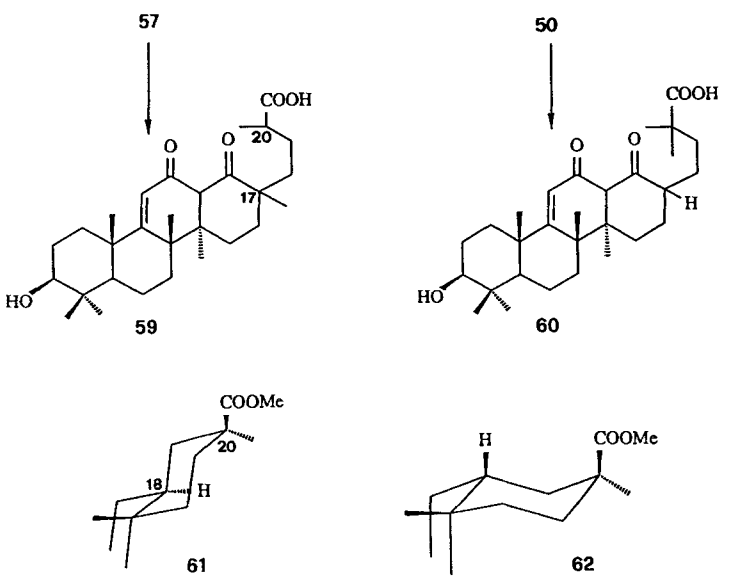
removed by hydrogenolysis on $PtO_2$ to yield the acids **57** [47] (*Scheme 11*). Compound **57** was converted to $\beta$-amyrin (**47**) using the same four-step sequence, as shown for **50** in *Scheme 9*. Accordingly **57** is isomeric with oleanic acid (**50**) [48]. Concerning the distance of the COOH group from the C=C bond, hints were obtained in the following way: hydrolysis of the methyl ester of **56** proceeded very smoothly and high-yielding in comparison to the more hindered ester of **50**. Furthermore, treatment of **57** with $CrO_3$ gave *inter alia* a oxo-lactone, most probably of structure **58** [48].

*Scheme 11*




Final proof for the position of the COOH group was then provided by a sequence of oxidations of **57** first with $SeO_2$, followed by $CrO_3$, ring-*E* scision, and decarboxylation under drastic alkaline conditions. The isolated carboxylic acid **59** was shown to be isomeric with a compound **60** obtained under the same conditions from oleanic acid **50** [49] (*Scheme 12*). The chirality at C(20) of glycyrrhetic acid as indicated in **56** (*cf. Scheme*

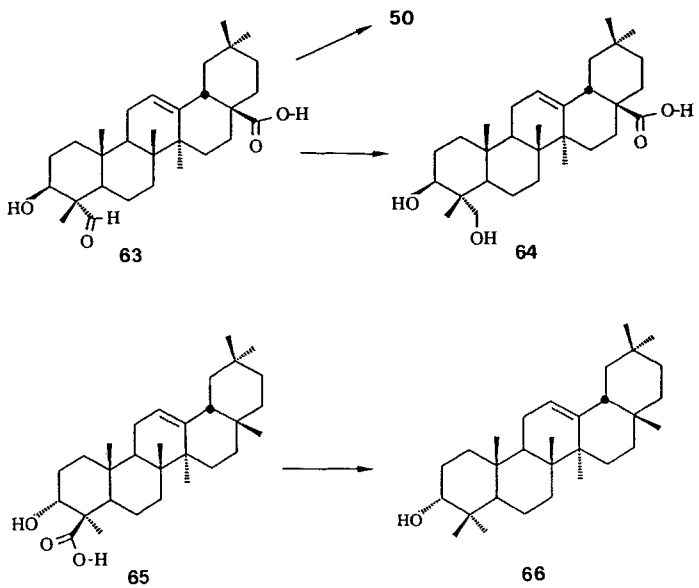
*Scheme 12*



*11*) was investigated much later by *Beaton* and *Spring* [50]. Under strongly basic conditions, they obtained the 18α-epimer of **56** and compared the saponification of the methyl ester **61** with the corresponding methyl ester of **56**. Since the former hydrolyzed ≥ 20 times more rapidly then the latter, it was argued that the MeOCO group of **62** occupies the sterically more congested axial position at C(20), whereas in **61** the ester rests equatorial. Accordingly, the configuration at C(20) of **56** is (*R*).

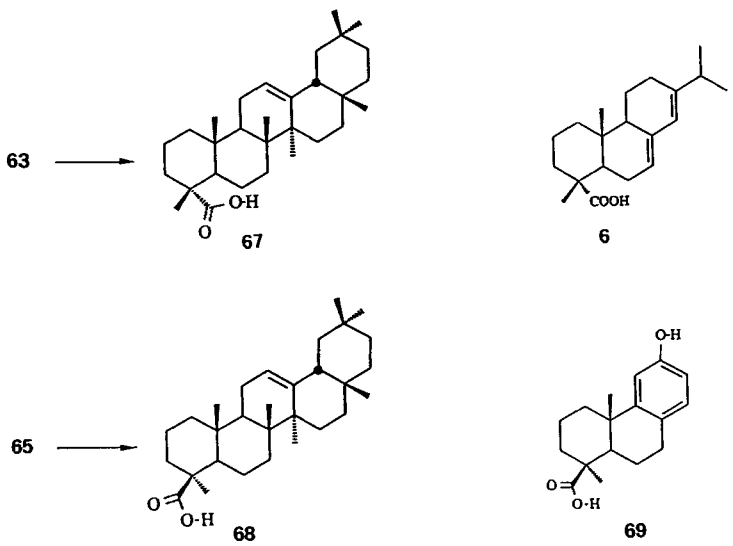
Several pentacyclic triterpenes like **gypsogenin** (**63**) and **hederagenin** (**64**) are oxidized forms of oleanic acid **50** (*Scheme 13*). Compound **63** could be converted to **50** on treatment of its semicarbazon derivative with NaOEt, and catalytic hydrogenation of **63** gave **64** [51]. Accordingly, both compounds have the same configuration at C(4). In

