Tetrahedron Letters, Vol.27, No.3, pp 381-382, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

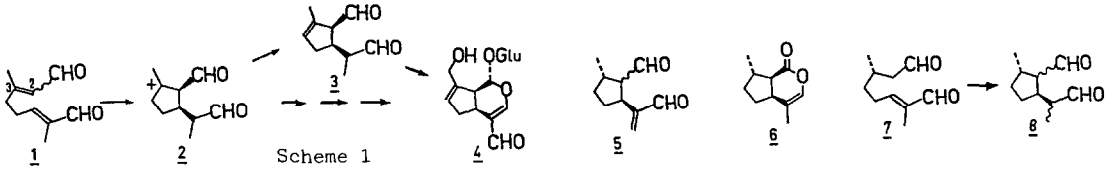
THE BASE-CATALYZED CYCLIZATION OF 10-OXOCITRAL
SYNTHESIS OF CHRYSOMELIDIAL AND DEHYDROIRIDODIAL

Franco Bellesia, Franco Ghelfi, Ugo M. Pagnoni* and Adriano Pinetti

Dipartimento di Chimica dell'Università, Via Campi 183, I-41100 Modena, Italy

Base treatment of 10-oxocitral (1) gives chrysomelidial (9) and dehydroiridodial (10), supporting the intermediacy of 1 in the biosynthesis of some iridoid glucosides. Cannizzaro reaction of 9 and 10 affords regioselectively a new iridolactone, 1,2-dehydroisoiridomirmecin (13).

The intermediacy of 10-oxocitral (1) and iridodial cation (2) in the biosynthesis of iridoid glucosides of Gardenia jasminoides F. has recently been discussed[1] in this Journal (Scheme 1).



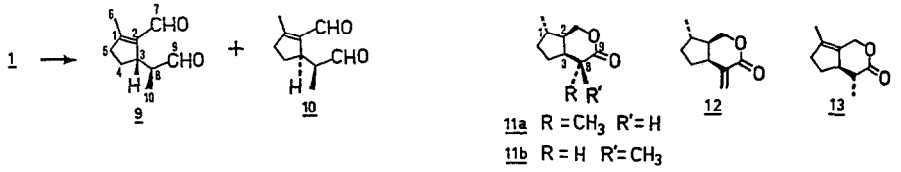
1 2 3 4 5 6 7 8

Scheme 1

The biological cyclization from a diolefinic intermediate to the iridane skeleton is not a general pathway. For instance, in the case of cyclopentanoid metabolites, such as dolichodial[2] (5) or nepetalactone[3] (6), structurally much simpler with respect to iridoid glucosides and indole alkaloids, 2,3-saturated acyclic precursors, such as 7, are involved in this step.

In the laboratory, the synthesis of iridodial (8) from 7 was realized[4] by R. Robinson in 1959, the ring formation being a normal Michael reaction. In view of this chemical result and of the biosynthetic observations concerning 10-oxocitral, we attempted to carry out the cyclization of 1, to check if a cyclopentane structure, such as dehydroiridodial (3), could be obtained.

Acid-catalyzed reactions on 2E-1[5] were quite unsuccessful, in any case affording only tars. Among the different bases[6] and conditions we tried, just with 0.01 N NaOH in MeOH-H_2O (98:2) (0.3 Molar, 10' at r.t.) was a smooth conversion achieved. The isolated (82% yield) product was a 1.2:1 (25 m gc capillary column of SE 54) mixture of chrysomelidial (9) (3R,8R and 3S,8S) and its diastereomer, dehydroiridodial (10) (3S,8R and 3R,8S), which are olefinic isomers of 3. This last compound was not found (gc, nmr) in the recovered material.



1 → 9 + 10

11a R = CH_3 R' = H
11b R = H R' = CH_3

12 13

Structures 9 and 10 have been determined by spectral (gc-ms, nmr) comparison[7,8] and chemical reduction[8] ($LiAlH_4$) into the corresponding known[8] isodehydroiridodiol and dehydroiridodiol, respectively. As natural compounds, they have been found in certain chrysomelid beetles[7,9] (9, 10 and/or their enantiomers) and in the cat-attracting plant Actinidia polygama Miq.[10] (10).

