Tetrahedron Letters, Vol. 34, No. 36, pp. 5723-5724, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

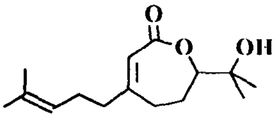
Preparation of the Hexanolide Isolated from *Conyza hypoleuca*

Bruno Simonot and Gérard Rousseau *

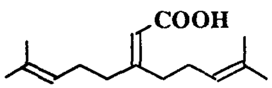
Laboratoire des Carbocycles, Associé au CNRS, Institut de Chimie Moléculaire d'Orsay,
Bât. 420, Université de Paris-Sud, 91405 Orsay (France)

Abstract: *A synthesis of racemic 13-hydroxy-10-sesquigeranic-1,12-olide is reported using bis(sym-collidine)iodine(I) hexafluorophosphate in the lactonisation key step.*

The aerial parts of *Conyza hypoleuca*, a tree of East Africa were shown to produce numerous original natural products.[1] Among them, we were especially interested in a particular metabolite, the 13-hydroxy-10-sesquigeranic-1,12-olide **1**, probably formed in the biosynthesis from the 10-sesquigeranic acid **2**.[2]

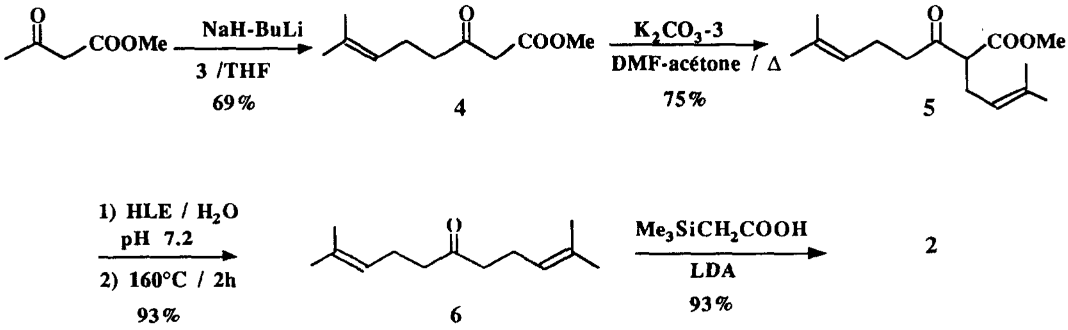


1



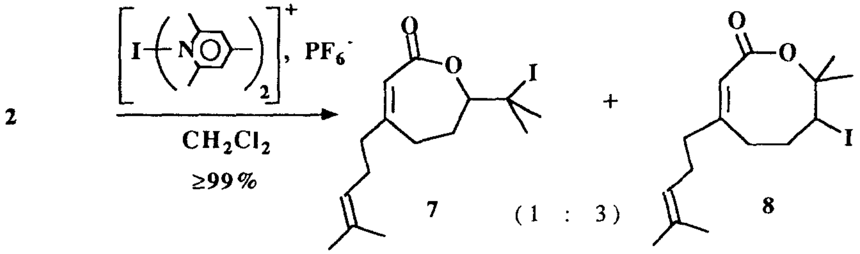
2

Indeed, recently we reported a new efficient method, which allowed the preparation of 7-membered lactones by an iodo-induced cyclisation using bis(*sym*-collidine)iodine(I) hexafluorophosphate as the reagent.[3] We decided to test this new reagent in the cyclisation of acid **2**, with a view to a short preparation of lactone **1**. Acid **2** was prepared by a straightforward method starting from ethyl acetylacetate.



