

Recent developments in iridoids chemistry

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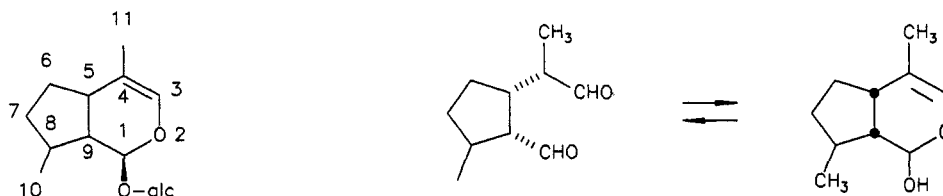
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Abstract: Modern approach to the structure elucidation and to the partial synthesis of some selected iridoids is described as well as the studies on the acid hydrolysis of iridoids and on the structures of the rearrangement products in this way obtained.

Iridoids constitute the more numerous family of cyclopentanoid monoterpene derivatives and can be subdivided into four groups: iridoid glycosides, simple iridoids or non glycosidic iridoids, secoiridoids and bisiridoids (ref.1). They are typical of the vegetable kingdom, but they are not found everywhere in nature, being their presence a characteristic of angiosperms, in particular of the superorder of Sympetalae.

Iridoids are structurally characterized by the presence of a partially hydrogenated *cis* fused cyclopenta[c]pyran system which arises from the intramolecular acetalization of a 1,5-cyclopentandialdehyde

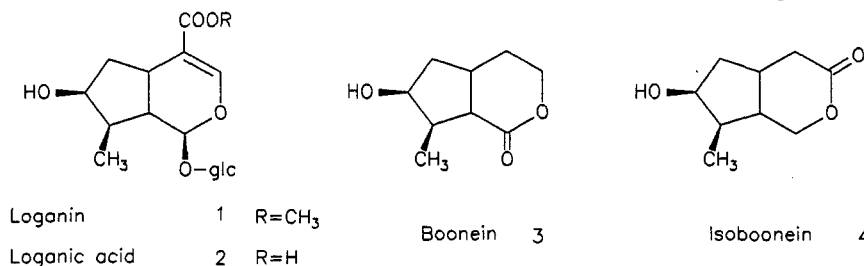
Figure 1



moiety (fig.1) and is usually stabilized by acetalization or esterification.

My work on iridoids started 25 years ago and it involved isolation and structural studies, which I remember with great pleasure, as well as partial syntheses and chemical modifications which seemed to me particularly fascinating. The isolation and structural determination of new iridoidic compounds is now easier owing to the NMR techniques which often allow to "photograph" the molecule. The boonein 3 and isoboonein 4 (fig.2) are simple iridoids of nepetalactone- and iridomyrmecin-type, structurally correlated to loganin 1, both present in very little quantities in roots of *Rauwolfia grandifolia* (Loganiaceae). They were detected by means of ^{13}C -NMR of a semipurified extract. Structure of 3 was previously determined by X ray analysis, while that of 4 was hypothesized on the basis of NMR data and demonstrated by its partial synthesis from

Figure 2

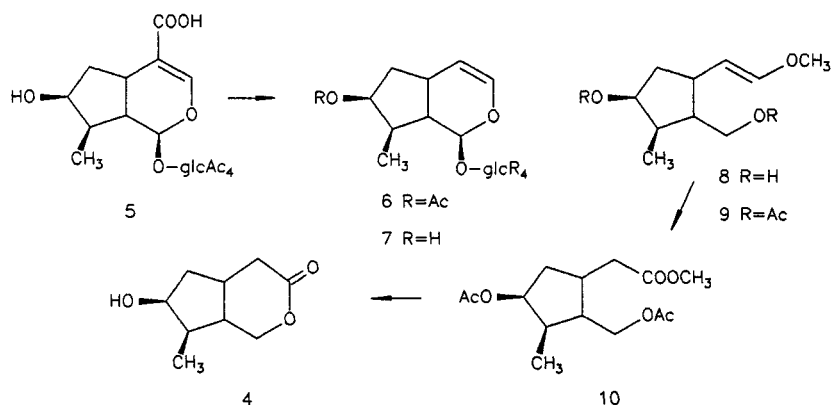


loganic acid 2, as reported in the scheme 1 (ref.2).

