

New Results in the Chemistry of Lichens

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Abstract

A review is given on new results in the chemistry of lichen substances during the past 7 years. Included are picroroccellin, paraconic acid derivatives, diphenylbutadienes, rangiformic acid, aspicilin, homoheveadride, naphthoquinones, anthraquinones, xanthonones, dibenzofuranes, depsides, depsidones, diphenyl ethers, retigeranic acids, and triterpenoids.

Keywords: lichens, lichen substances

Lichen chemistry belongs to the earliest fields of organic chemistry after its foundation in the last century and it is still a flowering branch of natural product chemistry. My aim is to demonstrate the progress in lichen chemistry during the last 7 years in the following. Lichen chemistry is attractive because it comprises many different types of organic compounds shown in Fig. 1 and arranged according to their biogenesis.

Diketopiperazines

Picroroccellin, was first isolated by Stenhouse and Groves (1877) from *Roccella fuciformis* (L.) D.C. more than one hundred years ago. Forster and Saville (1922) proposed the amino acid derived structure 1 for picroroccellin in 1922. As one can see it is a diketopiperazine; the configuration could not be determined. During our work on the chemistry of the Roccellaceae we analysed numerous samples of *R. fuciformis* and other *Roccella* species, but

Xanthenes

Anthraquinones

Naphthoquinones

Dibenzofuranes

Depsidones

Depsidies

Paraconic acid derivatives

Fatty acid derivatives

Carotenoids

Steroids

Triterpenes

Sesterterpenes

Diterpenes

AcetogeninsMevalonate group

LICHEN

Amino acid derivativesCarbohydrates

Polyporic acid

Cyclopeptides

Diphenylbutadienes

Sugar alcohols

Disaccharides

Polysaccharides

Figure 1. Lichen substances and their biogenesis

never found picroroccellin. Finally Marcuccio and Elix (1983, 1985) tackled the picroroccellin problem by a synthetic way. Starting from the diketopiperazine 2 they prepared a mixture of dimethylpicroroccellins which gave the pure and more stable trans-compound on treatment with hydrochloric acid. Dimethylpicroroccellin was found by Forster and Saville (1922) to be optically inactive and this is the case only for the trans-compound. The cis-isomere does not have an axis of symmetry and must be optically active for this reason. Hence Marcuccio and Elix revised the structure of picroroccellin to 2 (Fig. 2). The 8-step synthesis of racemic picroroccellin itself was reported by a Japanese group in 1986 (Shin et al., 1986), starting from the diketopiperazine 3 (Fig. 2). The total synthesis of optically active picroroccellin is still a challenging task for organic chemists.

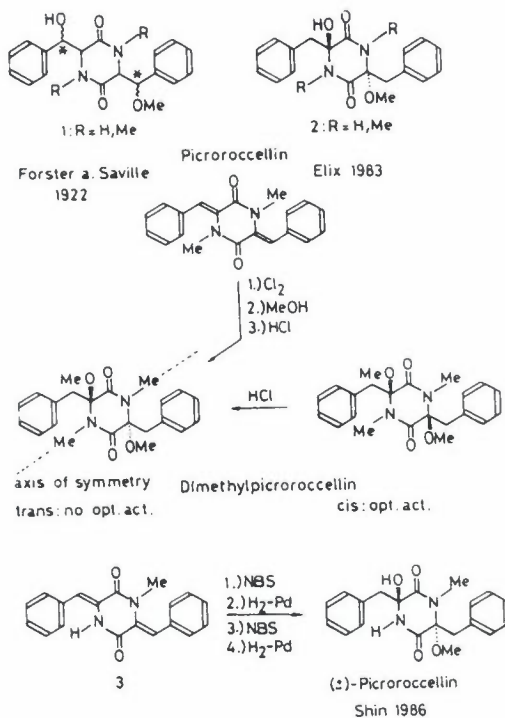


Figure 2. Synthesis of dimethylpicroroccellin and picroroccellin

Diphenylbutadienes

Ramage and coworkers (1984) developed a new biomimetical synthesis to the diphenylbutadienes pulvinic, vulpinic, and leprapinic acids. A biomimetic synthesis follows steps which are similar or perhaps identical to the biosynthesis in nature. The reaction of phosphoranes with methyl aryl glyoxylates gave dioxolan derivatives which yielded with the lithium enolates of tertiary-butyl phenylacetic esters the compounds just mentioned (Fig. 3). Demethylleprapinic acid is a new diphenylbutadiene from an Indian *Lepraria* species (Appa Rao et al., 1984).

Carbohydrates

A very up-to-date review on the low- and high-molecular weight carbohydrates from lichens has been given by Gorin et al. (1988). It may be mentioned here that the sulphate of the $\beta(1-6)$ -glucan GE-3, a widely distributed polysaccharide in lichens of the family Umbilicariaceae, has inhibitory activity against the human immunodeficiency virus (HIV) which is now considered to be the etiological agent of AIDS (Hirabayashi et al., 1989).

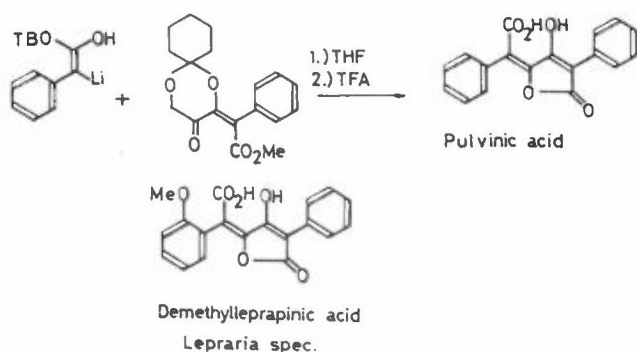


Figure 3. Synthesis of pulvinic acid derivatives

Paraconic acid derivatives and other aliphatic acids

The paraconic acid derivatives comprises a large group of aliphatic compounds of polyacetate origin. The structures of protolichesterinic, lichesterinic, allo-protolichesterinic, and nephromopsinic acids are known since the fundamental works of Asahina and Shibata (1954), but the relative and absolute configuration as well as the syntheses of optically pure compounds remained unsolved problems. In 1986 Huneck et al. (1986) elucidated the structures of two new paraconic acids, (-)-allo-pertusaric and (-)-dihydropertusaric acids from the crustaceous lichen *Pertusaria albescens* (Huds.) Choisy et Wern. The $^1\text{H-NMR}$ and CD spectra led to the structures shown in Fig. 4. Regarding the stereochemistry of these compounds: circular dichroism (CD) and optical rotatory dispersion (ORD) are very useful methods for the determination of configuration of chiral compounds. The comparison of the CD-spectra of (-)-allo-pertusaric acid and (-)-allo-protolichesterinic acid and the corresponding pyrazoline-methylesters showed identical stereochemistry at the carbon atoms 2, 3, and 4; (Figs. 5 and 6).