Alkylation of this ketoester with 1-bromo-3-methyl-2-butene **3** using first the Weiler [4] and then the Mori [5] procedure led to the ketoester **5** (60% yield) which was hydrolysed by horse liver esterase [6] and heated to afford the symmetrical ketone **6**. [7] Subjection of **6** to Peterson's reaction using trimethylsilylacetic acid [8] led to the desired acid **2**, which was characterised by comparison of its spectral data with those published.[2] The iodolactonisation of acid **2** was then carried out using bis(*sym*-collidine)iodine(I) hexafluorophosphate (1.2 eq.,

CH_2Cl_2). After completion of the reaction (r.t., 15 min) the two iodolactones **7** and **8** were separated by chromatography (SiO_2, hexane/ether : 9/1) and isolated in quantitative yield. The structure of these lactones were established using conventional analysis methods.[9] As expected the methyl subtitution of the 12,13-double bond favoured the *endo* cyclisation product **8** [10]. This result is the first example of preparation in such a high yield [3] of an 8-membered lactone by an electrophile-induced cyclisation.



The iodolactones **7** and **8** were separately submitted to the action of silver trifluoroacetate in nitromethane in the presence of a pH 7.0 phosphate buffer. The desired hydroxylactone **1** was isolated in 75% and 45% yields respectively. Spectral data of lactone **1** were in agreement with those previously published.[1] The racemic hexanolide **1** was thus obtained in an overall yield of 23%. Preparation of other unsaturated medium-ring lactones by this new procedure is under investigation.

***Acknowledgements*:** We wish to thank Rhône-Poulenc Rorer for their financial support to B. Simonot.

References and Notes

1. Zdero, C.; Bohlmann, F.; Mungai, G.M. *Phytochemistry*, **1991**, *30*, 575.
2. Zdero, C.; Ahmed, A.A.; Bohlmann, F.; Mungai, G.M. *Phytochemistry*, **1990**, *29*, 3167.
3. Simonot, B.; Rousseau, G. *J. Org. Chem.*, **1993**, *58*, 4.
4. Huckin, S.N.; Weiler, L. *J. Am. Chem. Soc.*, **1974**, *96*, 1082.
5. Mori, K.; Watanabe, H. *Tetrahedron*, **1986**, *42*, 295. 23% of a dialkylated product easily separated by liquid chromatography (SiO_2) was also obtained in this reaction.
6. Ahmar, M.; Bloch, R.; Bortolussi, M. *Synth. Commun.*, **1991**, 1071.
7. Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.*, **1978**, *43*, 2907.
8. Grieco, P.A.; Wang, C.-L.J.; Burke, S.D. *J. Chem. Soc., Chem. Commun.*, **1975**, 537.
9. Lactone **7**: ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.56 (bs, 3H), 1.64 (bs, 3H), 1.90 (bs, 3H), 1.96 (bs, 3H), 2.00 - 2.52 (m, 8H), 3.85 (dd, J = 8.9 and 2.1 Hz, 1H), 5.00 (m, 1H), 5.86 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) 17.7, 25.6, 26.1, 30.9, 31.4, 31.8, 34.3, 39.2, 47.9, 85.2, 117.7, 122.3, 132.8, 157.6, 167.2. Lactone **8**: ^1H NMR (200 MHz, C_6D_6) δ (ppm) 1.44 (bs, 3H), 1.47 (bs, 3H), 1.62 (bs, 3H), 1.70 (bs, 3H), 1.72 - 2.00 (m, 6H), 2.24 (m, 1H), 3.14 (m, 1H), 4.25 (dd, J = 12.1 and 2.6 Hz, 1H), 4.92 (m, 1H), 5.81 (s, 1H). ^{13}C NMR (50.3 MHz, C_6D_6) δ (ppm) 17.8, 23.2, 25.8, 25.9, 30.7, 33.6, 35.8, 36.2, 40.5, 83.3, 122.9, 123.2, 132.6, 160.4, 168.0.
10. See for example Bartlett, P.A. in "Asymmetric Synthesis", Ed. Morrison J.D., Academic Press, San Diego, 1984, vol. 3, p. 411.

(Received in France 1 July 1993; accepted 15 July 1993)