*Scheme 13*



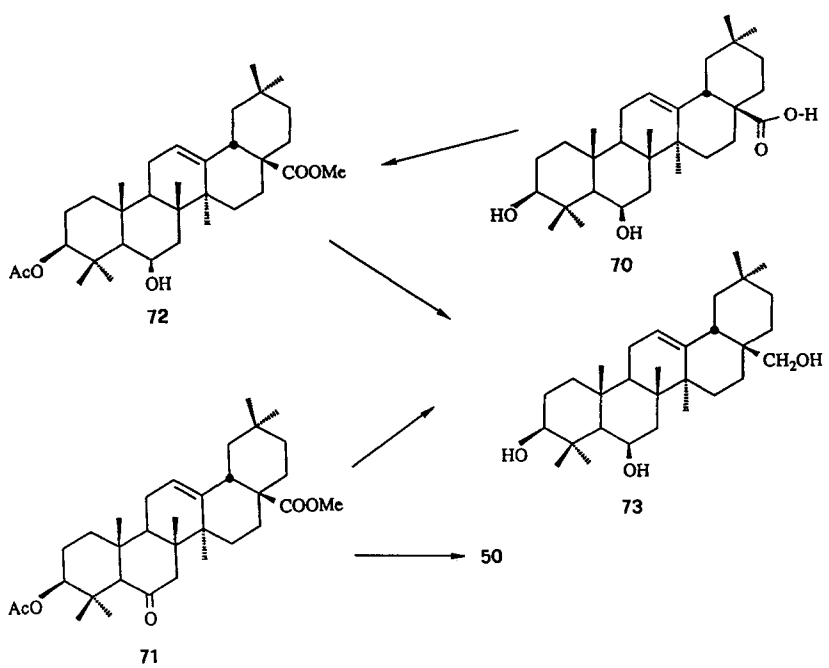

contrast, **α-boswellic acid** (**65**) has different configurations at C(3) and C(4). Using the procedure depicted in *Scheme 9*, **65** could be easily reduced to the ***3*-epi-β-amyrin** (**66**) [52]. The question whether C(23) or C(24) are oxidized to COOH was more difficult to answer. However, when molecular optical rotations of the acid **67** (and the corresponding ester and amide), derived from **gypsogenin** (**63**), were compared with the values measured for **68** and its derivatives, prepared from **α-boswellic acid** (**65**), it became obvious that there was a significant higher positive optical rotation for the latter series (*Scheme 14*). From this result, it was concluded by *Ruzicka* and coworkers [53] that **67** had the same configuration at C(4) as **abietic acid** (**6**) at C(1), and hence **65** was related to **podocarpic acid** (**69**). This argument was supported by the experimental fact that the esters of **α-boswellic acid** (**65**) with an axial MeOCO group were quite resistant to hydrolysis [54].

*Scheme 14*




**Hederagenin (64)** served a great deal for the structure determination of **sumaresinolic acid (70)**, since both compounds led to the same degradation products after oxidative cleavage of rings *A*/*B*, accounting for the equivalence of 27 out of 30 C-atoms [55]. The remaining problems concerning the configurations at C(3), C(5), C(10), and C(6) were solved in the following way (*Scheme 15*). It was reasoned that the OH group at C(6)