Cetraria komarovii Elenk. is a leafy lichen of the taiga and mountain forests of Mongolia while *Dactylina madreporiformis* (Ach.) Tuck. is an alpine element. We collected both species during our expeditions through this area of Central Asia and isolated (-)-allo-protolichesterinic and (-)-nephromopsinic acids respectively. Allo-Protolichesterinic acid with a cis-arrangement of the substituents at the carbon atoms 3 and 4 is a rather sensitive compound and isomerizes easily to (-)-lichesterinic acid. Hydrogenation leads to (-)-allo-dihydroprotolichesterinic and (-)-nephromopsinic acids. The two other possible dihydro compounds are (-)-dihydro-protolichesterinic and (-)-roccellaric acids. The structure and stereochemistry of (+)-roccellaric acid, the antipode of the naturally occurring compound has been proved finally by synthesis and X-ray analysis by Mulzer and Salimi (1988). Figure 7 shows the computer

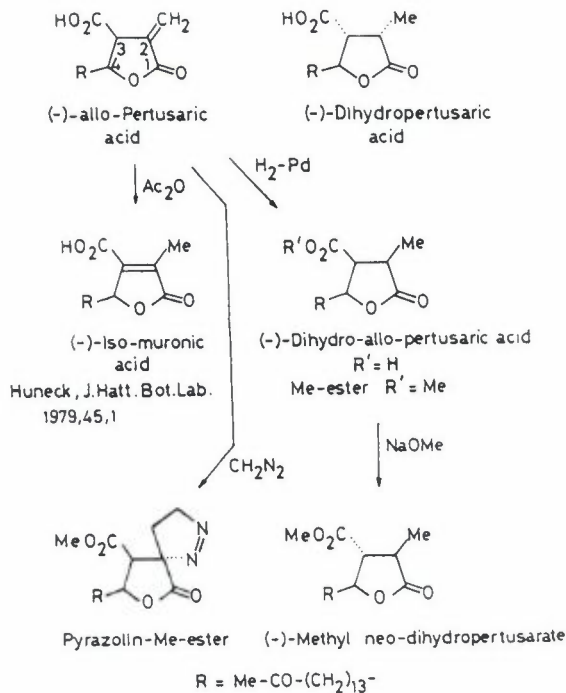


Figure 4. Structure of (-)-allo-pertusaric and (-)-dihydropertusaric acids

view of one molecule of (+)-roccellaric acid and a summary of the synthesis of this paraconic acid derivative and of (+)-nephromopsinic acid, starting from diacetonglucose (Mulzer and Steffen, 1989).

Like sodium protolichesterinate the sodium salts of (-)-allo-pertusaric and (-)-dihydropertusaric acids show growth retarding at concentrations between 10^{-2} to 10^{-4} mol/l and growth promotion at the concentration of 10^{-6} mol/l; test organisms were seedlings of *Lepidium sativum* L., *Triticum aestivum* L., and *Pisum sativum* L. (Huneck et al., 1986).

The structure of (+)-rangiformic acid from *Cladonia rangiformis* Hoffm. had been elucidated by Asahina and coworkers (1954) and by Åkermark (1967), but the position of the methylester group remained undetermined. To solve this problem we made a NMR double resonance experiment with the anhydride of (+)-rangiformic acid; (Fig. 8). On selective decoupling at the resonance of the -COOMe protons, the originally complex signal of the -CO-OMe carbonyl group at 170.66 ppm was simplified to a doublet, thus proving the structure shown (Huneck and Steglich, 1983).

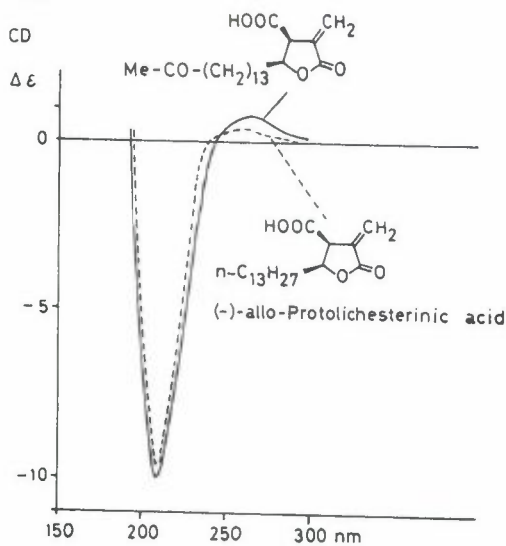
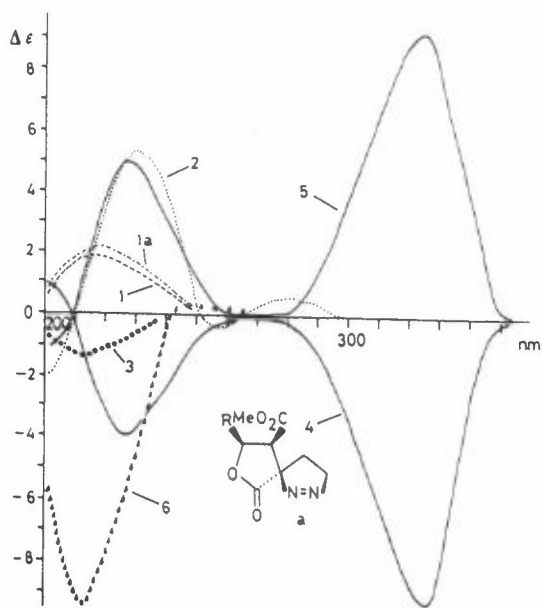
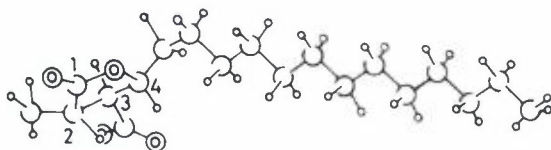


Figure 5. CD-spectra of (-)-allo-pertusaric and (-)-allo-protolichesterinic acids

