

Partial Synthesis of 6 β -Sesquiterpenolides from 6 α -Sesquiterpenolides

José L. Bretón

Instituto de Productos Naturales Orgánicos
Consejo Superior de Investigaciones Científicas
La Laguna, Tenerife, Spain

Juan J. Cejudo, Andrés García-Granados*, Andrés Parra and Francisco Rivas

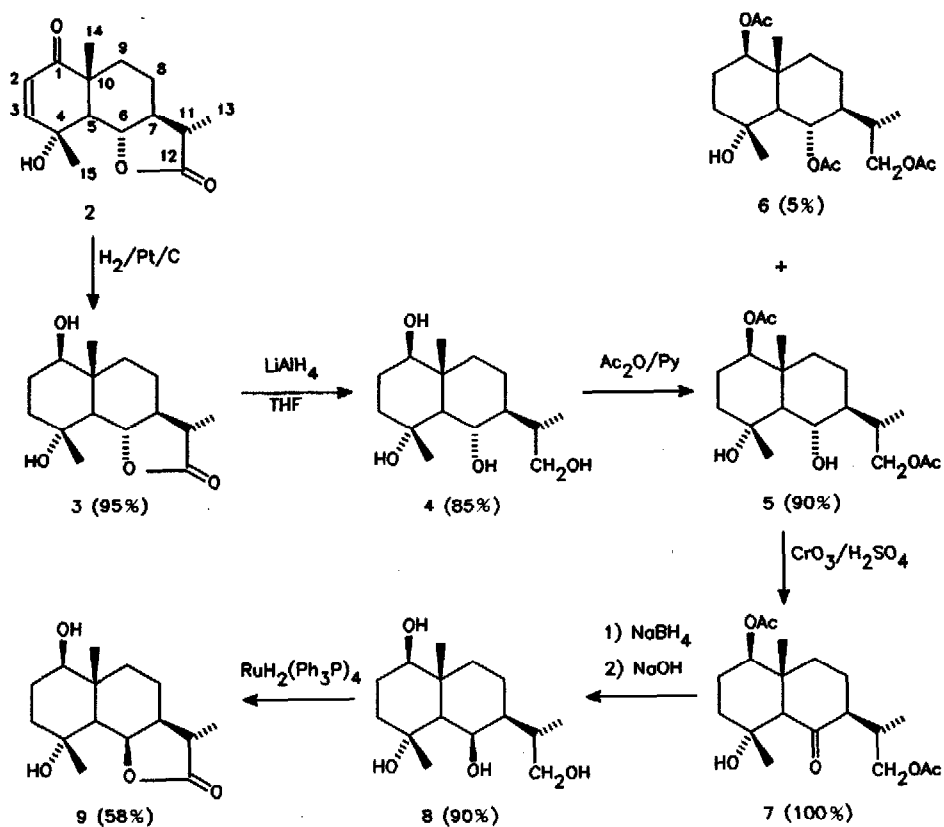
Departamento de Química Orgánica
Facultad de Ciencias, Universidad de Granada
18071 Granada, Spain

Key Words: Sesquiterpenoids, sesquiterpenolides, 6 α -eudesmanolides, 6 β -eudesmanolides, epimerization.

ABSTRACT: Chemical means were used to achieve the epimerization at C-6 of 6 α -eudesmanolides, with several functionalizations, to 6 β -eudesmanolides. The process consists of the LiAlH_4 reduction of a 6 α -lactone, selective acetylation of the hydroxymethylene group at C-12, oxidation and reduction at C-6 to epimerize this carbon, deacetylation at C-12 and final formation of a 6 β -lactone with $\text{RuH}_2(\text{Ph}_3\text{P})_4$. The whole process yields nearly 40% of the 6 β -lactone, oxidation with the ruthenium reagent (58 and 53%) being the limiting step.

