Pergamon

Tetrahedron Letters, Vol. 35, No. 22, pp. 3781-3784, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0618-8

Diastereoselective Ring–Opening of 12-Acetoxy-9α and 9β(11)-Epoxy-7-Drimene: Homochiral Semisynthesis of Poligodial and Warburganal

Julio G. Urones*, Isidro S. Marcos, Belén Gómez–Pérez, Anna M. Lithgow, David Díez, Pilar Basabe and Patricio M. Gómez

Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1–5, 37008 Salamanca, Spain

Abstract- Starting from a zamoranic acid derivative (Methyl 15–tetrahydropiranyloxy–7–labden–17–oate) poligodial and warburganal have been synthesized in several steps with a 55% overall yield and 27% overall yield, respectively.

Several semisynthetic procedures have been reported for drimanes with a wide range of biological activities:[1] for instance as antifeedant,[2] antimicrobial,[3] cytotoxic,[3] growth regulator,[4] molluscicide[5] or anticomplemental.[6] The more common templates used for semisynthetic work[7] are tricyclic diterpenoids as abietic acid, levopimaric acid, royleanone, podocarpic acid and hispanolone and bicyclic diterpenoids as manool or communic acid. A triterpenoid as glycirretinic acid has also been used.[7]

The major component of *Halimium viscosum* (Valparaíso) that we had isolated[8] is a diterpenic acid with a labdane backbone, zamoranic acid **1a**, that possesses functionalization on ring B (Δ^7 and a carboxylate at C–17) to be the ideal precursor for the semisynthesis of drimanes with biological activity as poligodial **2**[9] and warburganal **3**[10] or pereniporin A and pereniporin B.[11]

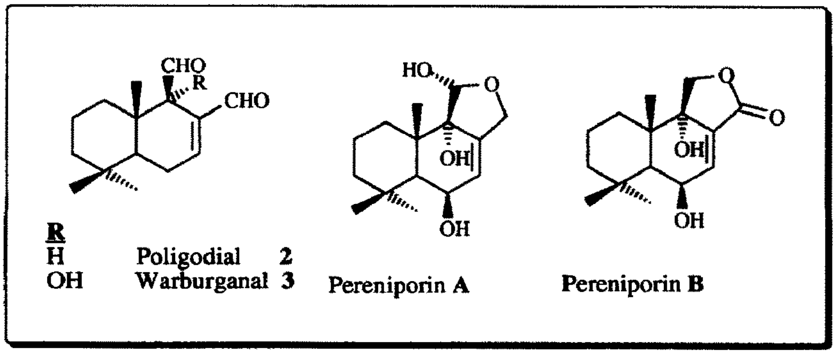
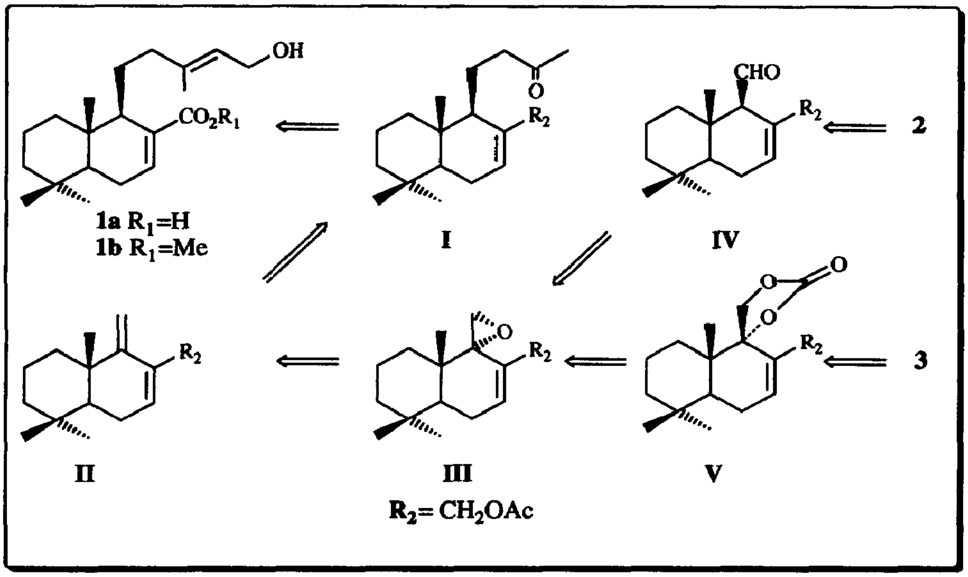


Figure 1. Some Bioactive Drimanes

The first semisyntheses undertaken in this line were those of poligodial **2** and warburganal **3**, very well known antifeedant dialdehydes against *Spodoptera exempta* and *S. littoralis* worms.[12] The first modification of the starting material is a five-carbon degradation of the side chain before introducing the adequate method for functionality modification.