The key step of this partial synthesis is the opening of dihydropyran ring of 4-nor-loganin 7 performed with thallium nitrate/sodium borohydride in methanol. This reagent allows the selective reduction of C-1 formyl with loss of the sugar and leaves a masked aldehydic function at C-3. This reaction constitutes therefore

a general method of differentiating the two formyl functions at C-1 and C-3. So it is easily possible to

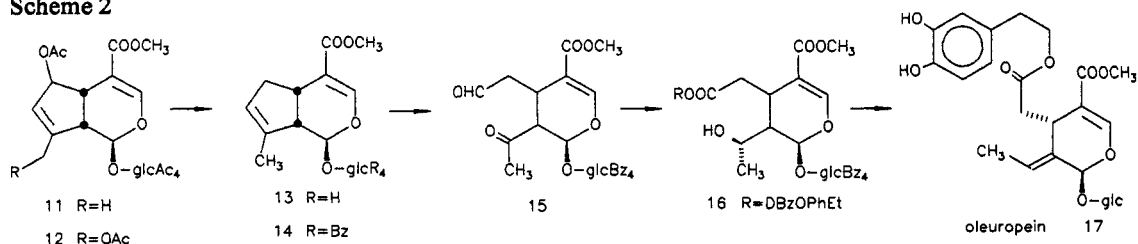
Scheme 1



synthesize iridoids of iridomyrmecin-type (ref.3).

Recently we succeeded in the partial synthesis of oleuropein 17 by a method which appears to be general for the conversion of iridoids into secoiridoids (ref.4). The starting iridoid was deoxygeniposide 13 we prepared from two derivatives 11 and 12 of aperuloside and shanzhiside (see scheme 2). Hydrogenolysis

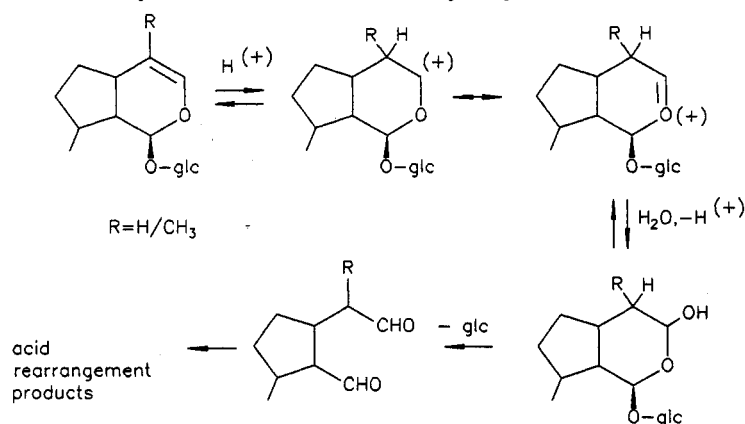
Scheme 2



of 11 and 12 was performed by a new procedure using $\text{Pd}(\text{OH})_2/\text{C}$ and cyclohexene. This method allows to achieve the hydrogenolysis in very high yields with no saturation of the double bond. Oxidative opening of 14 followed by the simple procedure described in ref.4, afforded stereoselectively oleuropein 17.

Iridoids reactivity arises from the presence of the dihydropyran ring which masks a 1,5-dialdehydic function. My recent studies in this field were oriented to examine how the unmasking process of this function occurs. In fact iridoids are very sensible to acids and are hydrolyzed also in mild conditions, showing a

Scheme 3



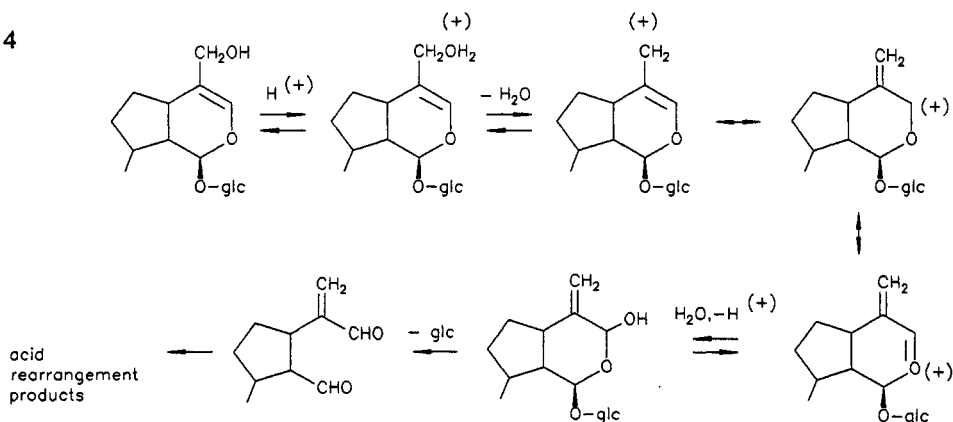
reactivity different from that of a glucosidic bond. Therefore I hypothesized a different hydrolysis course, in which the enol-ether function was involved (see schemes 3, 4, 7). Experimental results are in agreement with these suggestions and indicated that the course of acid hydrolysis of iridoids is also in relation with the kind

of substituents at C-4 and at C-5. The structure of subsequent rearrangement products is due to the functionalization of cyclopentane ring .