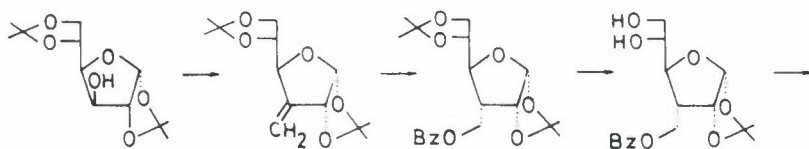


- 1: (-)-Nephromopsinic ac. fr. Cetraria komarovii
 1a: " " " (-)-allo-Protolichester. ac.
 2: (-)-Lichesterinic acid
 3: (-)-allo-Dihydroprotolichesterinic acid
 4: (-)-allo-Protolichesterinic acid methylesterpyrazolin (a)
 5: (+)- " " " "
 6: (-)-allo-Protolichesterinic acid

Figure 6. CD-spectra of the pyrazoline methylesters of (-)-allo-pertusaric and (-)-allo-protolichesterinic acids



(+)-Roccellaric acid



Diacetonglucose

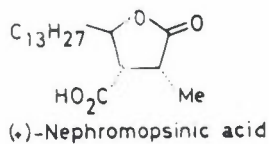
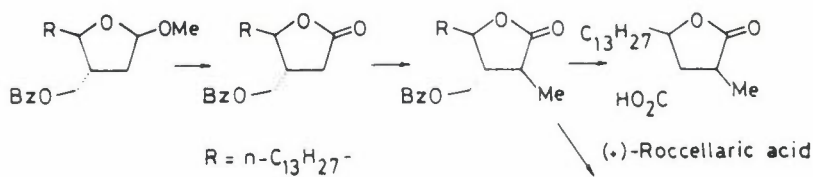
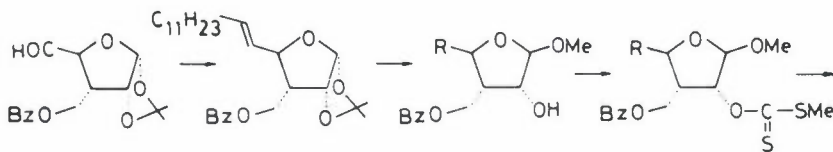


Figure 7. Computer view of a molecule of (+)-rocellaric acid and synthesis of (+)-rocellaric and (+)-nephromopsinic acids

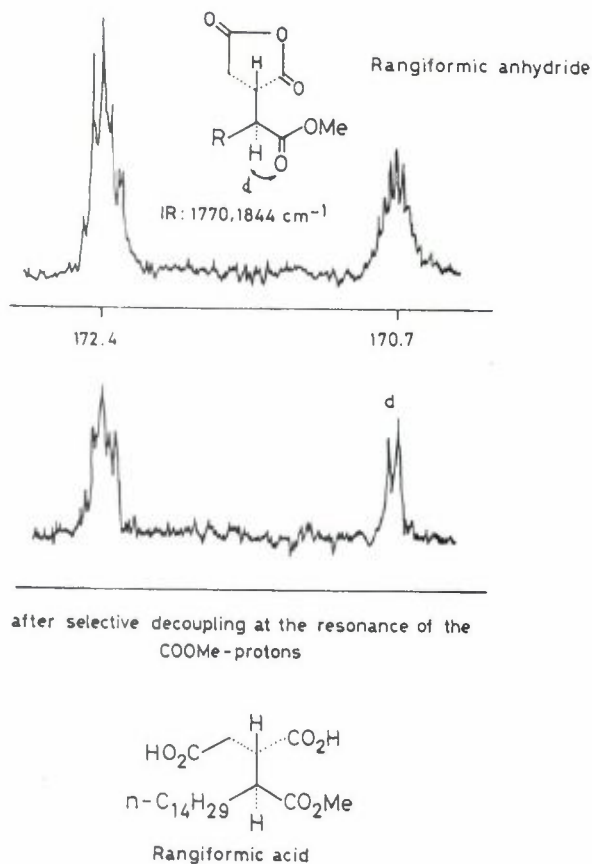


Figure 8. NMR-double resonance experiment with the anhydride of (+)-rangiformic acid

Macrocyclic compounds

In 1973 we elucidated the structure of aspicilin, a 18-membered cyclic lactone (Huneck et al., 1973). During the last 3 years several syntheses of aspicilin have been published. Waanders et al. (1987) made use of the photochemical rearrangement of α, β -epoxy diazomethyl ketones and the stereochemical control of the Sharpless epoxidation as key steps to the synthesis of unnatural (-)-aspicilin. Quinkert et al. (1985) determined the absolute configuration and the conformation of (+)-aspicilin by an X-ray analysis as 4R,5S,6R-trihydroxy-17S-methyl-2-heptadecenolide and built up (+)-aspicilin from phenol, 1,9-nonanediol, and (-)-S-methyloxirane (Quinkert et al., 1988). In Fig. 9 another synthesis of (+)-aspicilin is described (Quinkert et al., 1989).

Homoheveadride is a polyacetate of quite unusual structure (Fig. 10). Homoheveadride from *Cladonia polycarpoides* Nyl. in Zwakh (Archer and