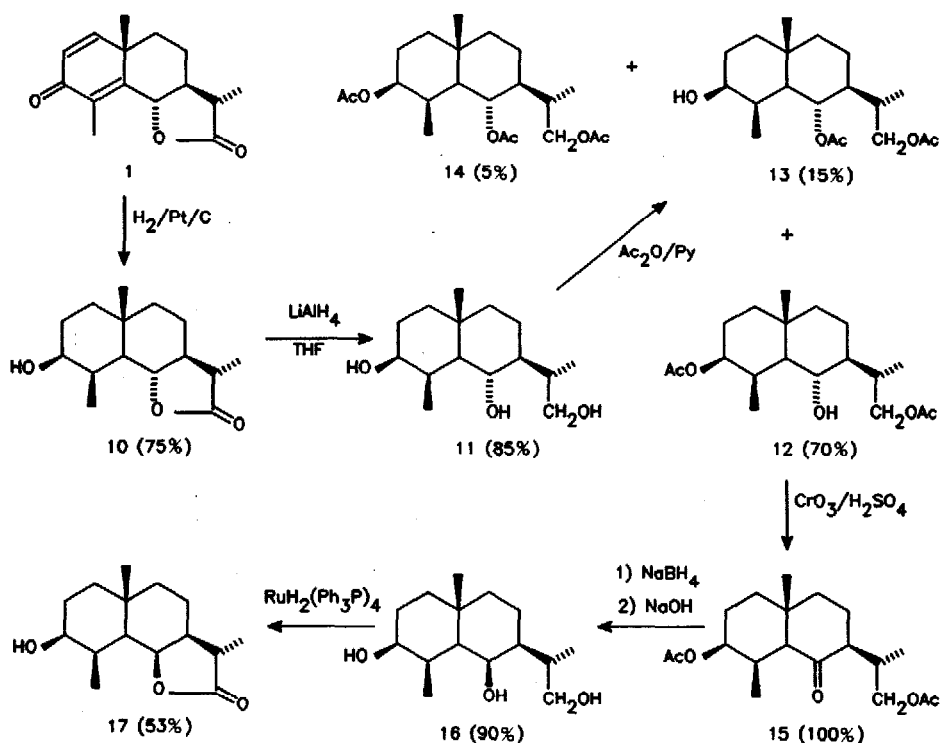
The 6 β -sesquiterpene lactones, scarce in nature¹, are the object of interesting studies on the biogenesis of pseudoguaianolides and elemanolides. The chemistry², photochemistry³, biomimetic synthesis⁴ and biotransformations⁵ of 6 β -sesquiterpene lactones have been extensively studied. We synthesized 6 β -sesquiterpene lactones with the aid of a microorganism to obtain the lactone function⁶ *de novo*. We have also obtained new 6 β -lactones by chemical and microbiological means⁷. The classical way to get 6 β -lactones from 6 α -lactones is the 6-epimerization of α -santonin (1) in acidic medium⁸. This epimerization is only possible through functionalization of this 6 α -eudesmanolide. The steric energy of 6 α -santonin (1) is about 0.55 Kcal/mol⁹ greater than that of its epimer in C-6, which allows its interconversion in acidic medium. We now report an easy way to epimerize the 6 α -lactones at C-6, and thus obtain 6 β -lactones by chemical means.

Vulgarin (**2**) is a very abundant sesquiterpene lactone in *Artemisia canariensis* Lees¹⁰. Hydrogenation of **2** gave the tetrahydro derivative **3** (95%), which was treated with LiAlH₄ to afford the tetrahydroxyl derivative **4** (85%). This product was acetylated under mild conditions to give **5** (90%) and **6** (5%). The 6-deacetylated product **5** was then quantitatively oxidized with Jones' reagent¹¹ to obtain the ketone **7**, which was reduced with NaBH₄ and saponified, producing a high yield of the tetrol **8**. This product (**8**), containing a 6β hydroxyl function, was oxidized with RuH₂(Ph₃P)₄¹² to obtain the 6β-lactone **9** (58%).



Similar yields were observed in the epimerization of the 6α-lactone **10**, obtained from hydrogenation of 6α-santonin (**1**, 75%). The reduction of **10** with LiAlH₄ took place with the same yield as the forementioned reaction, affording the product **11** (85%). Although acetylation of **11** gave a wider variety of acetates because its 6α-hydroxyl group is more accessible, the desired product **12** was also

obtained at a high yield (70%). The next steps gave yields similar to those described for the above mentioned synthesis, affording the 6 β -lactone 17. In both cases oxidation with the ruthenium reagent is the limiting step, with yields of 58 and 53% in each case, which we think can be improved. In conclusion, the entire process constitutes a useful and general way to epimerize 6 α -lactones to 6 β -lactones.



ACKNOWLEDGEMENTS: This work was supported by a grant from the Dirección General de Investigación Científica y Técnica. We thank Karen Shashok for her assistance in the translation of the text.