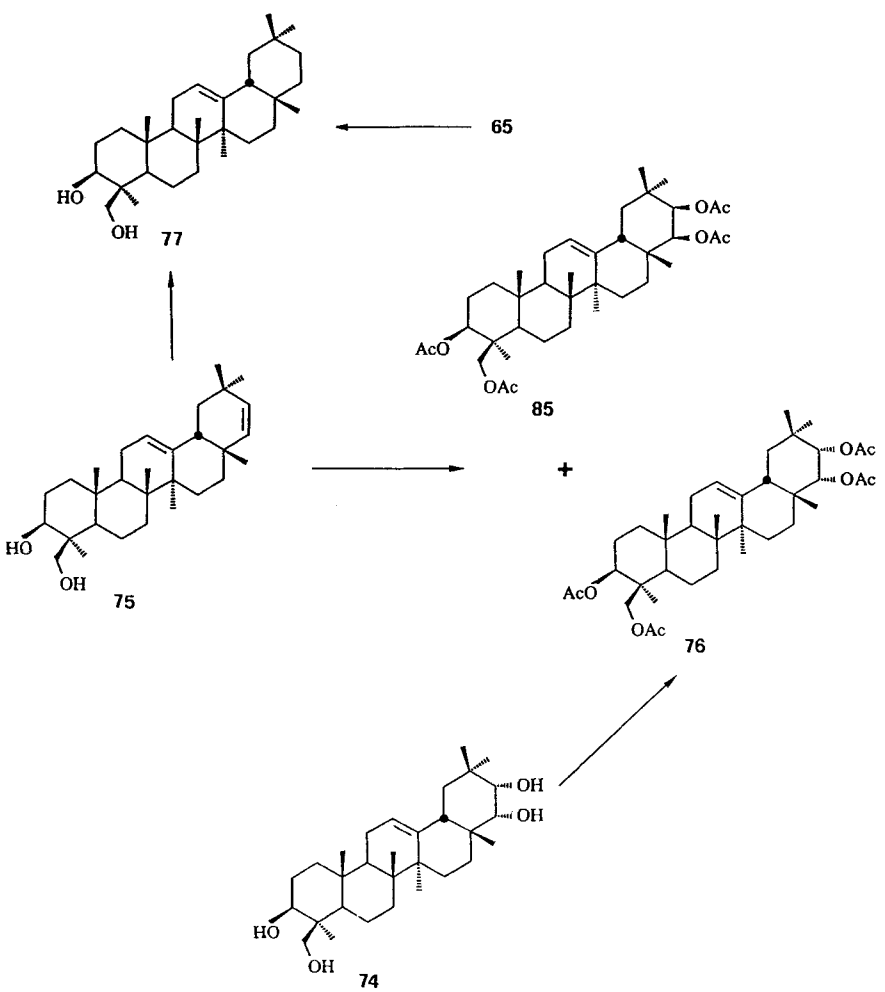
*Scheme 15*



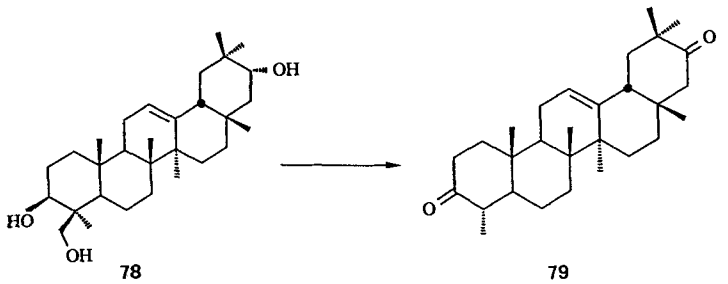
occupies an axial position, since the corresponding acetate was extremely difficult to hydrolyze. Furthermore, on treatment with $LiAlH_4$ the ketone **71**, prepared from the acetoxy-ester **72**, furnished the same tirol **73**, which could be obtained under the same conditions from **72**. The formation of an axial OH group in this experiment is due to severe steric hindrance at the C=O function [56], which is also obvious from unsuccessful attempts to apply normal *Wolff-Kishner* conditions. Only under forced conditions, it was possible to reduce C(6)=O to yield **oleanic acid (50)**, as the final proof for the constitution and configuration of **70**.

Four **soyasapogenols** were identified as hydrolysis products of the saponins from *Trifolium repens*. **Soyasapogenol A (74)** and **soyasapogenol C (75)** could be easily related, since $OsO_4$ treatment of the diacetate of **75** gave, after further acetylation, a tetraacetate **76**, identical with the acetate of **74** (*Scheme 16*). Moreover, one C=C bond of **75** could be

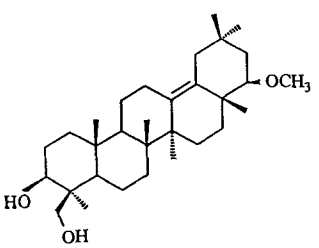
*Scheme 16*



catalytically hydrogenated to generate **77**, which was also accessible from **α-boswellic acid (65)**. Accordingly, both **74** and **75** have the same aboslute configuration at the *A*/*B*/*C*-ring system, but they are different with respect to one C=C bond and its *cis*-glycol congener [57]. In contrast, treatment of **soyasapogenol B (78)** with Cu-bronze revealed only two *sec*-OH groups and behaved similarly to **hederagenin (64)**, because the hydroxylated C(24) is lost as HCHO to furnish the diketone **79**. (*Scheme 17*). In **soyasapogenol D**



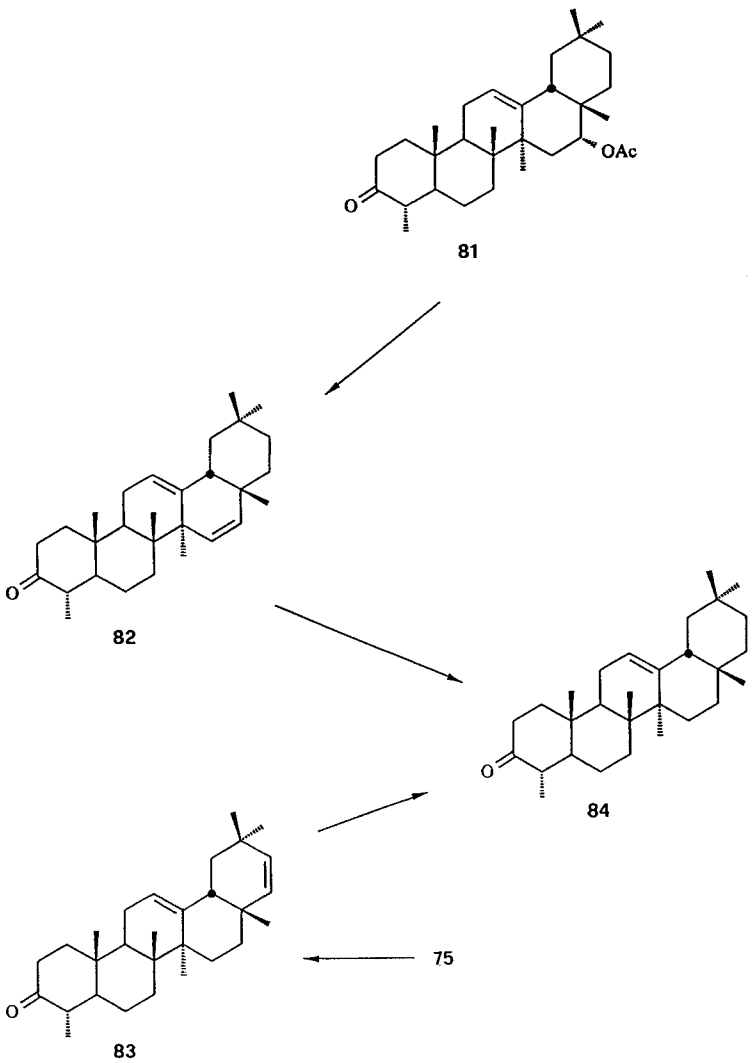

*Scheme 17*




(**80**), a tetrasubstituted C=C bond was identified by IR and an ether function by the *Zeisel* method [58]. The main problem in this series of pentacyclic triterpenes was to localize the functional groups to distinguish the four compounds. For a long time, *Ruzicka* and coworkers favored ring *D* as the site of substitution [57–59], until finally *Jeger* and coworkers came to the same conclusion as *Spring* and coworkers [60] that the differences between the soyasapogenols were due to changes in ring *E* [61].