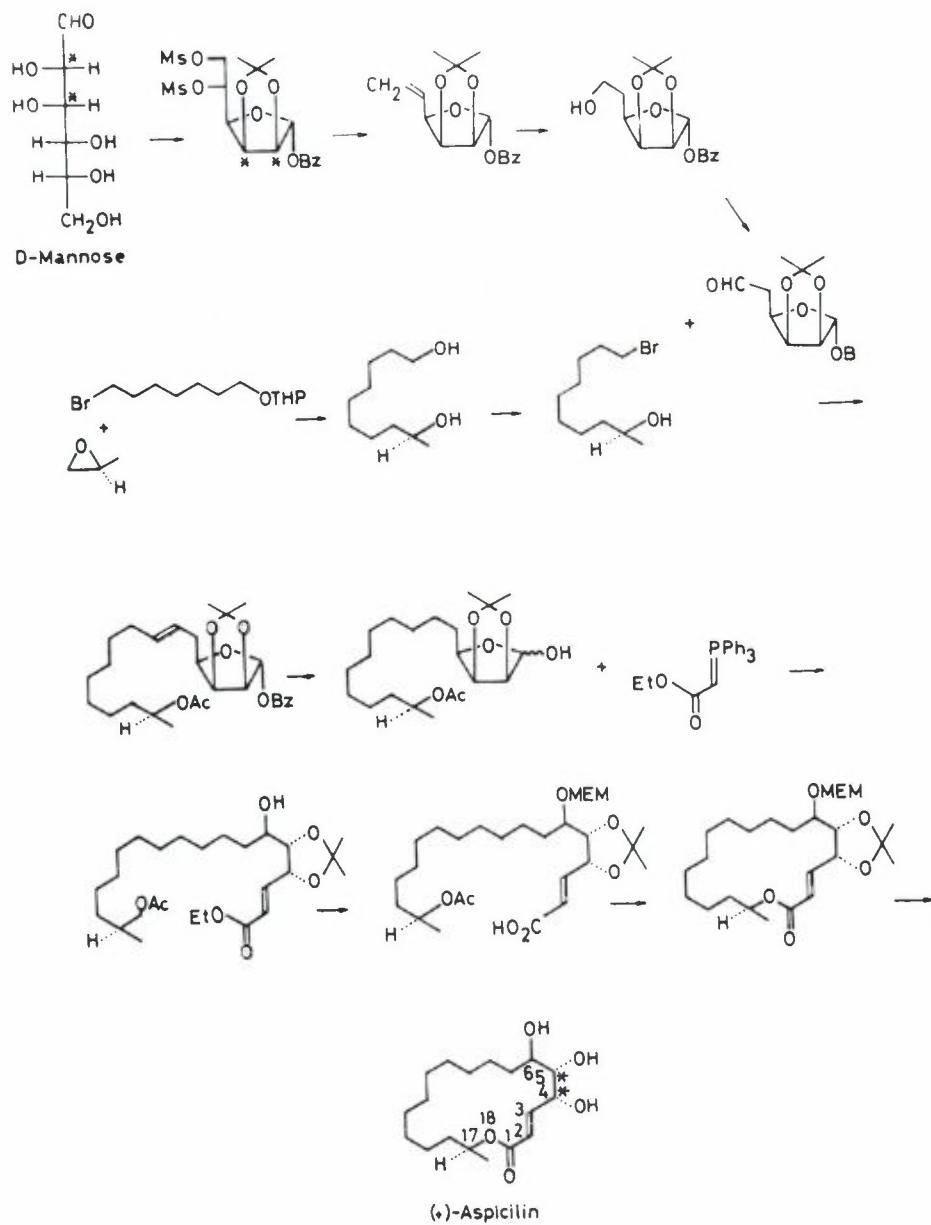


Figure 9. Synthesis of (+)-aspicilin after Quinkert et al. (1989)

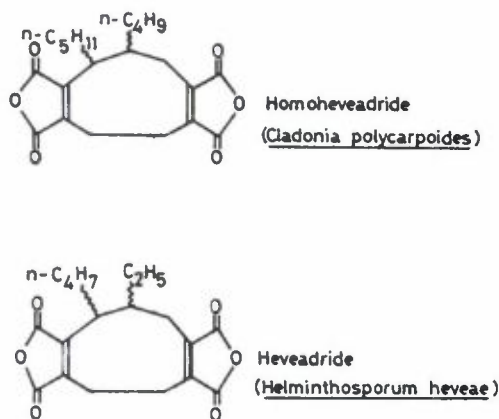


Figure 10. Structure of homoheveadride

Taylor, 1987) is a homologue of heveadride, known from the fungus *Helminthosporum heveae* (Crane et al., 1973).

Naphtha-, anthra- and phenanthren-quinones

Zopf (1907), one of the pioneers of lichen chemistry, isolated first the pigment of the red apothecia from Cladoniaceae and named it rhodocladonic acid. Shibata (Asahina and Shibata, 1954) put forward an anthraquinone structure which was called in question later on. Finally McLean and coworkers (1983) determined the structure of rhodocladonic acid by an X-ray analysis of its triacetate as a furano-naphthoquinone (Fig. 11).

Haematomma species are characterized by apotheciae with a red or brown disk. Bruun and Lamvik (1971) isolated the red pigment haemoventosin from *Haematomma ventosum* (L.) Massal. and proposed a dihydrofuranonaphthoquinone structure. This structure seems to be doubtful. Through the courtesy of Prof. Culberson, I received some material of *Haematomma puniceum* (Sm. ex Ach.) Massal. from the United States. The deep red apotheciae yielded the new anthraquinone haematommone, the structure of which is shown in Fig. 11 (Huneck et al., in press). Haematommone is a lower homologue of norsolorinic acid which makes together with solorinic acid the orange colour of the lower side of *Solorina crocea* (L.) Ach. These findings are perhaps of chemotaxonomic interest because *H. ventosum* was transferred to the new genus *Ophioparma* recently, because the identification of *H. puniceum* is not quite clear.

Asahinin is another new anthraquinone from *Asahinea chrysantha* (Tuck.) W. Culb et C. Culb. (Stepanenko et al., 1985) while biruloquinone represents

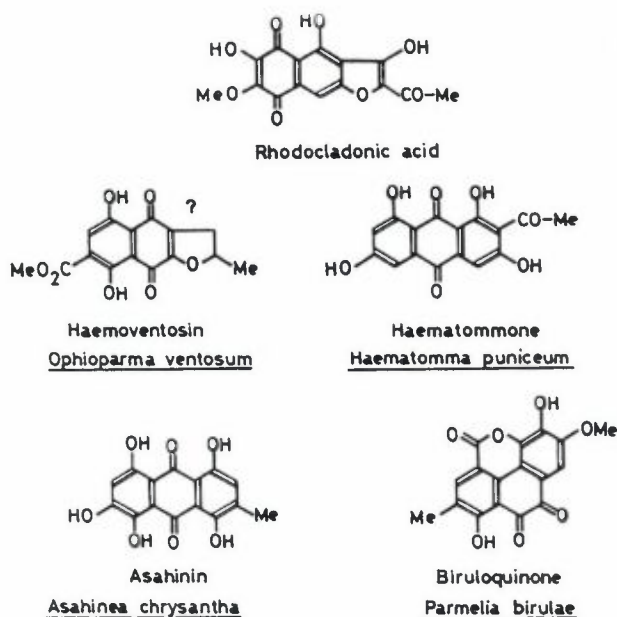


Figure 11. Structure of rhodocladonic acid, haematommone, and biruloquinone

a phenanthrenquinone from *Parmelia birulae* Elenk. (Krivoshchekova et al., 1983) (Fig. 11).