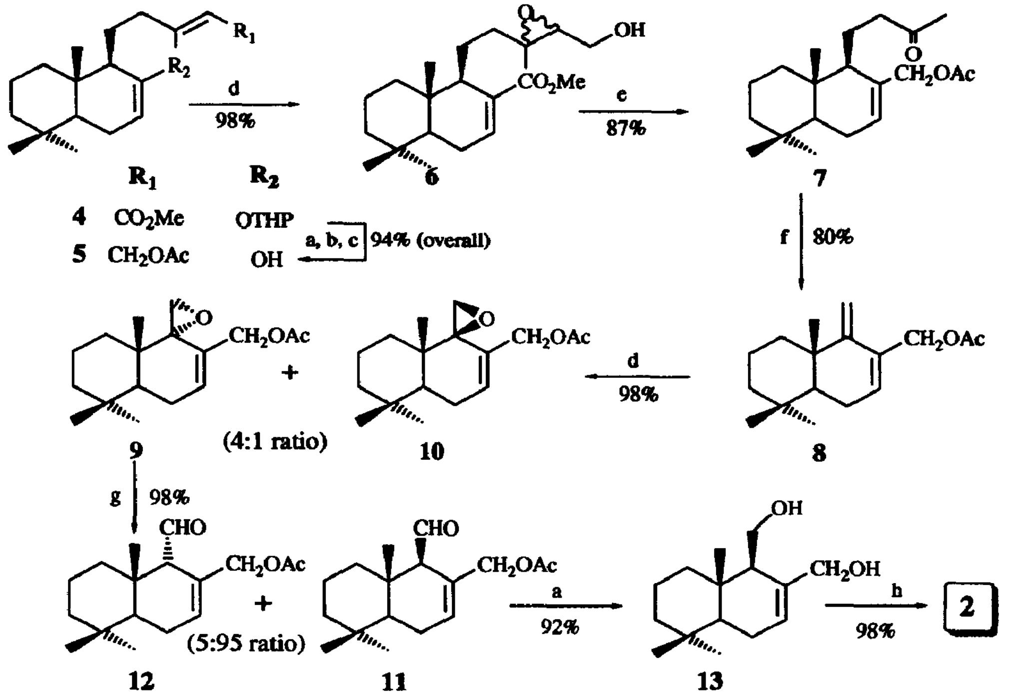
Scheme 1 shows the retrosemisynthetic analysis including the key dienic intermediate **II** obtained through a Norrish II photochemical rupture of methyl ketone **I**, available from the methyl ester of zamoranic acid, **1b**. The epoxide **III** obtained from diene **II** could be transformed either to the aldehyde **IV** or the carbonate **V** from which poligodial **2** or warburganal **3** were obtained, respectively.



Scheme 1: Retrosemisynthetic analysis from zamoranic acid methyl ester

The starting material **4** (Scheme **2**) is a derivative of **1b**, with the hydroxyl group at C-15 protected as a tetrahydropyranyl ether. The LAH reduction of **4** acetylation and subsequent acid hydrolysis led to **5** that was chemoselectively epoxidized with *m*–CPBA leading to a mixture of epoxides, **6**. Treatment of the latter with H_5IO_6 gave Methyl ketone **7** which Norrish II photochemical rupture (High Pressure Hg lamp, 500 W) afforded diene **8**, $[\alpha]_D^{22} = -88.4°(CHCl_3, c\ 1.1)$.[13]

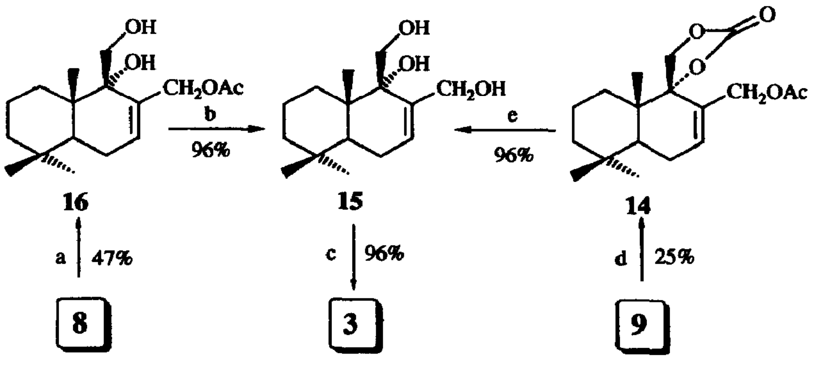
Epoxidation of diene **8** with *m*–CPBA afforded epoxides **9** and **10** (8:2) where the former predominates in the mixture, as expected, due to the proximity of the β–Methyl group at C-10. Ring–opening of the epoxide **9**,[14] $[\alpha]_D^{22} = -50.3°(CHCl_3, c\ 0.4)$, with $BF_3{\bullet}Et_2O$[15] occurs diastereoselectively giving aldehydes **11**[16] and **12** in a 95:5 ratio. When a mixture of **9** and **10** was treated under the same reaction conditions with $BF_3{\bullet}Et_2O$, rearrangement afforded the same aldehydes **11** and **12** with the same ratio as before, confirming that rearrangement goes through a cationic pathway and not a concerted one, where the geometry of the carbocation intermediate controlled by the Me–C_{10} guides hydride migration by the less hindered face.[15] LAH reduction of **11** afforded **13**[17] whose stereochemistry at C–9 is known. Swern oxidation gave poligodial **2**.[17]