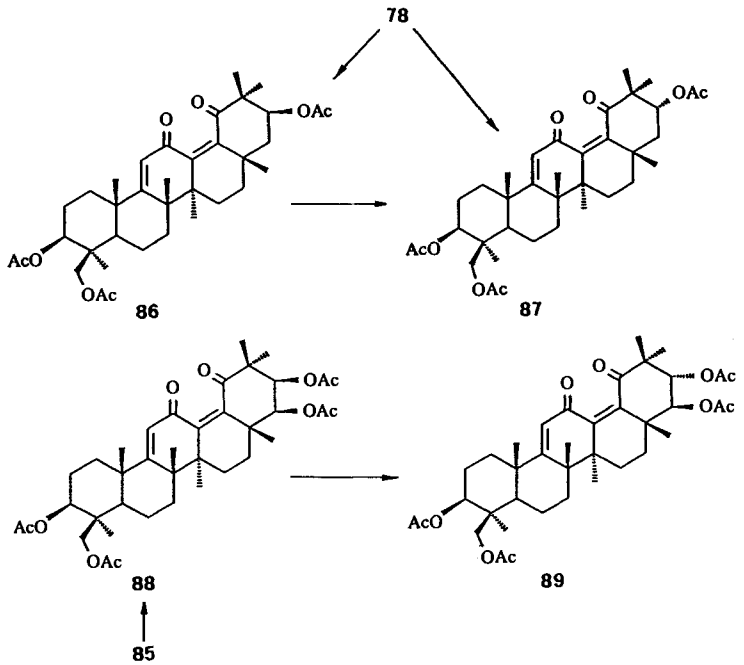
Evidence for the position of the second C=C bond of **soyasapogenol C (75)** was delivered by the pyrolysis of a known nor-triterpenoid **81** yielding the olefin **82**; this compound was indeed different from the olefin **83**, available from **75** on treatment with Cu-bronze (*Scheme 18*) [61]. Furthermore, catalytical hydrogenation of both **82** and **83** gave the same ketone **84**. Hence, the C=C bond in question is definitely C(21)=C(22), and this is also the site of the vicinal *cis*-glycol in **soyasapogenol A (74)**. Concerning the absolute configuration at C(21) and C(22) in **74**, *Spring* and coworkers argued in favor of the configuration shown in **74**, because osmylation of **75** gave mainly the acetate of the unnatural glycol **85**, due to hydroxylation from the less hindered β-face. For the MeO group of **soyasapogenol D (80)**, most likely is the equatorial position (β) at C(22), because solvolysis of C(22) derivatives of **80** proceed under retention of configuration at C(22) with anchimeric assistance of the C(13)=C(18) bond [61].

*Scheme 18*



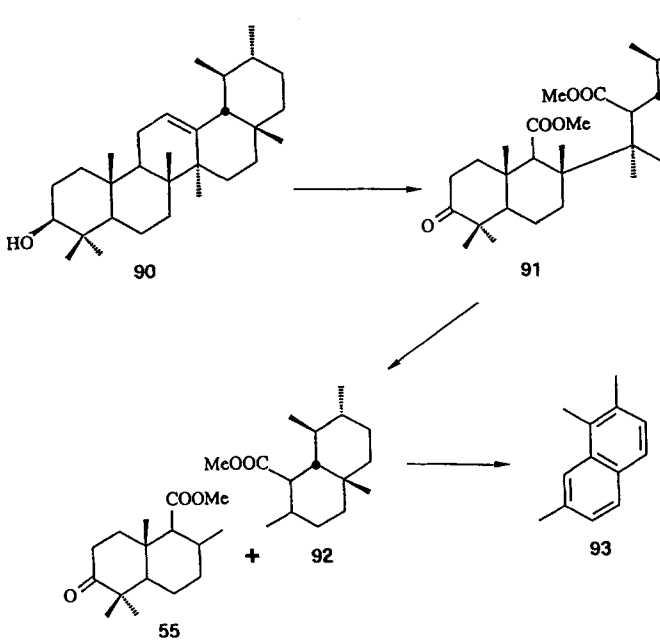

For the position of the OH group in ring-*E* of **soyasapogenol B** (**78**), *Spring* and coworkers put forward arguments in favor of an α-OH at C(21). The English group prepared the triacetate **86** in four steps from **78**, including one step which inverted the configuration at C(21). This material was epimerized with base and re-acetylated to give **87**, identical with a sample prepared directly from **78**. It was argued that the OH group at C(21) is α-configurated, because epimerization is only likely to occur at an intermediate β-hydroxy-ketone involving a *retro*-aldol cleavage of ring *E* followed by aldol-ring closure. This mechanism is supported by the fact that the tetraacetate **88** generated from **85** furnished the *trans*-glycol acetate **89** under the same conditions (*Scheme 19*).