Xanthones

Most lichen xanthones are derivatives of 1,3,6-trihydroxy-8-methylxanthone, but recently Elix and coworkers (1984a, 1987b) found in a *Diploschistes* species from Brazil and in *Rinodina thiomela* (Nyl.) Müll. Arg. xanthones with other substitution patterns (Fig. 12).

Dibenzofuranes

The structure of the dibenzofurane didymic acid, proposed 46 years ago by Shibata has been confirmed unequivocally by X-ray crystallography of the di-methylester shown in Fig. 13 (Shibata and Iitaka, 1984).

The synthesis of subdidymic acid has been achieved by Elix and Kennedy (1985) in the way demonstrated in Fig. 14. Elix and coworkers (Chester et al., 1986) synthesized in a quite analogous way isodidymic acid, a new dibenzofurane from *Cladonia didyma* (Fée) Vain. and Sargent (1987) described the total synthesis of methyl di-O-methylporphyrate (Fig. 15).

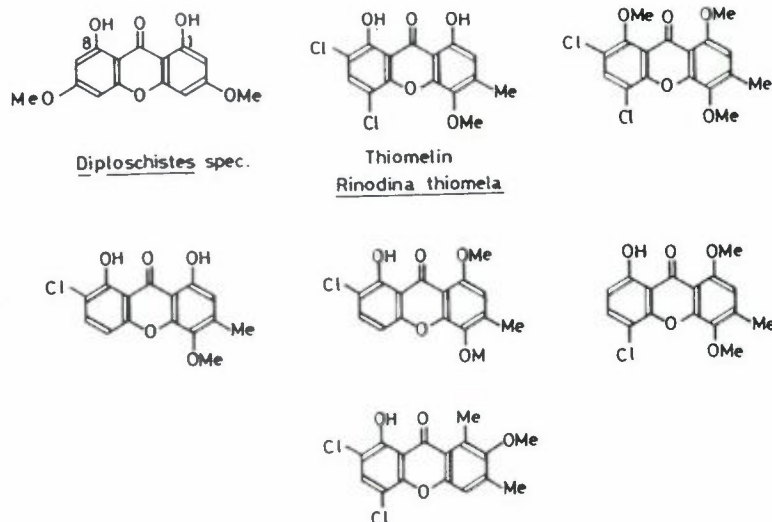
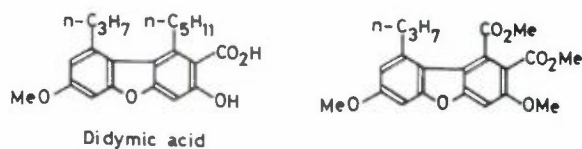
Figure 12. Structure of xanthonones from *Diploschistes*- and *Rinodina*-species

Figure 13. Structure of didymic acid and its derivative for the X-ray analysis

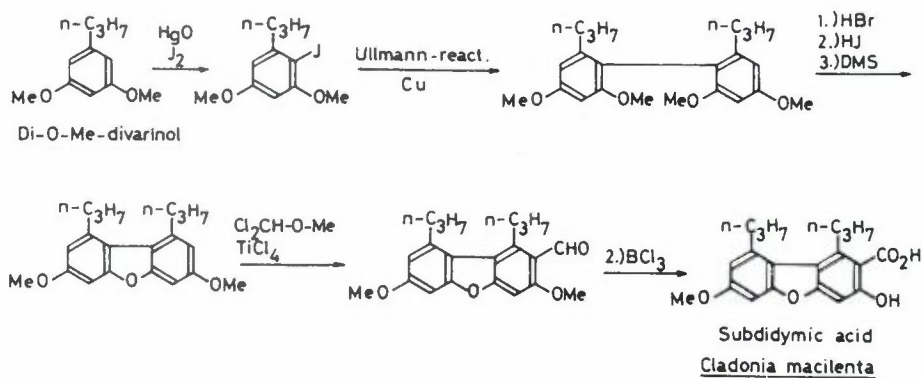


Figure 14. Synthesis of subdidymic acid after Elix and Kennedy (1985)

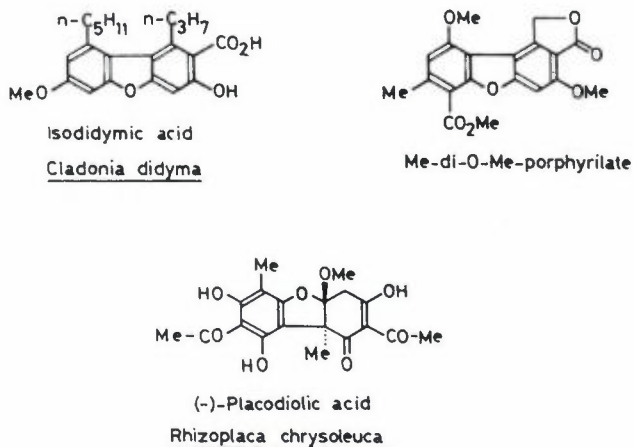


Figure 15. Synthesis of methyl di-O-methylporphyrilate after Sargent and the structure of (-)-placodiolic acid

The trans-configuration of (-)-placodiolic acid, an iso-usnic acid derivative from *Rhizoplaca chrysoleuca* (Smith) Zopf has been established by X-ray analysis (Connolly et al., 1984) (Fig. 15).

Depsides

By far most lichen substances belong to the group of depsides. Elix and Tabacchi and their coworkers have synthesized nearly all representatives of these phenolics in the course of the last years. The principle of these syntheses is demonstrated by means of two examples. There are two main problems in the synthesis of depsides: (1) the construction of the properly substituted subunits S and A, and (2) the connection of both units via the ester-bond, which is achieved nowadays by trifluoroacetic anhydride. Where necessary the phenolic and carboxyl groups of the precursors are protected by O-benylation. Catalytic hydrogenation of the so-formed O-benzyldepsides yields the natural depside finally. The first example concerns the synthesis of miriquidic acid, the structure of which we elucidated in 1971 (Hunecck et al., 1971). 2-Bromo-3,5-dimethoxybenzyl chloride was alkylated with diethyl sodiomalonate, the resulting malonate hydrolyzed and the malonic acid decarboxylated to the 3-phenylpropionic acid. The acid chloride afforded with diethylcopperlithium the ketone; the oxo group was protected as diethylacetal. Lithiation of the acetal followed by carbonation and demethylation gave the S-part of the

molecule, which was condensed with the benzylated A-part to benzyl miriquidate. Hydrogenolysis yielded miriquidic acid finally (Elix and Jayanthi, 1986 (Fig. 16).