The feasibility of a cyclization process from a diolefinic dialdehyde to an iridane skeleton is thus proved. The conversion has been only achieved in a base-catalyzed reaction, in which the formation of the hypothesized cation species 2 is not expected. However, this or an equivalent intermediate is rather likely to be formed in the biological enzyme-mediated transformation, through an intramolecular general acid catalysis[11].

Lactones with the carbonyl group at C_9, isoiridomirmecin (11a) and allodolicholactone (12), have been regioselectively obtained on subjecting iridodial (8)[4,12] and dolichodial (5)[13], respectively, to the Cannizzaro reaction conditions. By using this procedure[13] on the isolated reaction mixture (1.2:1) of chrysomelidial (9) and dehydroiridodial (10), a new dehydroiridolactone (13) was obtained (71% yield), again regioselectively, bp 106-8°C/0.2 mmHg; m/e (%): 166 (M^+, 13), 122 (51), 107 (100), 91 (56), 79 (56); ir (film), cm^{-1}: 1725, 1645; ^{1}Hnmr ($CDCl_3$), δ : 1.26 (3H,d(J 6.5 Hz),CH_3-C), 1.67 (3H,br s,CH_3-C=), 2.0-2.8 (6H) and 4.98 (2H,m,OCH_2-C).

The stereochemistry (3R,8R and 3S,8S) of 13 was established by reduction ($LiAlH_4$, 85% yield) into the known[8] isodehydroiridodiol. The formation of only one diastereomer (13), of the isoiridomirmecin (11a) type, from both 9 and 10 is easily explained with reference to the observed[14] base-promoted transformation of iridomirmecin (11b) into isoiridomirmecin (11a).

A regioselectivity which in any case yields lactones (11a, 12 and 13) with the carbonyl group at C_9, starting from both one saturated (8) and two isomeric unsaturated aldehydes having the olefin conjugation at C_9 (5) or at C_7 (9 and 10) carbonyl function, is unexpected; it means that conjugation does not influence the hydride donor or acceptor ability of the two aldehyde functions in the Cannizzaro reaction intermediate[15]. Steric factors thus have priority over electronic ones, and one explanation may be that the formation of a tetrahedral gem-diol group in these iridoid substrates causes a more severe steric constraint at C_7 than at C_9 position.

Acknowledgements: Financial supports from Min.PI and CNR (Rome) are gratefully acknowledged.

References: 1)S.Uesato, S.Ueda, K.Kobayashi, M.Miyauchi and H.Inouye, Tetrahedron Lett., 25, 573 (1984). 2)F.Bellesia, U.M.Pagnoni, A.Pinetti and R.Trave, Phytochemistry, 22, 2197 (1983). 3)F. Bellesia, R.Grandi, U.M.Pagnoni, A.Pinetti and R.Trave, Phytochemistry, 23, 83 (1984). 4)K.J. Clark, G.I.Fray, R.H.Jaeger and R.Robinson, Tetrahedron, 6, 217 (1959). 5)J.Balsevich, Can.J. Chem., 61, 1053 (1983). 6)A.F.Thomas and R.Guntz-Dubini, Helv.Chim.Acta, 59, 2261 (1976). 7)J. Meinwald and T.H.Jones, J.Am.Chem.Soc., 100, 1883 (1978). 8)T.Sakai, K.Nakajima, K.Yoshihara, T.Sakan and S.Isoe, Tetrahedron, 36, 3115 (1980). 9)J.M.Pasteels, J.C.Braekman, D.Daloze and R. Ottinger, Tetrahedron, 38, 1891 (1982). 10)K.Yoshihara, T.Sakai and T.Sakan, Chemistry Letters, 433 (1978). 11)Comprehensive Org. Chem., eds D.H.R.Barton and W.D.Ollis, Pergamon, Oxford, 1979, Vol 4, p. 404. 12)G.W.K.Cavill and D.L.Ford, Aust.J.Chem., 13, 296 (1960). 13)U.M.Pagnoni, A.Pinetti, R.Trave and L.Garanti, Aust.J.Chem., 29, 1375 (1976). 14)R.Fusco, R.Trave and A.Vercellone, Chim.Ind., 37, 251 (1955); G.W.K.Cavill and H.D.Locksley, Aust.J.Chem., 10, 352 (1957). 15) C.G.Swain, A.L.Powell, W.A.Sheppard and C.R.Morgan, J.Am.Chem.Soc., 101, 3576 (1979).

(Received in UK 15 November 1985)