*Scheme 19*




**α-Amyrin (90)** was recognized to be a stereoisomer of **β-amyrin (47)**. This was shown by ring-*C* fission of **90** to yield the keto-diester **91** (*Scheme 20*), in a similar fashion as for **oleanic acid (50)**. Pyrolysis of **91**, followed by hydrogenation, gave two interesting

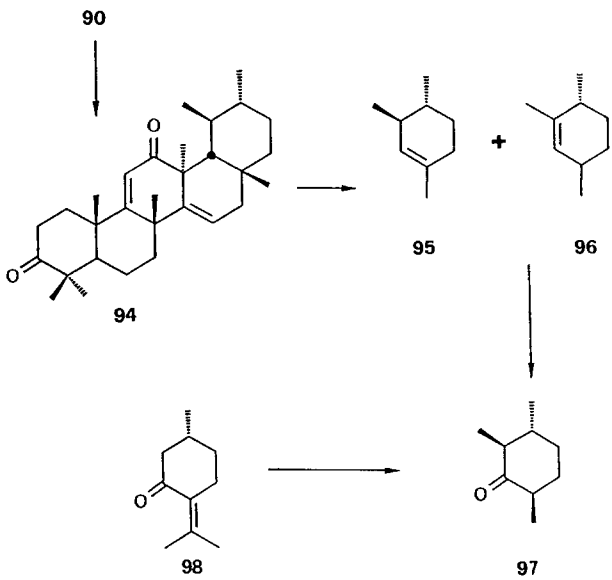
*Scheme 20*



products, of which **55** was already known from the degradation of **50**. Accordingly, **50**, **47**, and **90** have the same configuration at the *A*/*B*-ring system. The *D*/*E*-ring equivalent was isolated in the form of **92** and gave, under Se-dehydrogenation conditions, sapotalin **93**, revealing that **α-** and **β-amyrin** are only different with respect to the positions of the Me groups attached to ring *E* [62].

The absolute configuration of C(20) of **α-amyrin (90)** was determined by *Ruzicka* and coworkers according to *Scheme 21* [63]. Using an established sequence, **90** was converted

*Scheme 21*




into the diketone **94** in six steps. A novel pyrolytic method, for which mechanistic considerations are given in *Fig. 11* [63], was developed in order to cleave ring *D* and to isolate an *A*/*B*/*C* fragment and the isomeric olefins **95** and **96**. Further oxidation of the olefins generated the ketone **97**, which was found to be configurationally stable under

*Fig. 11*

**51. Zur Kenntnis der Triterpene.**

192. Mitteilung[1]).

**Absolute Konfiguration des Kohlenstoffatoms 20 in α-Amyrin, ein Beitrag zur Konstitution des Ringes E**

von **A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger** und **L. Ruzicka.**

(26. I. 56.)

*Fig. 11 (cont.)*

Falls im α-Amyrin die Ringe D und E tatsächlich eine cis-Verknüpfung besitzen, so sind in dieser Verbindung die konstitutionellen Voraussetzungen für eine Umkehrung der *Diels-Alder*-Reaktion (Dien-Spaltung) im Sinne des Reaktionsschemas A → B + C gegeben. Diese Annahme gründet sich auf die bekannte Tatsache, dass entsprechende Dien-Kondensationen stereospezifisch zur Bildung von cis-Addukten führen[13]). Daher ist zu erwarten, dass für eine allfällige Umkehrung solcher Reaktionen sich im besonderen entsprechende cis-verknüpfte Ringsysteme eignen sollten. Es ist aber auch denkbar, dass der pyrolytische Zerfall von IV unter Beteiligung des Wasserstoffs am C-19 z. B. im Sinne des Schemas D → E → B + F stattfindet. Deshalb ist die Zuordnung der Doppelbindungslage im Kohlenwasserstoff $C_9H_{16}$ gemäss Formelbild F mit einer gewissen Unsicherheit behaftet. Aus dem gleichen Grunde darf die beobachtete Leichtigkeit der erwähnten Spaltung nicht unbedingt als Argument zugunsten einer cis-Verknüpfung der Ringe D und E des α-Amyrins verwendet werden.

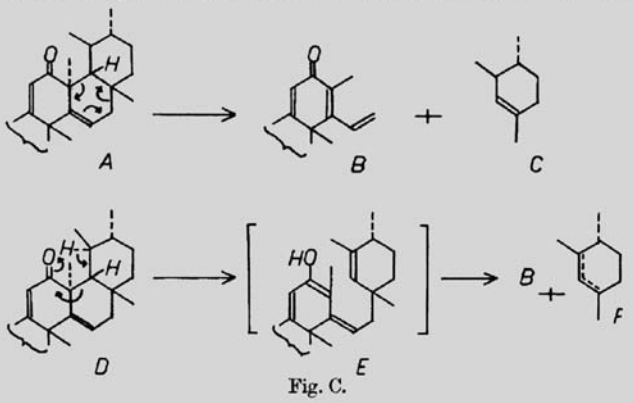
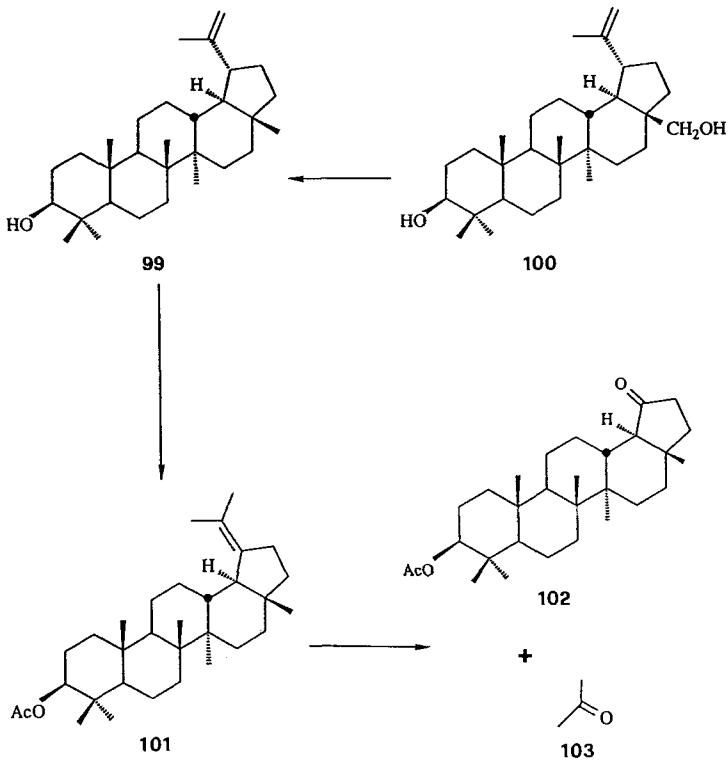



Fig. C.

basic conditions indicating that the Me groups vicinal to the C=O function occupy equatorial positions. The configuration at C(3), originally C(20) of **90** and unchanged throughout the sequence **90** → **97**, was confirmed by a four-step synthesis from (+)-D-pulegon (**98**). The (*R*)-configuration at C(20) of **α-amyrin** (**90**) is in agreement with the *biogenetic isoprene rule* and theoretical considerations by *Corey* and *Ursprung* [64], stating that if rings *D* and *E* are *cis*-fused, both Me groups at C(19) and C(20) are likely to occupy equatorial positions.