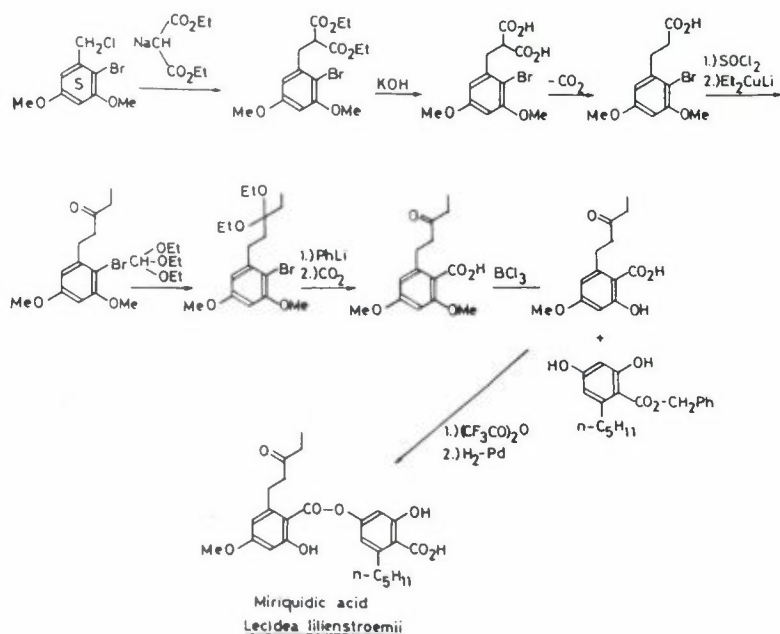


Figure 16. Synthesis of miriquidic acid after Elix and Jayanthi (1986)

The second example describes the syntheses of the pseudocyphellarins A and B, two fully substituted depsides from *Pseudocyphellaria vaccina* Malme (Huneck, 1984). Pseudocyphellarin A and B have been synthesized independently by Elix and Lajide (1984) and by Pulgarin et al. (1985). The synthesis by the latter is demonstrated in Fig. 17.

Certain ethnic groups in Pakistan use a glowing mixture of the lichen *Lethariella cladonioides* (Nyl.) Krog and *Juniperus* species as incense for sensual excitation. Because some lichens contain depsides and depsidones with an olivetol unit and *Juniperus* species synthesize p-menthane derivatives it might be that under pyrolytic conditions psychotropic active cannabinol derivatives could be build (Fig. 18). For this reason we investigated the chemistry of *Lethariella cladonioides* (Huneck and Frembgen, 1989) and the thermal decomposition of lichen depsides (Huneck et al., 1989). *L. cladonioides* contained rather common compounds: gyrophoric acid and atranorin. Gyrophoric acid yielded on pyrolysis 1,6-dihydroxy-3,8-dimethylxanthone (Fig. 19), while

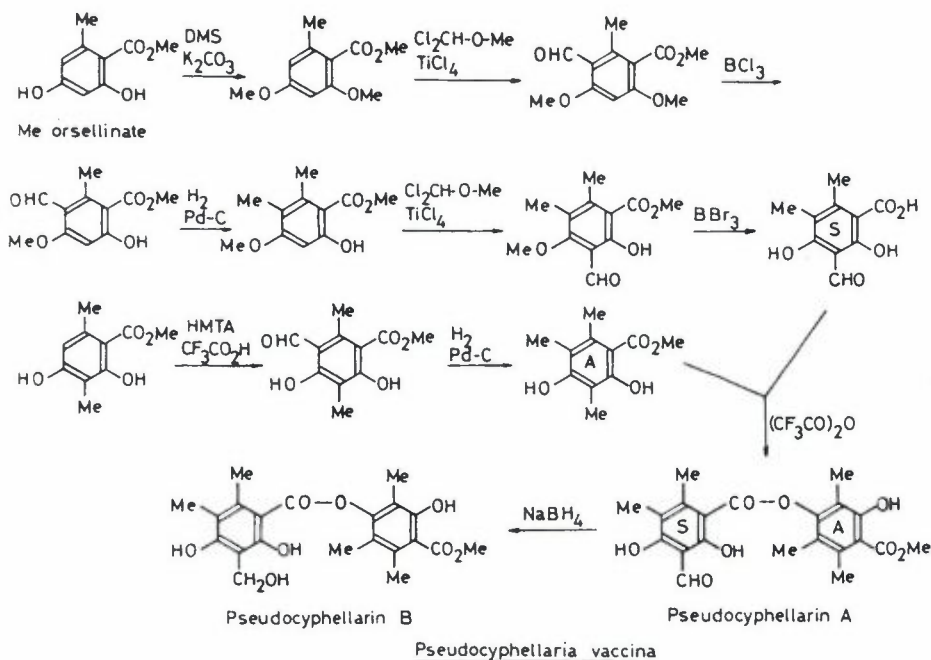


Figure 17. Synthesis of pseudocyphellarin A and B after Pulgarin et al. (1985)

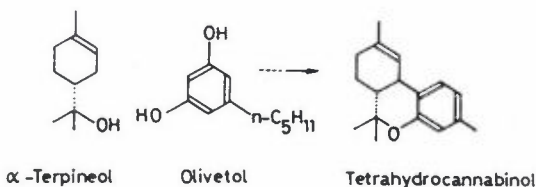


Figure 18. Assumed formation of psychotropic active cannabinol derivatives from lichen phenolics and p-menthane

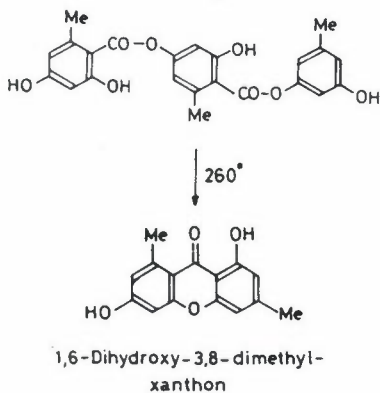


Figure 19. Pyrolysis of gyrophoric acid

the thermal decomposition of atranorin gave orcinol, β -orcinol, methyl β -orcinolcarboxylate, methyl haematommate, and 4-O-demethylbarbatol, phenolic compounds which are quite capable to combine with p-menthane derivatives to potential psychotropically active cannabinol derivatives (Fig. 20).

