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SYNTHESIS OF (+)-LIMONIDILACTONE: ABSOLUTE CONFIGURATION OF (-)-LIMONIDILACTONE

Isidro S. Marcos, Rosalina F. Moro, Santiago Carballares M. and Julio G. Urones*

Dept. de Química Orgánica. Universidad de Salamanca. Plaza de los Caídos 1-5, 37008 Salamanca, SPAIN.

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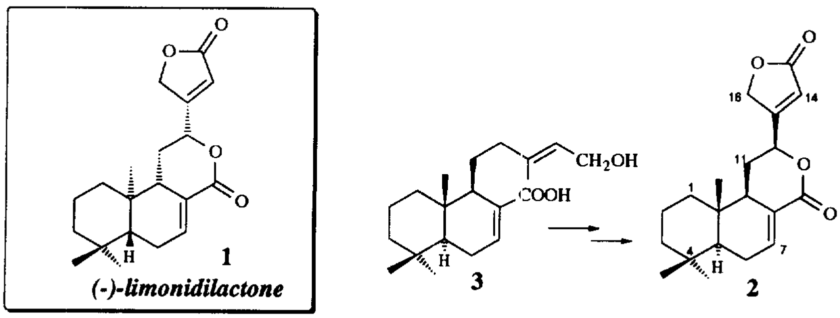
Abstract: The synthesis of (+)-limonidilactone has been achieved from zamoranic acid in 6 steps with an overall yield of 25%. The absolute configuration of (-)-limonidilactone has been established, as a natural labdane belonging to the antipode series.

The labdanes are bicyclic diterpenes that exhibit a wide range of biological activities.[1] Since they are readily available, some natural labdanes have been useful starting materials for chemical transformations into other natural products.[2]

Limonidilactone, **1**, is a labdane diterpene, from the leaves of *Vitex* limonifolia,[3] which possesses in its structure γ-butenolide and δ-lactone systems. The structure of (-)-limonidilactone, **1**, was established by spectroscopic methods and was confirmed by X-ray analysis; however, the existing data did not permit the assignment of the absolute configuration.[3]



Scheme 1

Zamoranic acid, **3**, the major component from *Halimium viscosum*,[4] has been used as a starting material in the synthesis of biologically active natural products such as drimanes.[5]

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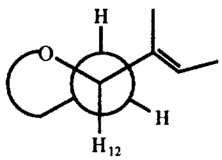
At present, zamoranic acid is being employed in the synthesis of diterpenic lactones with a labdane skeleton. In this work we report specifically the synthesis of (+)-limonidilactone from zamoranic acid, **3**, (Scheme **1**) in 6 steps, with an overall yield of 25% (Scheme **2**). Thus the absolute configuration of natural (-)-limonidilactone, **1**, is also established.

The synthesis of (+)-limonidilactone **2** from zamoranic acid presented two main problems: the manipulation of the functionality on C-12 and C-16 and control of the stereochemistry at C-12.

Treatment of compound **3** in acidic medium (HCOOH, rt or *p*-TsOH)[6] afforded a mixture of **4/5**, in excellent yield (90%) and high diastereoselectivity (95/5). This mixture was separated by chromatography. The configuration on C-12 in **4** and **5** was established by considering the signals of the geminal hydrogen at this carbon: δ 4.60 (dd, J=2.2 and 13.6 Hz) for compound **4** and δ 4.82 (broad singlet) for compound **5**. In conclusion H-12 was assigned as axial in **4**, hence the configuration for this compound is 12*S* and the side chain is equatorial.



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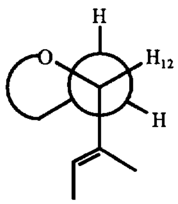

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It was found that the mixture of **4/5** could be used directly in order to degrade the side chain, and to functionalize C-16. Thus, chemoselective epoxidation of **4/5** with *m*-CPBA led to a mixture of epoxides **6**, in 94% yield, followed by oxidation with H_5IO_6 afforded a mixture of the methylketones **7** (73%) and **8** (7%), which were easily separated by chromatography.