When at C-4 "neutral" groups, as hydrogen or methyl, are present, the course of the hydrolysis is that depicted in scheme 3 and the rearrangement depends essentially on the functionalization of cyclopentane ring (see aucubin, lamiol, harpagide, antirride, bisdeoxyaucubin in ref.1).

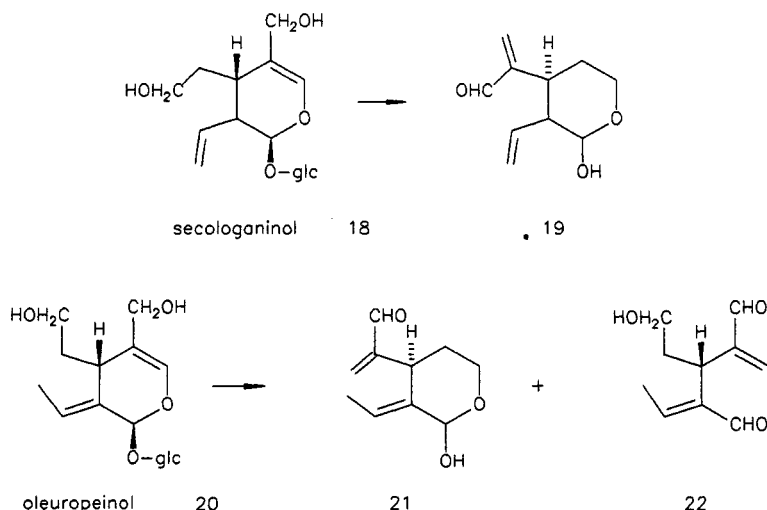
The course of hydrolysis can be different, as in scheme 4, when at C-4 is present the hydroxymethyl group (see α -dihydroverbenol, shanzhisidol in ref.1). This trend is showed also by secoiridoids as secol-

Scheme 4



ganinol **18** or oleuropeinol **20** which afford the rearrangement products **19** or **21** and **22** respectively, as described in scheme 5. The 4-hydroxymethyl substituted iridoids can be hydrolyzed also according scheme 3 and, in this case, the C-4 substituent participates to the acid rearrangement being involved in an acetalization

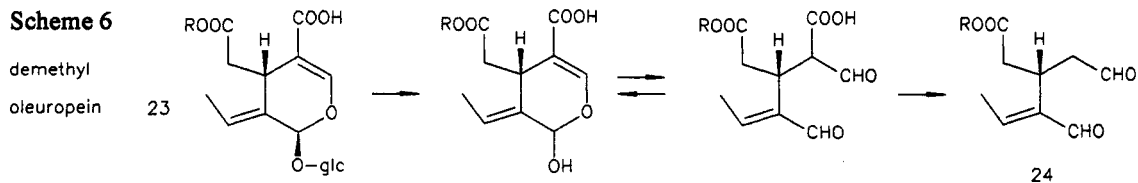
Scheme 5



reaction (see lamiidol, ipolamiidol, thevesidol, asperulosidol in ref.1).

The presence of a carbonyl function at C-4 causes generally a stabilization of the aglycone structure. The aglycones of 4-carbomethoxy substituted iridoids are in fact relatively stable also in acidic medium as