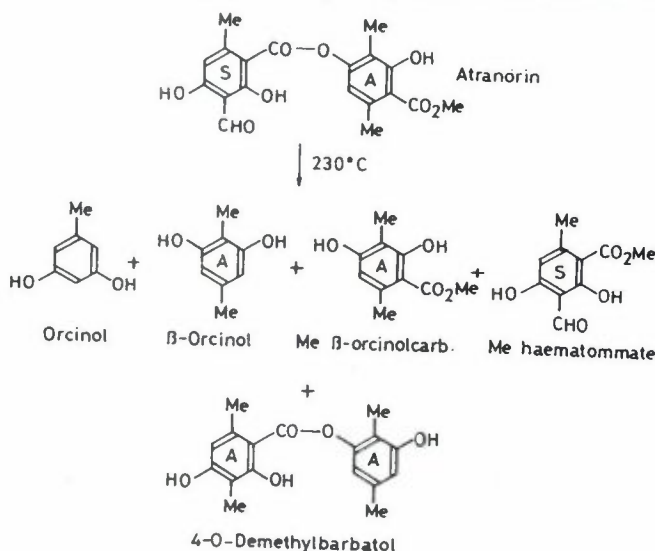


Figure 20. Pyrolysis of atranorin

Depsidones

The second large group of lichen substances are the depsidones, which are biogenetically derived from the depsides by phenol oxidation. Elix and Tabacchi have isolated and synthesized many new compounds, which cannot be enumerated here. Depsidone syntheses are more difficult than the syntheses of dipsides. The principles of their syntheses are demonstrated by the two following compounds: divaronic acid, a metabolite of *Cladonia grayi* Merr. ex Sandst. has been synthesized by Elix and coworkers (1987) as shown in the following way (Fig. 21). One key step is the Smiles-rearrangement of a depside to a diphenyl ether (Fig. 21). The second example describes the synthesis of methyl virensate, a depsidone found in *Pseudocyphellaria physciospora* by Renner et al. (1978). It has been synthesized by Pulgarin and Tabacchi (1989) (Fig. 22); the decisive steps of this synthesis are the oxydation of the benzophenone and the rearrangement of the grisadienone to the diphenyl ether.

Some new diphenyl ethers have been described during the last years: micareic and methoxymicareic acids from *Micareia prasina* (Elix et al., 1984) and

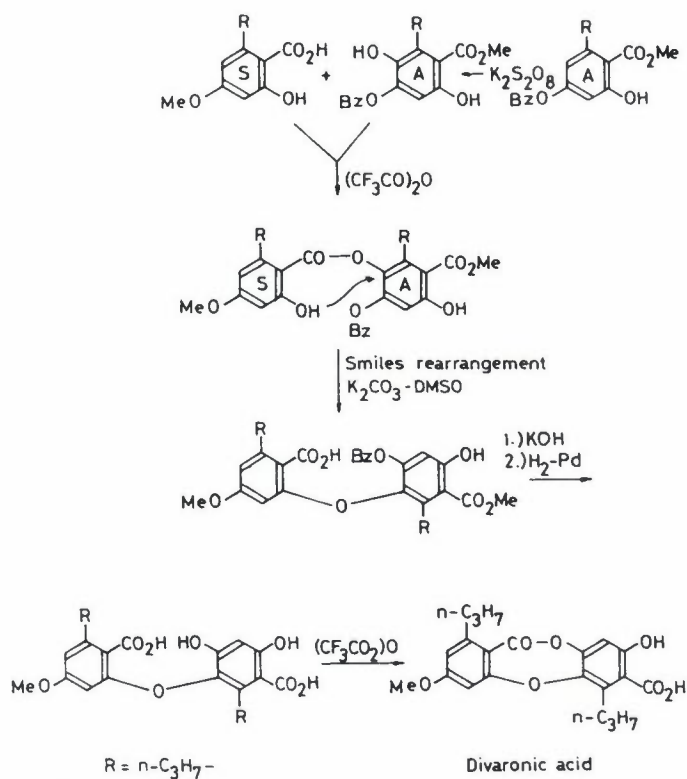


Figure 21. Synthesis of divaronic acid after Elix et al. (1987)

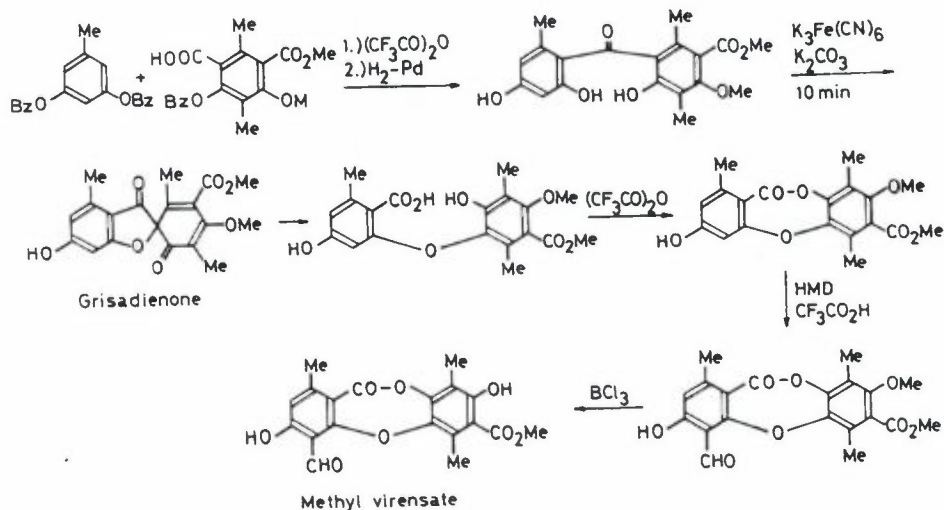


Figure 22. Synthesis of methyl virensate after Pulgarin and Tabacchi (1989)

the epiphorellic acids 1 and 2 from *Cornicularia epiphorella* (Nyl.) Du Rietz (Fiedler et al., 1986) (Fig. 23).