For more then 20 years, *Ruzicka* and his group worked on triterpenes belonging to the **lupeol** class, providing important contributions to structural elements of **lupeol** (**99**) and **betulin** (**100**; *Scheme 22*). It was soon recognized that both compounds are only different with respect to one Me group in **99** which is hydroxylated in **100** [65]. However, the

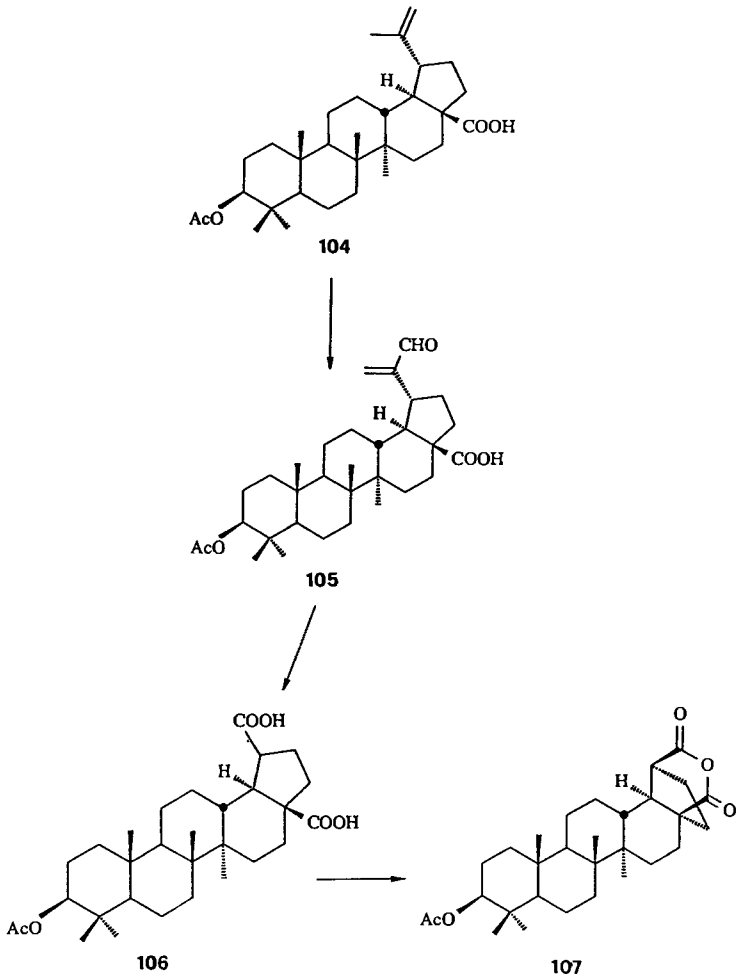
*Scheme 22*




identification of that Me group as well as the attachment of the isopropylidene group to the five-membered ring have been very difficult, and the Zurich group did not succeed solving these problems. For convenience, the results of *Ruzicka*'s laboratory in this area are interpreted with insight taking into account the correct structures of **9** and **100** as they have been determined finally by British chemists.

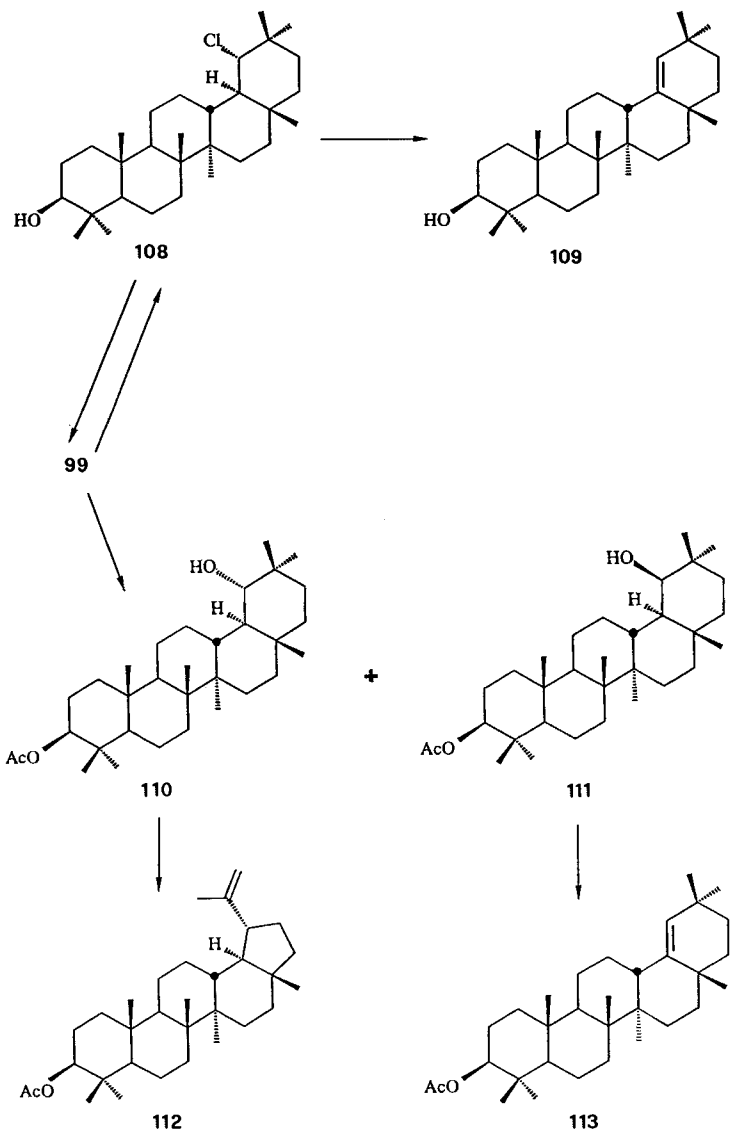
Important transformation are summarized in *Scheme 22* [66]. Se dehydrogenation yielded *inter alia* agathalin (**7**), relating the *A*/*B*-ring system of **99** and **100** to the amyrin framework, and sapotalin (**93**), representing the *D*/*E* rings of **99**. The identification of the isopropylidene substructure was carried out mainly with the acetate of **99**, which, after isomerisation to the olefin **101**, osmylation, and $Pb(OAc)_4$ cleavage, furnished the ketone **102** and acetone **103** [67]. The vicinity of the Me group at C(17) and the isopropenyl side chain became apparent, when acetoxybetulinic acid **104** was treated with $SeO_2$, and the resulting aldehyde **105** oxidatively cleaved to give the dicarboxylic acid **106**; treatment with $Ac_2O$ yielded the anhydride **107** (*Scheme 23*) [68].