Scheme 2. a) LAH/Et$_2$O; b) Ac$_2$O/Py; c) TsOH/MeOH; d) *m*-CPBA/CH$_2$Cl$_2$; e) H$_5$IO$_6$; f) hν/Hexane;
g) BF$_3$•Et$_2$O; h) Swern Oxidation

Treatment of **9** with Chlorosulfonyl isocyanate (CSI) afforded carbonate **14** with retention of configuration;[18] hydrolysis of the latter led to the triol **15** whose Swern oxidation led to warburganal **3**.[10,17]

The *cis*-hydroxylation of diene **8** with catalytic OsO$_4$/N-Methylmorpholine-N-oxide(NMO)[19] afforded the diol **16** in a 47 % yield (Scheme 3). The latter, after LAH reduction and Swern oxidation of the intermediate triol, also afforded warburganal **3**. The overall yield (55 % yield for poligodial and 27 % yield for warburganal) are much better than those previously reported.[7]



Scheme 3. a) Catalytic OsO$_4$/NMO; b) LAH/Et$_2$O; c) Swern Oxidation; d) CSI; e) 4 % NaOH/1,4-dioxane

Acknowledgement The authors thank the CICYT for financial support (PB 91-0193).

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13. Spectroscopic data for compound **8**: IR ν_{max} cm^{-1}: 3080, 1745, 1470, 1380, 1360, 1240, 1005, 890. MS m/z (rel. int.): 262 (M^{+}, 38), 220 (20), 202 (80), 187 (81), 159 (80), 133 (100), 119 (90), 105 (70), 91 (73), 69 (72). ^{1}H NMR δ (ppm): 5.96 (1H, m, H-7), 4.89(1H, bs, H$_a$-11), 4.81 (1H, s, H$_b$-11), 4.73 (1H, d, J =12.2 Hz, H$_a$-12), 4.64 (1H, d, J =12.2 Hz, H$_b$-12), 2.06 (3H, s, –OCOMe), 0.96, 0.93 and 0.87 (3H, s, ea., Me-15, Me-14 and Me-13, respectively).
14. Spectroscopic data for compound **9**: IR ν_{max} cm^{-1}: 1750, 1675, 1470, 1380, 1360, 1270, 840. MS m/z (rel. int.): 278 (M^{+}, 5), 263 (7), 235 (55), 218 (27), 203 (33), 189 (27), 133 (41), 119 (55), 109 (75), 105 (81), 91 (80), 69 (81), 55 (100). ^{1}H NMR δ (ppm): 6.26 (1H, dd, J = 6.4 and 2.9 Hz, H-7), 4.45(1H, d, J =12.2 Hz, H$_a$-12), 4.21 (1H, d, J =12.2 Hz, H$_b$-12), 2.91 (1H, d, J = 3.8 Hz, H$_a$-11), 2.86 (1H, d, J = 3.8 Hz, H$_b$-11), 2.02 (3H, s, –OCOMe), 0.99, 0.91 and 0.89 (3H, s, ea.).
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16. Spectroscopic data for compound **11**: IR ν_{max} cm^{-1}: 2840, 2760, 1745, 1720, 1470, 1380, 1365, 1240. MS m/z (rel. int.): 278 (M^{+}, 2), 249 (3), 234 (10), 218 (2), 205 (6), 189 (17), 124 (30), 109 (87), 91 (45), 81 (54), 69 (100), 55 (70). ^{1}H NMR δ (ppm): 9.76 (1H, d, J = 5.3, H-11), 6.01 (1H, m, H-7), 4.57 (1H, d, J =12.3 Hz, H$_a$-12), 4.43 (1H, d, J =12.3 Hz, H$_b$-12), 2.84 (1H, m, H–9), 2.01 (3H, s, –OCOMe), 1.04, 0.93 and 0.88 (3H, s, ea.).
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(*Received in UK* 22 *February* 1994; *revised* 21 *March* 1994; *accepted* 24 *March* 1994)