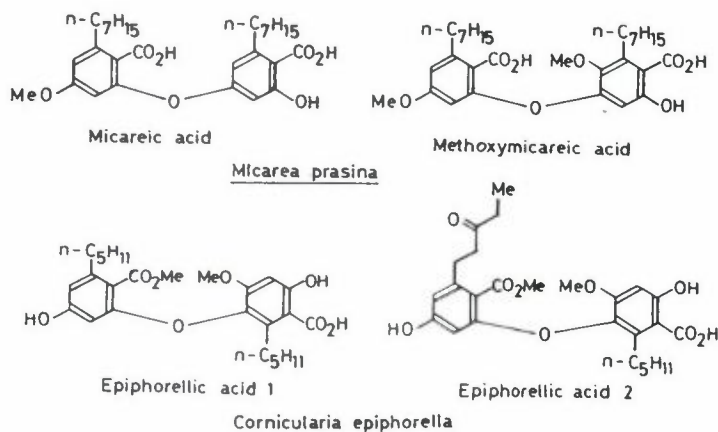


Figure 23. Structure of micareic, methoxymicareic, and epiphorellic acids 1 and 2

Biphenyls

Contortin from *Psoroma contortum* Müll. Arg. belongs to a new class of lichen substances, the biphenyls (Elix et al., 1984a) and its biogenesis includes probably the phenolic oxidation of two molecules of di-O-methyl-methylphloroacetophenone as shown in Fig. 24.

Sester- and tri-terpenoids

Retigeranic acid from *Lobaria retigera* (Bory) Trevis. belongs to the sestert-erpenoids, a rather small group of natural products with 25 carbon atoms. It was first described by the group of Seshadri in 1965 and its structure was determined by Shibata and coworkers (Kaneda et al., 1974) by X-ray analysis. Later on the existence of two isomers in *L. retigera*, retigeranic acids A and B was disclosed (Corey et al., 1985) (Fig. 25). The retigeranic acids are unique in two aspects: they are the first terpenes with an angular triquinane, and they have a pentacyclic structure, unlike other sesterterpenes. No wonder that the synthesis of this intricate molecule was a challenge to the leading organic chemists of the world: Corey et al. (1985), Paquette et al. (1987), and Wright et al. (1988). The synthesis by Hudlicky et al. (1989) is shown

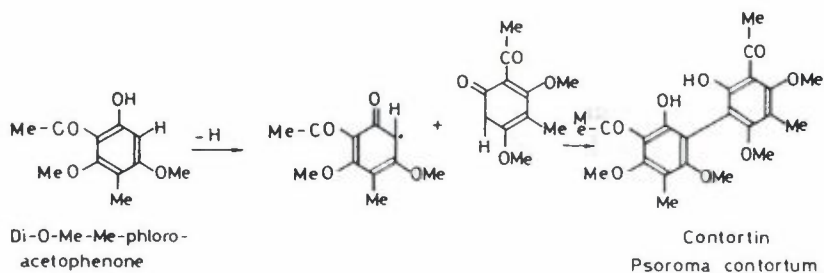


Figure 24. Assumed biogenesis of contortin

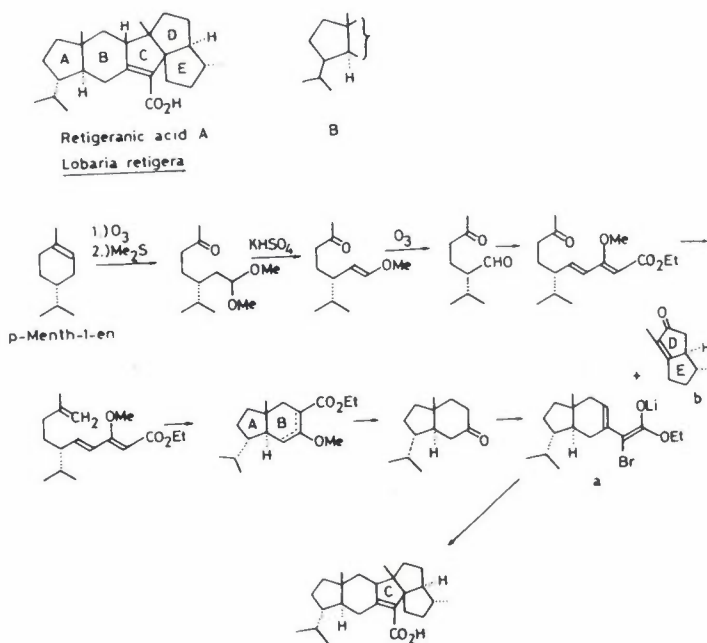


Figure 25. Synthesis of retigeranic acid

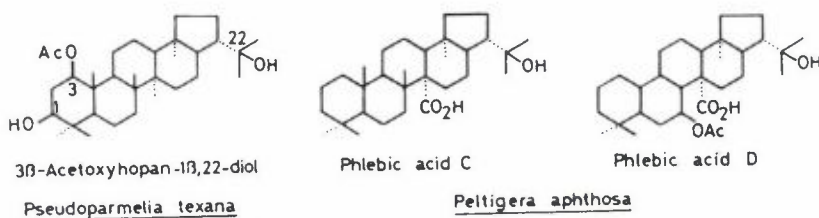


Figure 26. Structure of 3β-Acetoxyhopan-1β,22-diol, phlebic acid C and phlebic acid D

in Fig. 25. The crucial step of the synthesis is the annulation of the lithium dienolate a to the enole b in a Diels-Alder process.

3 β -Acetoxycopan-1 β ,22-diol, phlebic acid C, and phlebic acid D are new hopane triterpenes from *Pseudoparmelia texana* (Tuckerman) Hale (Huneck et al., 1983) and *Peltigera aphthosa* (L.) Willd. (Bachelor et al., 1990) respectively (Fig. 26).

Carotenoids

In a series of papers Czczuga (1988) has investigated the carotenoids of numerous lichens.

Methodology

Culberson and coworkers (Culberson et al., 1984, 1985, 1987) applied the combination of thin layer chromatography, hydrolysis, and mass spectrometry to the structural elucidation of numerous depsides in microamounts. Huovinen and Ahti (1988, 1989, 1989a) developed high performance liquid chromatography (HPLC) to a valuable method for the analysis of aromatic lichen substances and Holzmann and Leuckert (1990) used the mass spectrometry of crude extracts of lichens for the determination of the corresponding components; depsides, depsidones and dibenzofuranes were identified by their specific fragmentation patterns without any isolation or purification. Wilkins et al. (1990) assigned the ¹H- and ¹³C-NMR resonances of lichen triterpenoids of the pyxinol group and Jakupovic and Huneck (1989) correlated the proton signals of numerous depsides, depsidones, depsones, and dibenzofuranes by Nuclear Overhauser Effect (NOE) difference spectroscopy.

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