Scheme 6

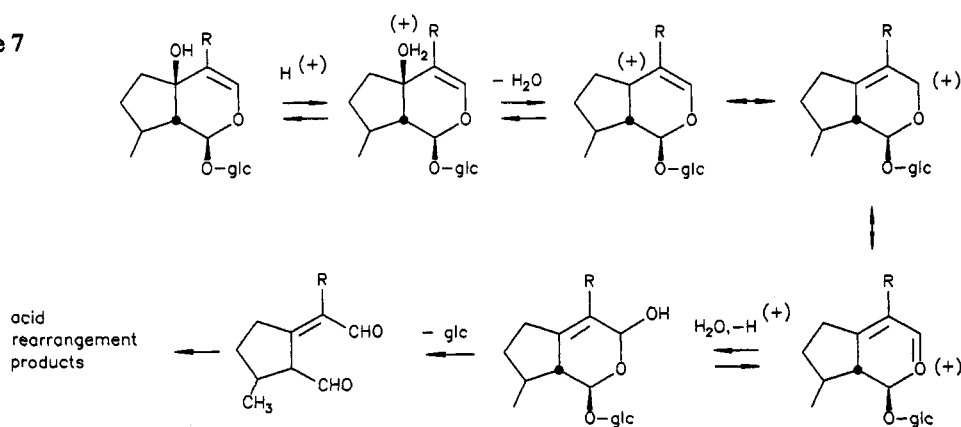


those of 4-formyl ones. Only the aglycones of 4-carboxy substituted iridoids are generally unstable, giving

rise to decarboxylation, and this trend is showed also in the case of secoiridoids; e.g. the aglucone of demethyloleuropein **23** affords, as shown in scheme 6 (ref.5) the product **24**.

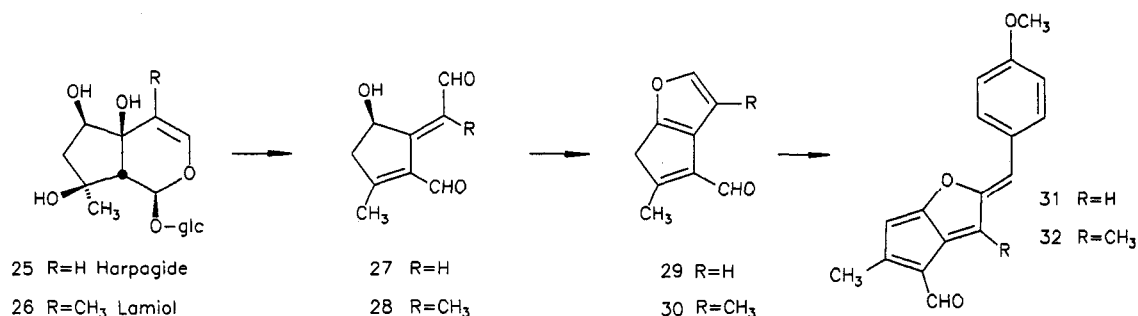
Independently from the kind of substituent at C-4, the acid hydrolysis can occur in a third different way when a hydroxyl group at C-5 is present. In this case, the hydrolysis can also follow the scheme 7.

Scheme 7



A strictly related consequence of the acid rearrangement is the chromatic reaction of iridoids in acidic medium. This chemical behaviour of iridoids was investigated and our recent results are presented. The fulvoharpagide **31** and the fulvolamiol **32** are the compounds responsible of the characteristic chromatic reaction of the corresponding iridoids **25** and **26** with vanillin or anisaldehyde reagents (ref.6). They result

Scheme 8



by the condensation of the furan intermediates **29** or **30** (see scheme 8) with aromatic aldehydes in acidic medium. These furan derivatives arise, by dehydration, from the corresponding insaturated aldehydes **27** or **28** which derive from the relative iridoids **25** or **26** by hydrolysis. This behaviour seems to be general for iridoids 6-hydroxy-substituted, but this statement needs further researches.

Bibliography

- 1 A.Bianco, "The Chemistry of Iridoids" in *"Studies in Natural Products Chemistry"*, Atta-ur-Rahman Ed., ...vol.7 p.329, Elsevier Science Publishers, Amsterdam 1990.
- 2 A.Bianco, A. De Luca, P.Passacantilli, M.Nicoletti, R.Alves de Lima, *Phytochemistry*, in press (1994).
- 3 R.Berdini, A.Bianco, M.Guiso, E.Marini, M.Nicoletti, P.Passacantilli, G.Righi, *J.Nat Prod. (Lloydia)*, **54**, ...1400 (1991).
- 4 A.Bianco, G.Naccarato, P.Passacantilli, G.Righi, M.L.Scarpati, *J.Nat.Prod. (Lloydia)*, **55**, 760 (1992).
- 5 R.Lo Scalzo, M.L.Scarpati, *J.Nat Prod. (Lloydia)*, **56**, 621 (1993).
- 6 A.Bianco, G.Cerichelli, M.Guiso, P.Passacantilli, G.Lo Baido, A.Mazzei, *Gazz.Chim.Ital.*, **123**, 437 (1993).