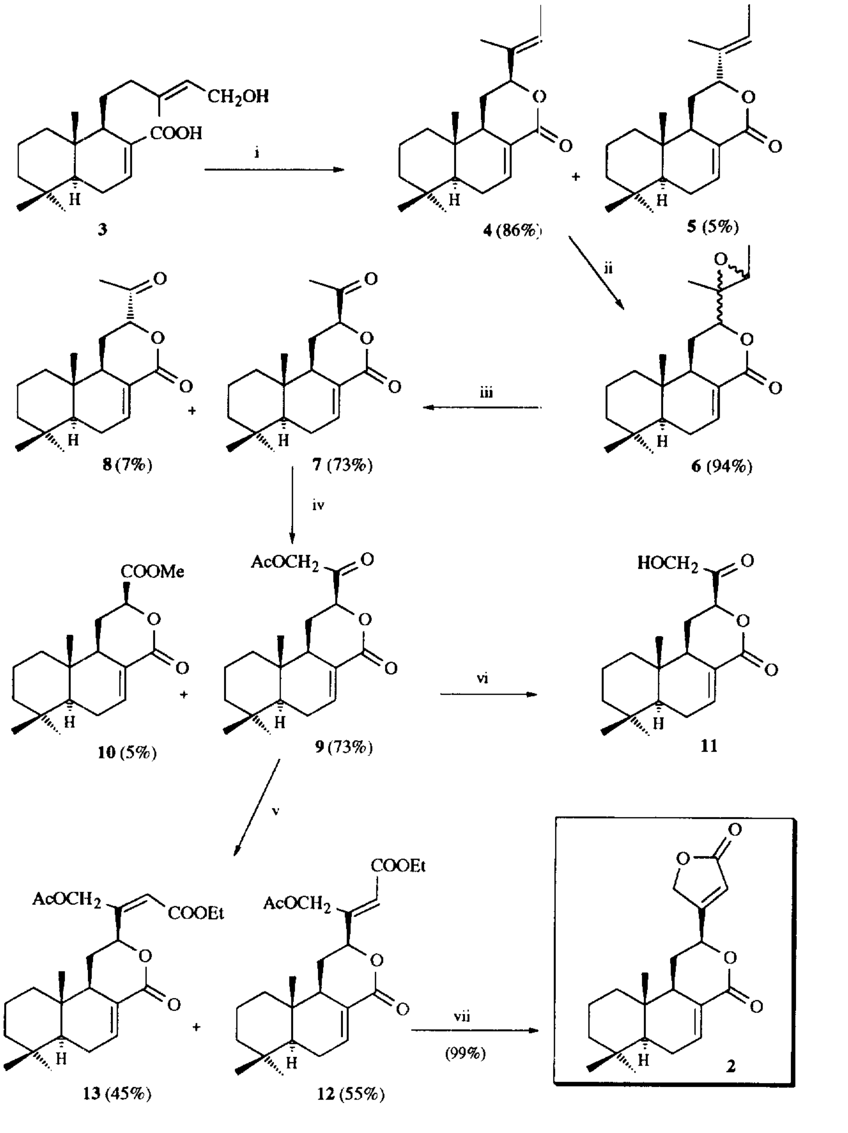
Attempts to functionalize C-16 by oxidation of the silylenolether of **7** gave poor results. Direct oxidation of **7** with reagents such as Na_2CrO_4 or LTA/AcOH was also disappointing. However, **9** was finally obtained by oxidation of **7** with LTA/BF_3 Et_2O,[7] in excellent yield (73%), accompanied by **10** as a minor product (5%).

It was envisaged that (+)-limonidilactone, **2**, would be prepared by reaction of **11** with the Bestmann ketene.[8] However, this approach was discarded when the hydrolysis of **9** to give **11** was found to be low yielding.

The γ-butenolide **2** was synthesised by hydrolysis of the acetoxyester **12**, which was prepared by reaction of **9** with the appropriate phosphorus ylide. Unfortunately, the Wittig reaction[9] proceeded with low stereoselectivity *E*/*Z* (45/55).

The melting point and the spectroscopic data for **2**[10] were identical to those for (-)-limonilactone, **1**.[3] The rest of the compounds, in this synthesis, are in agreement with their spectroscopic data (IR, ^{1}H, ^{13}C NMR).

The natural limonilactone **1** presents an $[\alpha]_D$= -23.8 (c, 0.12 in $CHCl_3$) while **2** presents $[\alpha]_D$=+14.2 (c, 1.4 in $CHCl_3$), which indicates that natural (-)-limonidilactone, **1**, belongs to the antipodal series of labdanes.



Reagents and conditions: (i) *p*-TsOH, benzene, 60°C, or HCOOH, r.t. ; (ii) *m*-CPBA, DCM, r.t.; (iii) H_5IO_6, THF:H_2O (2:1), r.t.; (iv) lead (IV) tetraacetate, benzene, BF_3 Et_2O, MeOH; (v) $Ph_3PCHCOOEt$, benzene, reflux; (vi) acetone, H_2O, *p*-TsOH, r.t.; (vii) *p*-TsOH, MeOH, r.t.

Scheme 2

ACKNOWLEDGMENTS

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10. Data for compound **2** [(+)-limonidilactone]: $[\alpha]_D^{20°C}$= +14.2 (c=1.4, $CHCl_3$); **mp** = 225-228 °C; **IR** υ_{max} **cm^{-1}**: 2928, 1790, 1740, 1713, 1638, 1352, 1248, 1171, 1146, 1171, 1146, 1088, 1030, 893, 862, 743, 721, 683 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)**: 7.41 (1H, td, J=2.5 and 5.0Hz, H-7), 6.08 (1H, dt, J=2.0 and 1.5Hz, H-14), 5.21 (1H, br d, J=11.0Hz, H-12), 4.95 (2H, dd, J=1.0 and 1.5Hz, H-16), 2.43 (1H, m, H-6), 2.37 (1H, m, H-9), 2.15 (1H, m, H-6), 2.06 and 1.58 (1H, m each, H-11_α and H11_β), 1.34 (1H, dd, J=12.0 and 5.0Hz, H-5), 1.81 (1H, br d, J=12.5Hz) and 1.72-1.50 (3H, m) and 1.27-1.05 (2H, m) H-1_α, H-1_β, H-2_α, H-2_β, H-3_α and H-3_β, 0.93, 0.91 and 0.78 (3Me, s each, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: 13.4 (C-20); 18.4 (C-2); 21.3 (C-19); 25.6 (C-11); 28.1 (C-6); 32.8 (C-4 and C-18); 34.8 (C-10); 38.7 (C-1); 41.7 (C-3); 48.7 and 48.9 (C-5 and C-9); 70.6 (C-16); 74.8 (C-12); 116.2 (C-14); 124.7 (C-8); 145.2 (C-7); 163.9 and 166.5 (C-17 and C-15); 172.4 (C-13).