*Scheme 23*




Decisive experiments concerning the configuration at ring *E* were performed by *Jones* and coworkers [69] (*Scheme 24*). On addition of HCl to lupeol (**99**), a rearranged hydrochloride **108** was isolated, which, in boiling $Ac_2O$, gave the ring-enlarged olefin **109**, an isomer of **β-amyrin (47)**. On the other hand, when **108** was treated with AgOAc, which does not affect the *D*/*E*-ring fusion, known to be *trans*, **lupeol (99)** was reformed. This result indicated the α-configuration of Cl at C(19) of **108**, and moreover the isopropylidene group in **99** being *trans* to the Me group at C(17). Similar experiments were repeated with formic acid [70], resulting in the characterization of two epimeric C(19) alcohols **110** and **111**, of which the former, under dehydrating conditions, underwent ring-contraction to lupenyl acetate **112**, and the latter gave germanicyl acetate **113**. The quite divers reactivities of both **110** and **111** were of significance for the biosynthesis of the pentacyclic triterpenes, since it became evident that the absolute configuration at the carbinol C-atom controls reaction pathways leading to different metabolites [71].

*Scheme 24*




**Recent Developments in Various Areas of Triterpene Research.** – Investigations in triterpene chemistry certainly did not stop with *Ruzicka*'s retirement, but the interest shifted gradually from plant terpenoids to those of marine origin [72], geochemical significance [73], and those isolated from microorganisms [74] and fungi [75]. This development was encouraged by continously advanced analytical and spectroscopical methods. A few examples of triterpene work published in *HCA* are given at the end of this overview. The elucidation of these complex structures should demonstrate the state of the art in this area.

In the late seventies, ***Christoph Tamm*** and coworkers started the isolation and structure elucidation of a number of very similar, highly oxidized tetranortriterpenes from Meliaceae. They succeeded identifying five new **chukrasins A–E** [76] and ten new **busseins C–M** [77]; the former are shown in *Fig. 12* [76]. Both classes have an identical C-framework but show differences in the peripheric substitution pattern. Most remarkable are the common cyclic orthoacetate substructure, the furan substituent, and the enolized $\beta$-ketolactone.

*Fig. 12*

**174. Die Chukrasine A, B, C, D und E, fünf neue Tetranortriterpene aus *Chukrasia tabularis* A. JUSS**

von **Thomas Ragettli** und **Christoph Tamm**

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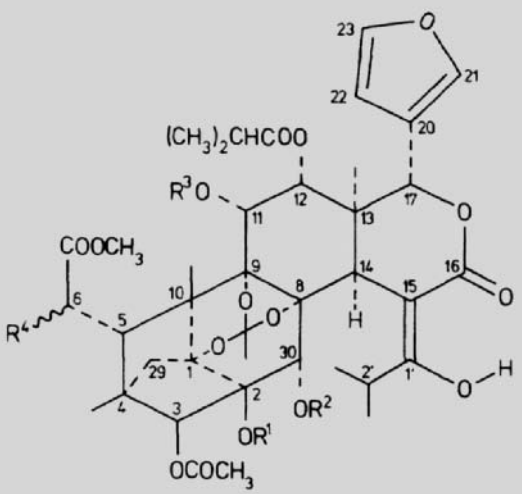
St.-Johanns-Ring 19, CH-4056 Basel

(10.IV.78)

**The Chukrasines A, B, C, D and E, Five New Tetranortriterpenes From *Chukrasia tabularis* A. JUSS**

*Summary*

Five new tetranortriterpenes, chukrasins A, B, C, D and E, have been isolated from the wood of *Chukrasia tabularis* A. JUSS. On the basis of spectral and chemical evidence structures **1a–1e** were assigned to the new compounds.