REFERENCES AND NOTES

- Fischer, N.H., Oliver, E.J. and Fischer, H.D.: "The Biogenesis and Chemistry of Sesquiterpene Lactones". In: *Progress in the Chemistry of Organic Natural Products*. (Ed. Herz, W., Grisebach, H. and Kirby, G.W.), Springer-Verlag, Wien, New York, 1979, 38, 47-390.
- a) Ando, M., Akahane, A. and Takase, K., *Bull. Chem. Soc. Japan*, 1978, 51(1), 283.
b) Jain, T.C. and Banks, C.M., *Can. J. Chem.*, 1980, 58, 447.

- c) Ando, M., Tajima, K. and Takase, K., *J. Org. Chem.*, **1983**, *48*, 1210.
3. Lange, G.L. and Lee, M., *J. Org. Chem.*, **1987**, *52*, 325.
4. a) Bordoloi, M.J., Sharma, R.P. and Sarmah, J.C., *Tetrahedron Lett.*, **1986**, *27*, 4633.
b) Parodi, F.J. and Fisher, N.H., *J. Chem. Soc. Chem. Comm.*, **1986**, 1405.
c) G. Gonzalez, A., Galindo, A., Alonso, M.M., Mansilla, H. and Lopez, H., *Tetrahedron*, **1988**, *44*, 4585.
d) G. Gonzalez, A., Galindo, A., Alonso, M.M., Mansilla, H. and Palenzuela, J.A., *Tetrahedron*, **1988**, *44*, 4575.
e) Harapanhalli, R.S., *J. Chem. Soc. Perkin Trans I*, **1988**, 2633.
f) Bordoloi, M.J., Sharma, R.P. and Sarmah, J.C., *Tetrahedron*, **1989**, *45*, 289.
g) Ortega, A. and Maldonado, E., *Heterocycles*, **1989**, *29*, 635.
5. a) Yamakawa, K., Nishitani, K., Iida, M. and Mikami, A., *Chem. Pharm. Bull.*, **1986**, *34*(3), 1319.
b) Arias, J.M., Bretón, J.L., Gavin, J.A., García-Granados, A., Martínez, A. and Onorato, M.E., *J. Chem. Soc. Perkin Trans I*, **1987**, 471-474.
c) Naik, V.P., Mavinkurve, S., Naik, V.S. and Paknikar, S.K., *Indian J. Chem., Sect. B.*, **1988**, *27B*(4), 381.
d) Amate, Y., García-Granados, A., Martínez, A., Sáenz de Buruaga, A., Bretón, J.L., Onorato, M.E. and Arias, J.M., *Tetrahedron*, **1991**, *47*(30), 5811-5818.
6. García-Granados, A., Martínez, A., Onorato, M.E., Rivas, F. and Arias, J.M., *Tetrahedron*, **1991**, *47*(1), 91-102.
7. Amate, Y., Bretón, J.L., García-Granados, A., Martínez, A., Onorato, M.E. and Sáenz de Buruaga, A., *Tetrahedron*, **1990**, *46*(19), 6939-6950.
8. Ishikawa, H. and Zasshi, Y., *J. Pharm. Soc., Japan*, **1956**, *76*, 500-504.
9. a) White, D.N.J., and Sim, G.A., *Tetrahedron*, **1973**, *29*, 3933-3938.
b) Calculation with an interactive molecular modelling program (NEMESIS, Oxford Molecular LTD) of the difference between the *steric* energies for both lactones showed this energy to be 0.83 Kcal/mol greater for the 6 α -lactone.
10. G. González, A., Bermejo, J., Bretón, J.L. and Fajardo M., *An. Quím.*, **1973**, *69*, 667.
11. Curtis, R.G., Heilbron, H., Jones, E.H.R. and Woods, Q.F., *J. Chem. Soc.*, **1953**, 457.
12. a) Murahashi, S.I., Naota, T., Ito, K., Maeda, Y. and Taki, H., *J. Org. Chem.*, **1987**, *52*, 4319-4327.
b) Reaction conditions: a mixture of alcohol (**8** or **16**) (2.5 mmol), acetone (7.5 mmol), and RuH₂(Ph₃P)₄ (0.05 mmol) in dry toluene (0.5 mL) was heated at 180 °C for five hours under argon.

(Received in UK 27 April 1992)