Chukrasin A (**1a**) $R^1 = H$; $R^2, R^3 = CH_3CO$ und $(CH_3)_2CHCO$; $R^4 = OH$
Chukrasin B (**1b**) $R^1 = H$; $R^2 = R^3 = (CH_3)_2CHCO$; $R^4 = H$
Chukrasin C (**1c**) $R^1 = H$; $R^2, R^3 = CH_3CO$ und $(CH_3)_2CHCO$; $R^4 = H$
Chukrasin D (**1d**) $R^1 = CH_3CO$; $R^2, R^3 = CH_3CO$ und $(CH_3)_2CHCO$; $R^4 = H$
Chukrasin E (**1e**) $R^1 = CH_3CO$; $R^2, R^3 = (CH_3)_2CHCO$; $R^4 = H$

*Marner* and *Jaenicke* discovered that the natural irones **114** and **115** (*Fig. 13*) [78] are products of the oxidative degradation of *inter alia* the **iridals 116** and **117**, respectively, members of a new class of methylated triterpenoids from the rhizome of *Iris pallida* [78]. The ozonolysis of all iridals gave one cyclic hemiacetal **118** indicating the same chirality at C(6),C(10), and C(11). Accordingly, the cyclization from squalenepoxide takes the same stereochemical course in all *Iris* species; however, the methylation and concommittant cyclization of the homofarnesyl side chain to the iron system varies in different plants [79], since irones of opposite chirality and their corresponding cycloiridals are found. Even more complex are some **spiro-iridals** isolated from *Iris foetidissima* [80], the formation of *e.g.* **119** can be explained by oxidation of C(26) to an aldehyde, which is prone to an intramolecular *Prins* reaction.

*Fig. 13*

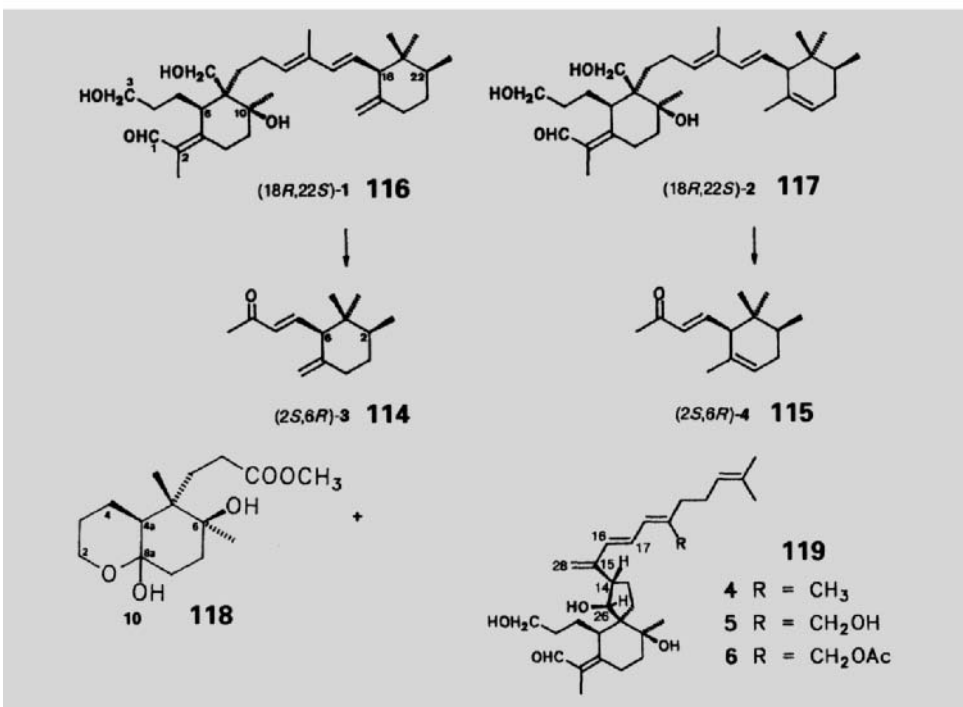
**35. Die absolute Konfiguration der Iridale und Cycloiridale unterschiedlicher Herkunft**

von **Franz-Josef Marner** und **Lothar Jaenicke***

Institut für Biochemie der Universität zu Köln, An der Bottmühle 2, D-5000 Köln 1

Dr. *G. Ohloff* zum 65. Geburtstag mit den besten Wünschen gewidmet

(18. XI. 88)



The research on **saponins** has a long tradition in *HCA* since 1919 [81]; however, the complete characterization of these molecules had to wait the advent of modern spectroscopy and separation techniques. Recently, ***Kurt Hostettmann*** and his group published a series of papers on the isolation and structure elucidation of saponins like **aridanin** (**1**; *Fig. 14*) [82]. It may be possible that these type of compounds will gain some significance in the treatment of endemic diseases and after all showing some value of triterpenes beyond theoretical significance.

*Fig. 14*

**75. New Triterpenoid *N*-Acetylglycosides with Molluscicidal Activity from *Tetrapleura tetraptera* TAUB.**

by **Marc Maillard**[a]), **Clement O. Adewunmi**[b]), and **Kurt Hostettmann**[a])*

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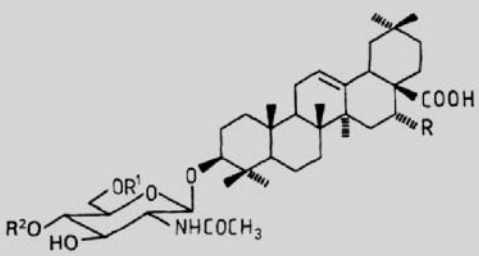
(13. III. 89)

Activity-guided fractionation of the MeOH extract of the fruits of *Tetrapleura tetraptera* TAUB. (Mimosaceae) afforded 4 saponins **1**–**4**, which exhibited strong molluscicidal properties against the schistosomiasis-transmitting snails *Biomphalaria glabrata*. Chemical, enzymatic, and spectral methods (DCI-MS, $^1$H-NMR, $^{13}$C-NMR) showed that they were *N*-acetylglycosides of oleanolic acid and of echinocystic acid. Apart from saponin **1** (aridanin), previously isolated from this plant, glycosides **2**–**4** are new naturally occurring compounds.




**1** R = R¹ = R² = H, Aridanin
**2** R = α-OH, R¹ = R² = H
**3** R = R¹ = H, R² = Gal
**4** R = H, R¹ = Glc, R² = H

Overlooking part of the history of triterpenes in *HCA*, the first 15 years appear as a rather odd puzzle, from 1935 to 1955 it reads like a fascinating detective story, thereafter lots of things became routine.

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